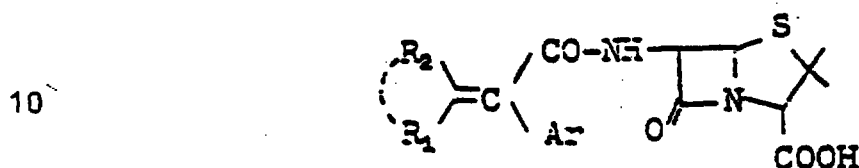


The invention relates to β -lactam compounds, processes for their preparation and agents, such as medicaments, in particular antibacterial agents, and also agents for promoting growth and for improving feed utilization in animals, as well as antioxidants.

β -lactam compounds which carry a substituted acrylamido side chain have already been described.

Thus, for example, penicillin compounds which contain the structural element

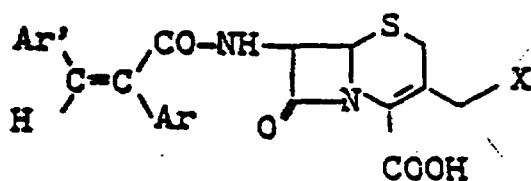


wherein

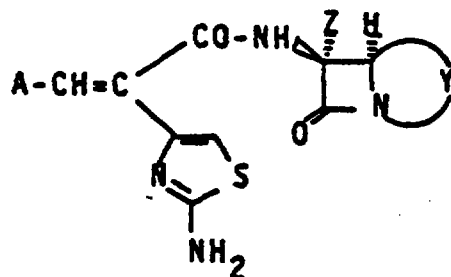
Ar can be a substituted phenyl ring or a heterocyclic radical and

R^1 and R^2 represent substituted or unsubstituted alkyl groups or a cycloalkyl group, are mentioned in Belgian Patent Specification 633,397 and in US Patent Specification 3,622,569.

Furthermore, US Patent Specification 4,014,869 describes cephalosporin compounds with an acrylamido side chain which is in the Z-configuration and carries, inter alia, aromatic or heterocyclic radicals in the 2-position and 3-position:



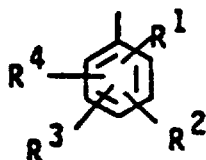
The present invention relates to β -lactam compounds which correspond to the general formula I



I

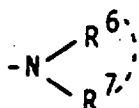
wherein

A denotes hydrogen, optionally cyclic, alkyl, alkenyl or alkynyl with up to 18 C atoms, any of which may be substituted by O, S or methoxyimino, or denotes a radical of the formula



wherein

R¹, R², R³ and R⁴ independently of one another denote hydrogen, halogen, alkyl with up to 6 carbon atoms, aryl, an -OCOR⁵ group, a



group, nitro, cyano, trifluoromethyl,

hydroxyl, alkoxy or alkylthio with up to 6 C atoms, hydroxycarbonyl, alkoxycarbonyl with up to 6 C atoms in the alkyl part, aminocarbonyloxy, sulphonyl or sulpho,

wherein

aryl in turn denotes a substituted or unsubstituted carbocyclic aromatic ring or 5-membered or 6-membered heterocyclic ring,

and wherein

R⁵ denotes optionally substituted and optionally cyclic alkyl, alkenyl or alkynyl with up to 6 C atoms,

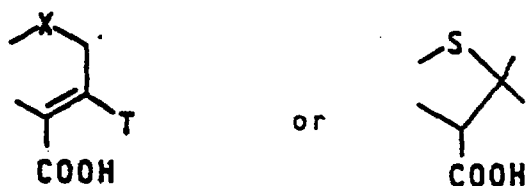
and wherein

R⁶ and R⁷ independently of one another denote hydrogen, optionally substituted and optionally cyclic alkyl, alkenyl or alkynyl with up to 6 C atoms or alkanoyl with up to 6 C atoms, or together denote alkyl or alkanoyl with up to 6 C atoms, or denotes naphthyl, 5-methylisoxazol-3-yl, furyl, thienyl or pyridinyl,

and wherein

Y in the form of the free acid represents a

radical of the formula



wherein

X denotes sulphur or oxygen and

5 T is a conventional radical in cephalosporin chemistry,

and wherein

Z denotes H or methoxy.

10 The compounds according to the invention have very good antibacterial properties.

If A represents an alkyl radical, it is preferably a straight-chain or branched, optionally substituted radical with up to 12 C atoms, especially with up to 6 C atoms.

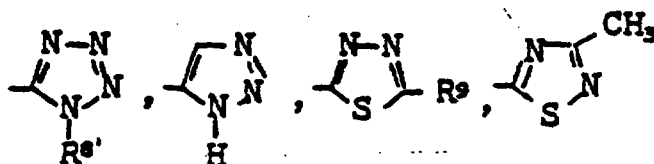
15 With regard to the definition of Y, preferred compounds are those in which

X denotes sulphur or oxygen and

20 T denotes hydrogen, C₁-C₄-alkyl, halogen, C₁-C₄-alkoxy, hydroxymethyl, formyloxymethyl, C₁-C₄-alkylcarbonyloxymethyl, aminocarbonyloxymethyl, pyridiniummethyl, 4-carbamoylpyridiniummethyl or heterocyclylthiomethyl,

wherein

25 heterocyclyl preferably represents a radical of the formula



wherein

30 R⁸ denotes hydrogen, methyl, 2-dimethylamino-ethyl, carboxymethyl or sulphomethyl and R⁹ denotes hydrogen or methyl.

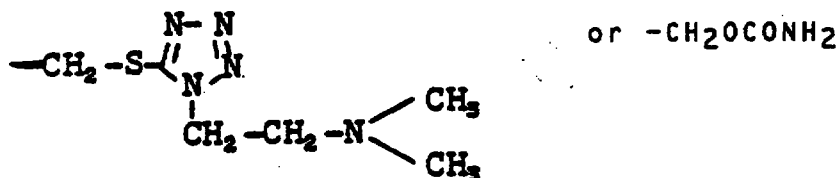
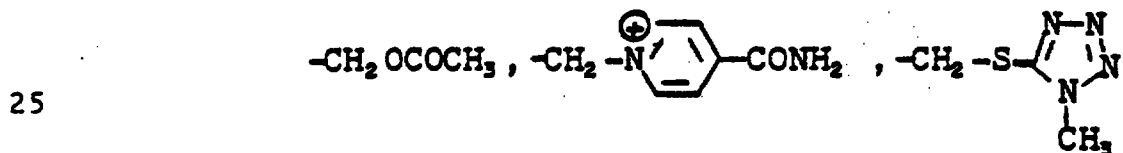
In the compounds of the formula I, for each

structural formula there exists a compound with the E-configuration and a compound with the Z-configuration according to the E/Z nomenclature described in J. Amer. Chem. Soc. 90, 509 (1968). Compounds which are preferred according to the invention are those with the Z-configuration.

The compounds of the formula I can be in the form of free acids, of esters, of inner salts or of non-toxic, pharmaceutically acceptable salts of the acid carboxyl group, such as the sodium, potassium, magnesium, calcium, aluminium and ammonium salts and non-toxic substituted ammonium salts, with amines, such as di- and tri-lower alkylamines, procaine, dibenzylamine, N,N'-dibenzylethylenediamine, N-benzyl-β-phenylethylamine, N-methyl- and N-ethyl-morpholine, 1-ephedrine, dehydroabietylamine, N,N'-bis-dehydroabiethylethylenediamine, N-lower alkyl-piperidine and other amines which can be used for the formation of salts of penicillins or cephalosporins.

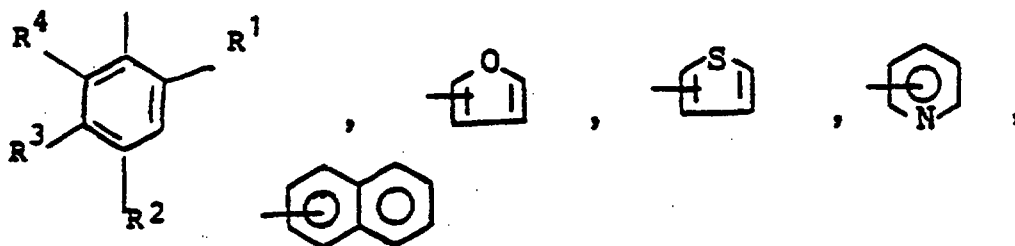
Preferred compounds with the Z-configuration are those wherein

Z denotes hydrogen or methoxy,
X denotes sulphur,
T denotes a radical



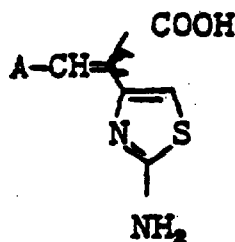
and

A denotes a radical of the formula



The particular Z- and E-forms of the same structural formula are as a rule substances which have a different activity and which can be prepared separately from one another or together.

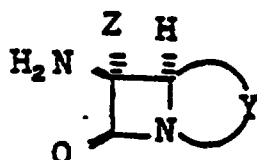
The compounds of the general formula I can be obtained by a process in which compounds of the general formula II



II

wherein

A has the abovementioned meaning, and in which the amino group can be in the protected or unprotected form, are reacted, after the carboxyl group has been activated by being converted into a mixed anhydride, for example using ethyl or isobutyl chloroformate, or after being converted into the acid halide, or after being converted into an activated ester using, for example, N-hydroxysuccinimide and dicyclohexylcarbodiimide, with compounds of the general formula III (which can also be in the monosilyl or disilyl form or in the form of esters which can be split)

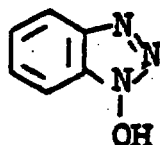


III

wherein

Y and Z have the abovementioned meaning, and, if appropriate, the protective groups are then removed.

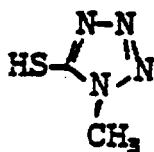
- 5 Preferably, the compounds of the formula II are reacted, after the carboxyl group has been activated with a phosphorus oxychloride or phosphorus pentachloride or in the form of esters with an alcohol of the formula IV



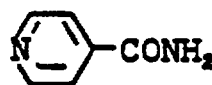
IV

- 10 with a compound of the formula III without prior introduction of an amino-protective group.

The compounds of the formula I according to the invention can also be obtained by a process in which compounds of the formula I in which T denotes $-\text{CH}_2-\text{OCO}$ lower alkyl, in particular $-\text{CH}_2-\text{OCOCH}_3$, are reacted with nucleophiles, for example



or

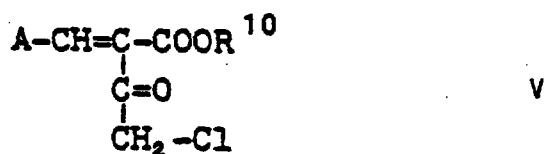


- 20 Compounds of the formula I are furthermore obtained when compounds of the general formula I in which T denotes CH_2OH are reacted with $\text{O}=\text{C}=\text{NSO}_2\text{Cl}$ or $\text{O}=\text{C}=\text{N}-\text{COCCl}_3$ and the SO_2Cl group or $-\text{COCCl}_3$ group is then split off.

- 25 Compounds of the formula I can also be obtained when compounds of the formula I in which Z denotes hydrogen and which are in the form of the free acids, the salts or esters which can be split are reacted with a hypochlorite, for example $(\text{CH}_3)_3\text{COCl}$, in the presence of an alcoholate, preferably a methanolate, for example LiOCH_3 , and, if appropriate, the protective groups are removed.

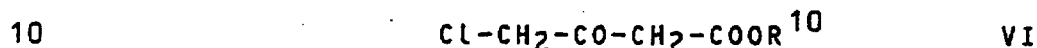
- 30 The compounds of the formula II which are required for the preparation of the compounds according to the invention and which have not yet been described in the literature can be prepared by a number of processes.

It has been found that the following three processes are most appropriate. According to process (1), a compound of the formula V



5 in which

A has the abovementioned meaning and R^{10} denotes $\text{C}_1\text{-C}_4$ - lower alkyl, preferably ethyl, is prepared, in a first step, by condensation of a compound of the formula VI



10 in which

R^{10} has the abovementioned meaning, with a carbonyl compound of the formula VII

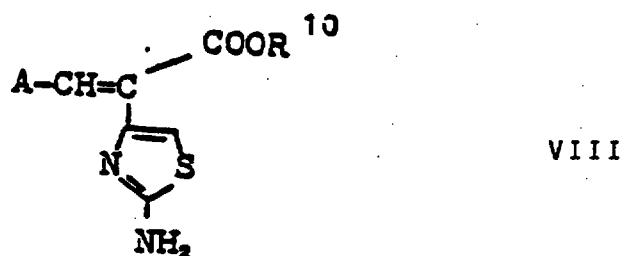


15 in which

A has the abovementioned meaning.

A number of processes have been described for this reaction in the literature, but it has been found that the process in J. Amer. Chem. Soc. 66, 1933 (1944), which has been tested on only one example and which uses the piperidine/glacial acetic acid catalyst system, can be employed for the synthesis of a large number of compounds of the formula V. This process can be carried out in various solvents under various conditions (for example benzene/water separator/reflux or dimethylformamide/drying agent, for example molecular sieve/ 50°). The reaction of a compound of the formula V with thiourea in a polar solvent, such as, for example, acetonitrile, but preferably in a solvent containing hydroxyl groups, such as, for example, methanol or ethanol, or a solvent mixture such as, for example, ethanol/water or tetrahydrofuran/water, in a

temperature range between 0° and 100°C, preferably between 20° and 50°C, if appropriate with the addition of a buffer, such as, for example, sodium acetate, leads to a compound which, in the form of the free base, corresponds to the formula VIII

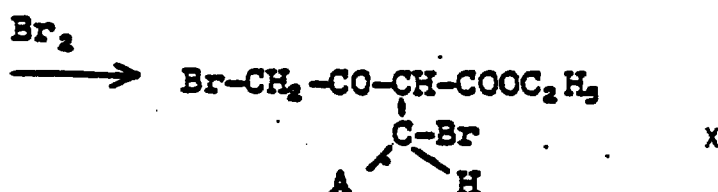
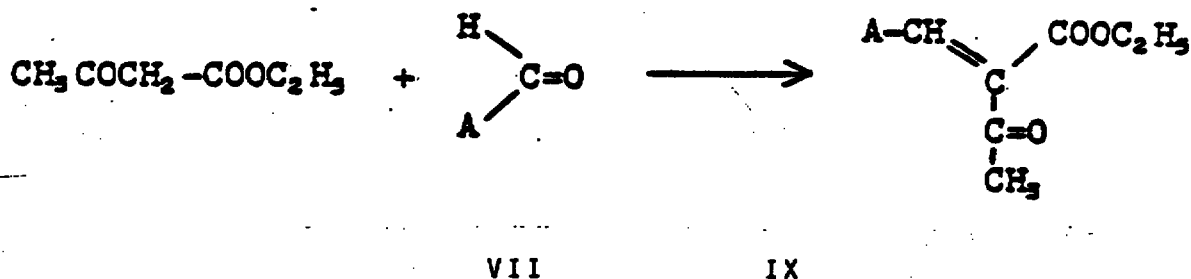


in which

A and R¹⁰ have the abovementioned meaning.

A compound of the formula VIII can be isolated either in the form of the free base corresponding to formula VIII or in the form of the hydrochloride thereof. It can be converted into a carboxylic acid of the formula II by alkaline ester-hydrolysis with, for example, 2N NaOH in methanol, ethanol or dioxane as the solvent, at temperatures from 0° to the reflux temperature.

According to process variant (2), a compound of the formula VIII is obtained by a route which in principle differs from route (1) only by the sequence of the steps. The condensation product IX of ethyl acetoacetate and a carbonyl compound of the formula VII reacts with bromine to give a 1,4-dibromide X



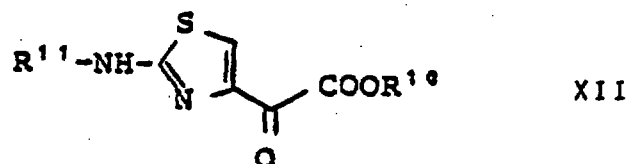
in which

A has the abovementioned meaning.

The reaction proceeds most advantageously when it is carried out at -10° to 0°C in a non-polar solvent, such as, for example, methylene chloride, chloroform or toluene.

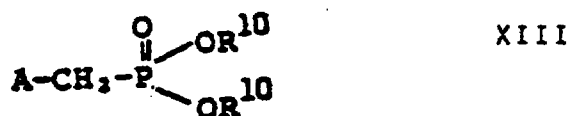
A compound of the formula X can be reacted with thiourea under the conditions already mentioned to give a compound of the formula VIII, with simultaneous cyclization and elimination of HBr.

According to a further process for the preparation of the compounds according to the invention, the compound of the general formula XII



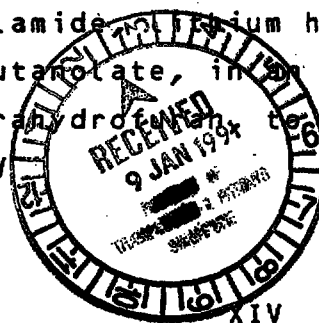
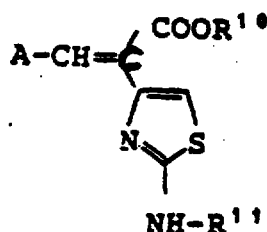
in which

R^{10} has the abovementioned meaning and R^{11} represents an amino-protective group, such as, for example, formyl or tert.-butoxycarbonyl, is reacted with a phosphonate of the general formula XIII

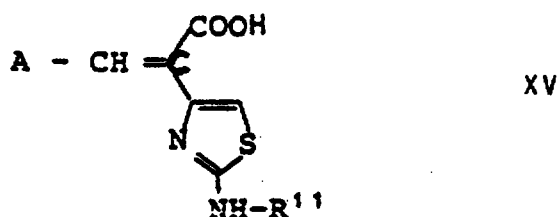


in which

A and R^{10} have the abovementioned meanings, after deprotonation of XIII with a base, such as, for example, sodium hydride, lithium diisopropylamide, lithium hydride, butyl-lithium or potassium tert.-butoxide, in an organic solvent, such as, for example, tetrahydrofuran, to give a compound of the general formula XIV



A carboxylic acid of the formula XV



can be obtained from this compound XIV by alkaline ester-hydrolysis, and, as described for compounds of the formula II, can then be activated and reacted with compounds of the formula III, a compound of the formula I being obtained after the protective groups have been split off.

It is furthermore possible to change the substituent A at one of the synthesis intermediate stages described.

If the compounds according to the invention are prepared as a mixture of the E- and Z-isomers, these isomers can be separated at any of the synthesis intermediate stages V, VIII or II which have been described, with the aid of customary separation methods, such as, for example, distillation, crystallization or chromatography, or by selective chemical reaction of only one isomer to give the product of the next synthesis stage.

In a number of cases, it is furthermore possible to achieve isomerization, i.e. conversion of one isomer into the other by treatment with acids or with bases in a polar organic or aqueous-organic or aqueous solvent, such as, for example, HCl in ethanol or dilute sodium hydroxide solution.

The compounds according to the invention exhibit a broad antibacterial spectrum against Gram-positive and Gram-negative germs, in particular against Enterobacteriaceae, above all against those with β -lactamase formation.

Furthermore, the compounds according to the invention improve the growth and feed utilization in animals and can be used as antioxidants.

The compounds according to the invention display a powerful and broad antimicrobial activity, coupled with low toxicity. These properties enable them to be used as

chemotherapeutic active compounds in medicine and as substances for preserving inorganic and organic materials, especially organic materials of all kinds, for example polymers, lubricants, paints, fibres, leather, paper and timber, and foodstuffs and water.

The compounds according to the invention are active against a very broad spectrum of microorganisms. With their aid, it is possible to combat Gram-negative and Gram-positive bacteria and bacteria-like microorganisms and to prevent, alleviate and/or cure illnesses caused by these pathogens.

The compounds according to the invention are particularly active against bacteria and bacteria-like microorganisms. They are therefore particularly suitable, in human medicine and veterinary medicine, for the prophylaxis and chemotherapy of local and systemic infections caused by these pathogens.

For example, local and/or systemic illnesses which are caused by the following pathogens or by mixtures of the following pathogens can be treated and/or prevented:

Micrococcaceae, such as Staphylococci, for example *Staphylococcus aureus*, *Staph. epidermidis* and *Staph. aerogenes*, and *Gaffkya tetragena* (*Staph.* = *Staphylococcus*); Lactobacteriaceae, such as Streptococci, for example Streptococcus pyogenes, α - and β -haemolysing Streptococci, non-(γ)-haemolysing Streptococci, *Str. viridans* and *Str. faecalis* (Enterococci), and *Diplococcus pneumoniae* (Pneumococci) (*Str.* = *Streptococcus*); Enterobacteriaceae, such as Escherichiae bacteria of the Coli group: *Escherichia* bacteria, for example *Escherichia coli*, *Enterobacter* bacteria, for example *E. aerogenes* and *E. cloacae*, *Klebsiella* bacteria, for example *K. pneumoniae*, and *Serratia*, for example *Serratia marcescens* (*E.* = *Enterobacter*) (*K* = *Klebsiella*), and Proteae bacteria of the Proteus group: *Proteus*, for example *Proteus vulgaris*, *Pr. Morganii*, *Pr. rettgeri* and *Pr. mirabilis* (*Pr.* = *Proteus*); Pseudomonadaceae, such as *Pseudomonas* bacteria, for example *Pseudomonas aeruginosa* (*PS.* = *Pseudomonas*); and Bacteroidaceae, such as *Bacteroides* bacteria, for example

Bacteroides fragilis (B. = *Bacteroides*).

The above list of pathogens is purely illustrative and is in no way to be interpreted as restrictive.

5 Examples which may be mentioned of illnesses which can be prevented, alleviated and/or cured by the compounds according to the invention are: illnesses of the respiratory tract and of the pharyngeal cavity; otitis; pharyngitis; pneumonia; peritonitis; pyelonephritis; cystitis; endocarditis; systemic infections; bronchitis; arthritis;
10 and local infections.

The present invention includes pharmaceutical formulations which, in addition to non-toxic, inert pharmaceutically suitable excipients, contain one or more compounds according to the invention, or which consist of
15 one or more active compounds according to the invention, as well as processes for the preparation of these formulations.

The present invention also includes pharmaceutical formulations in dosage units. This means that the formulation is in the form of individual parts, for example
20 tablets, dragees, capsules, pills, suppositories and ampoules, of which the content of active compound correspond to a fraction or a multiple of an individual dose. The dosage units can contain, for example, 1, 2, 3 or 4
25 individual doses or 1/2, 1/3 or 1/4 of an individual dose. An individual dose preferably contains the amount of active compound which is given in one administration and which usually corresponds to a whole daily dose or a half, a third or a quarter of a daily dose.

30 By non-toxic, inert pharmaceutically suitable excipients there are to be understood solid, semi-solid or liquid diluents, fillers and formulation auxiliaries of every kind.

35 Tablets, dragees, capsules, pills, granules, suppositories, solutions, suspensions and emulsions, pastes, ointments, gels, creams, lotions, powders and sprays may be mentioned as preferred pharmaceutical formulations.

Tablets, dragees, capsules, pills and granules can contain the active compound or compounds alongside

the customary excipients, they (a) fillers and extenders, for example starches, lactose, sucrose, glucose, mannitol and silica, (b) binders, for example carboxymethylcellulose, alginates, gelatine and polyvinylpyrrolidone, (c) humectants, for example glycerol, (d) disintegrating agents, for example agar-agar, calcium carbonate and sodium carbonate, (e) solution retarders, for example paraffin, and (f) resorption accelerators, for example quaternary ammonium compounds, (g) wetting agents, for example cetyl alcohol and glycerol monostearate, (h) adsorbents, for example kaolin and bentonite, and (i) lubricants, for example talc, calcium stearate and magnesium stearate and solid polyethylene glycols, or mixtures of the compounds listed under (a) to (i).

The tablets, dragees, capsules, pills and granules can be provided with the customary coatings and shells, optionally containing opacifying agents, and can also be of such composition that they release the active compound or compounds only, or preferentially, in a certain part of the intestinal tract, optionally in a delayed manner, examples of embedding compositions which can be used being polymeric substances and waxes.

The active compound or compounds, optionally together with one or more of the abovementioned excipients, can also be in a micro-encapsulated form.

Suppositories can contain, in addition to the active compound or compounds, the customary water-soluble or water-insoluble excipients, for example polyethylene glycols, fats, for example cacao fat, and higher esters (for example C₁₄-alcohol with C₁₆-fatty acid), or mixtures of these substances.

Ointments, pastes, creams and gels can contain, in addition to the active compound or compounds, the customary excipients, for example animal and vegetable fats, waxes, paraffins, starches, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silica, talc and zinc oxide, or mixtures of these substances.

Powders and sprays can contain, in addition to

the active compound or compounds, the customary excipients, for example lactose, talc, silica, aluminium hydroxide, calcium silicate and polyamide powder or mixtures of these substances. Sprays can additionally contain the customary propellants, for example chlorofluorohydrocarbons.

Solutions and emulsions can contain, in addition to the active compound or compounds, the customary excipients, such as solvents, solubilizing agents and emulsifiers, for example water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, especially cottonseed oil, groundnut oil, maize germ oil, olive oil, castor oil and sesame oil, glycerol, glycerol-formal, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, or mixtures of these substances.

For parenteral administration, the solutions and emulsions can also be in a sterile form which is isotonic with blood.

Suspensions can contain, in addition to the active compound or compounds, the customary excipients, such as liquid diluents, for example water, ethyl alcohol or propylene glycol, suspending agents, for example ethoxylated isostearyl alcohols, polyoxyethylene sorbitol esters and sorbitan esters, micro-crystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances.

The formulation forms mentioned can also contain colorants, preservatives and additives which improve the odour and flavour, for example peppermint oil and eucalyptus oil, and sweeteners, for example saccharin.

The therapeutically active compounds should preferably be present in the abovementioned pharmaceutical formulations in a concentration of about 0.1 to 99.5, preferably of about 0.5 to 95, per cent by weight of the total mixture.

The abovementioned pharmaceutical formulations can also contain other pharmaceutical active compounds in

addition to the compounds according to the invention.

The abovementioned pharmaceutical formulations are prepared in the customary manner according to known methods, for example by mixing the active compound or compounds with the excipient or excipients.

The active compounds or the pharmaceutical formulations can be administered locally, orally, parenterally, intraperitoneally and/or rectally, preferably orally or parenterally, such as intravenously or intramuscularly.

In general, it has proved advantageous, both in human medicine and in veterinary medicine, to administer the active compound or compounds according to the invention in total amounts of about 5 to about 1,000, preferably 10 to 200, mg/kg of body weight every 24 hours, optionally in the form of several individual administrations, in order to achieve the desired results. An individual administration preferably contains the active compound or compounds according to the invention in amounts of about 1 to about 250, in particular 3 to 60, mg/kg of body weight. However, it can be necessary to deviate from the dosages mentioned, and in particular to do so as a function of the species and the body weight of the subject to be treated, the nature and severity of the illness, the nature of the formulation and of the administration of the medicament and the time or interval over which the administration takes place. Thus it can in some cases suffice to manage with less than the abovementioned amount of active compound, whilst in other cases the abovementioned amount of active compound must be exceeded. The particular optimum dosage required and the type of administration of the active compounds can easily be determined by anyone skilled in the art on the basis of his expert knowledge.

When used as feed additives, the new compounds can be administered in the customary concentrations and formulations together with the feed or with the feed formulations or with the drinking water. By this means, it is possible to prevent, alleviate and/or cure an infection by Gram-negative or Gram-positive bacteria and also to

achieve promotion of growth and better utilization of the feed.

5 The new compounds are distinguished by powerful antibacterial actions, which have been tested in vivo and in vitro, and by their ease of absorption on oral administration.

10 For the purpose of broadening the action spectrum and in order to achieve a more powerful action, especially in the case of bacteria which form β -lactamase, the compounds according to the invention can be combined with other antimicrobial active compounds, for example with penicillins which are particularly resistant to penicillinase. Such a combination would be, for example, that with oxacillin or dicloxacillin.

15 For the purpose of broadening the action spectrum and in order to achieve a more powerful action, the compounds according to the invention can also be combined with aminoglycoside antibiotics, such as, for example, gentamicin, sisomicin, kanamycin, amikacin or tobramycin.

20 The compounds according to the invention prevent the degradation of, for example, penicillins by β -lactamases, which usually hydrolyse sensitive penicillins and thus render them inactive. If an amount of 100 mg of mezlocillin per millilitre is added to a crude extract of β -lactamase obtained from E. coli A 261, the penicillin is completely inactivated within 60 minutes. However, if a combination of 100 mg of mezlocillin plus 100 mg of the compound from Example 23 is added, the mezlocillin remains completely antibacterially active.

30 The activity of the β -lactam antibiotics according to the invention can be demonstrated, by way of example, by the following in vitro experiments:

In vitro experiments

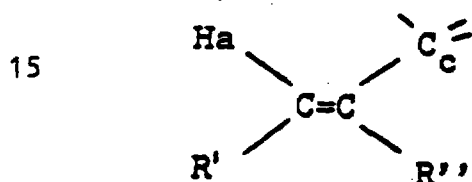
35 The antibacterial action of the compounds of Examples 18 and 23, which can be regarded as typical representatives of the compounds according to the invention, was tested in an agar dilution test under German DIN standard conditions. The concentration was 100 mcg per millilitre of agar. A complete inhibition of growth

was found with the following strains of bacteria:

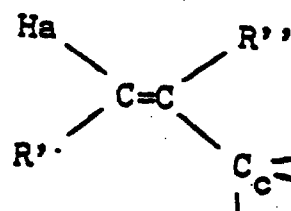
E. coli T 7, *Klebsiella* 57 US, *Serratia marcescens* 16001, *Providencia* 12012, *Proteus morganii* 932, *Proteus vulgaris* 1017, *Proteus rettgeri*, *Enterobacter aerogens* 55 US, *Pseudomonas aeruginosa* W, *Bacteroides fragilis* 012 999, *Staphylococcus aureus* 133 and *Enterococcus* ATCC 9790.

Examples

The determination of the double bond configuration in the compounds according to the invention was carried out with the aid of ^{13}C -nuclear magnetic resonance spectroscopy. It is known that in tri-substituted olefins of the type XII



XIIa



XIIb

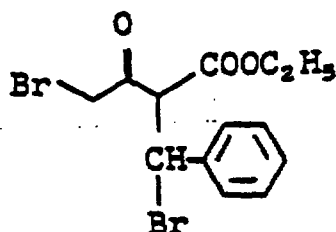
wherein

20 R' and R'' represent organic radicals, the $^3\text{I-Ha C}_\text{C}$ -hetero-coupling is always substantially greater if Ha and C_C are in the trans-position (XIIb) than if they are in the corresponding cis-position (XIIa). This observation was used to allocate the configuration in one of the precursors V, VIII or II of the compounds according to the invention.

Example 1

2-(2-Bromo-2-phenyl)-methyl-3-oxo-4-bromobutyric acid ethyl ester

30



430 g of bromine are added dropwise to 595 g of 2-benzylideneacetoacetic acid ethyl ester in 3 l of methylene chloride at -10 to -5° . The mixture is subsequently

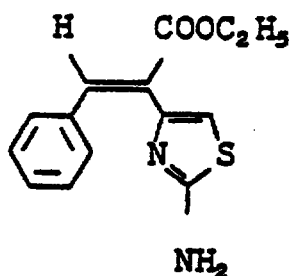
stirred at room temperature for one hour, the solvent is then stripped off at room temperature, ligroin is added to the residue and the residue is decanted. Ligroin is again added to the residue and the mixture is left to stand overnight. The product which has precipitated is filtered off and recrystallized twice from ligroin. Yield: 23.5%, melting point: 99-101°.

IR (Nujol): 1738, 1712, 1575, 1460, 1320, 1290, 1270, 1208, 1181, 1143, 1092, 1030, 1005 cm^{-1} .

NMR (CDCl_3): δ = 0.91[3] t, J = 7 Hz, 3.92[2] q, J = 7 Hz, 4.25[2] s, 4.83[1] d, J = 11 Hz, 5.54[1] d, J = 11 Hz, 7.36[5] m ppm.

Example 2

2-(2-Aminothiazol-4-yl)-3-phenylpropenoic acid ethyl ester. (E-isomer).



323.5 g of the substance prepared according to Example 1 are dissolved in 5 l of ethanol. 65 g of thio-urea are introduced in portions into this solution at 50°. The mixture is subsequently stirred at 50° for 2 hours, the solvent is stripped off and the oily residue is taken up in water. After the mixture has been adjusted to pH 9 with concentrated ammonia solution, it is extracted three times with ethyl acetate. The purified extracts are dried over magnesium sulphate and evaporated. The residue is recrystallized from ethanol and acetone.

Yield: 45%, melting point: 162°.

IR (Nujol): 1680, 1620, 1520, 1365, 1260, 1205 cm^{-1} .

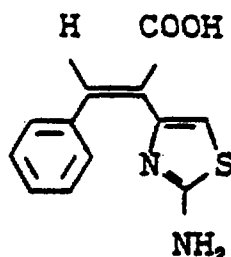
NMR (CDCl_3 + DMSO): δ = 7.75[1] s, 7.22[5] s, 6.25[1] s, 6.19[2] s, broad, 4.21[2] q, J = 7 Hz, 1.25[3] t, J = 7 Hz ppm.

calculated: C 61.3 H 5.1 N 10.2 S 11.7

found: C 61.0 H 5.3 N 10.2 S 11.2

Example 3

2-(2-Aminothiazol-4-yl)-3-phenylpropenoic acid (E-isomer)

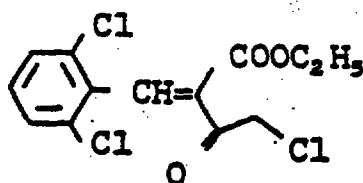


20 g of the compound prepared according to Example 2, dissolved in 250 ml of methanol, are added to 222 ml of 1N sodium hydroxide solution. After the mixture has been stirred overnight at room temperature, the methanol is stripped off. The aqueous phase which remains is adjusted to pH 6.5 with 2N hydrochloric acid and extracted twice with ethyl acetate, and the extract is then slowly adjusted to pH 4. The product which has precipitated is filtered off and recrystallized from ethanol. Yield: 75.2%, melting point: 206-7° (decomposition). IR (Nujol): 1660, 1620, 1602, 1589, 1321, 1226, 1196 cm⁻¹. NMR (CDCl₃ + DMSO): δ = 7.67[1] s, 7.23[5] s, 6.90[2] s, broad, 6.25[1] s ppm.

calculated:	C 58.5	H 4.1	N 11.4	S 13.0
found:	C 58.0	H 4.2	N 11.2	S 12.7

Example 4

2-(2,6-Dichlorobenzylidene)-3-oxo-4-chlorobutyric acid ethyl ester



10 g of 4-chloroacetoacetic acid ethyl ester, 10.5 g of 2,6-dichlorobenzaldehyde, 0.7 ml of glacial acetic acid and 0.35 ml of piperidine are dissolved in 15 ml of benzene. The solution is boiled for 6 hours using a water separator and is then allowed to cool, 100 ml of ether are added and the mixture is extracted in each case once with saturated sodium bicarbonate solution,

water, 1n citric acid solution and again with water. The organic phase is dried over magnesium sulphate and concentrated. The oil which remains is subjected to incident distillation under a high vacuum. The product remains as an oily residue which contains the two isomers, according to gas chromatography and NMR, as a 3:1 mixture. Yield: 64.5%.

The Z-isomer, which is present as the main component, can be crystallized out of this mixture in a pure form using isopropanol. 5.5 g, melting point: 74-6°. A 1:1 E/Z mixture which can no longer be crystallized remains in the mother liquor.

a.) Z-isomer:

IR (KBr): 1727, 1708, 1619, 1557, 1441, 1430, 1377, 1232 cm^{-1} .

NMR (CDCl_3): δ = 7.82[1] s, 7.32[3] m, 4.60[2] s, 4.12[2] q, J = 7 Hz, 0.98[3] t, J = 7 Hz ppm.

calculated: C 48.6 H 3.4 Cl 33.1

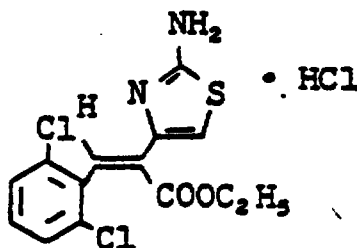
found: C 48.4 H 3.4 Cl 33.1

b.) E-isomer:

NMR (CDCl_3): δ = 7.80[1] s, 7.32[3] m, 4.43[2] s, 4.40[2] g, J = 7 Hz, 1.38[3] t, J = 7 Hz ppm.

Example 5

2-(2-Aminothiazol-4-yl)-3-(2,6-dichlorophenyl)-propenoic acid ethyl ester hydrochloride (Z-isomer)



52.2 g of the crude E/Z mixture prepared according to Example 4 and 12.3 g of thiourea are dissolved in 500 ml of ethanol. After 5 hours, the solution is heated to 50°C and is then left to stand at room temperature for 16 hours. After the product has been filtered off, a second crystalline fraction of the same purity can be crystallized by concentration of the mother liquor. The

product is recrystallized from ethanol. Yield: 36.5%,
melting point: 250°C.

IR (Nujol): 1710, 1635, 1588, 1315, 1240, 1160, 1020 cm^{-1} .

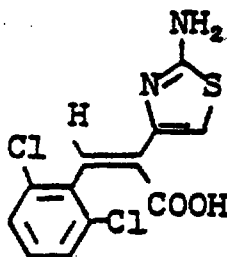
NMR (DMSO): δ = 8.41[3] s, broad, 7.62[1] s, 7.50[3] m,
5 7.07[1] s, 4.04[2] q, J = 7 Hz, 0.91[3] t, J = 7 Hz ppm.

calculated: C 44.3 H 3.4 N 7.4 S 8.4 Cl 28.1

found: C 44.2 H 3.6 N 6.4 S 8.0 Cl 27.8

Example 6

2-(2-Aminothiazol-4-yl)-3-(2,6-dichlorophenyl)-propenoic
10 acid (Z-isomer)



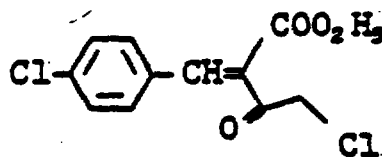
6.5 g of 45 per cent strength sodium hydroxide
solution are added to a solution of 10 g of the ester
prepared according to Example 5 in a mixture of 50 ml of
15 dioxane and 20 ml of water, and the mixture is then dried
under reflux for 56 hours. 100 ml of water are added,
the dioxane is stripped off and the aqueous phase is
adjusted to pH 7.5 with 2N hydrochloric acid. After the
mixture has been extracted twice with ethyl acetate, the
20 extract is adjusted to pH 2 and the product which has
precipitated is filtered off. Yield: 88.7%, melting
point: 163-65° (decomposition).

IR (Nujol): 1642, 1601 (shoulder), 1580, 1405, 1285,
1198 cm^{-1} .

25 NMR (DMSO): δ = 7.45[4] m, 7.16[2] s, broad, 6.90[1] s,
ppm.

Example 7

2-(4-Chlorobenzylidene)-3-oxo-4-chlorobutyric acid ethyl
ester



25.7 g of 4-chloroacetoacetic acid ethylene ester, 23.9 g of 4-chlorobenzaldehyde, 0.7 ml of piperidine and 18 ml of glacial acetic acid are dissolved in 15 ml of benzene. The solution is boiled for 5 hours, using a water separator, and is allowed to cool, and 300 ml of ether are added. After the mixture has been washed three times with water, it is dried over magnesium sulphate and the solvent is evaporated off. The residue is distilled under a high vacuum. The product obtained is a Z/E mixture in a ratio of 3/1. Yield: 23.4%, boiling point 0.5: 161-65°.

IR (film): 1720, 1695 (shoulder), 1622, 1592, 1494, 1395, 1315, 1290, 1260, 2000 cm^{-1} .

NMR (CDCl_3):

a.) Z-isomer α = 7.75[1] s, 7.30[4] s, 4.32[2] s, 4.30[2] q, J = 7 Hz, 1.31[3] t, J = 7 Hz ppm.

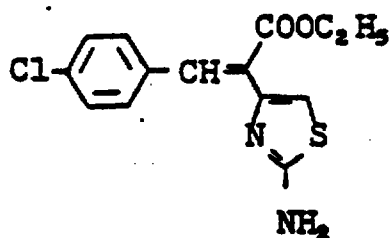
b.) E-isomer α = 7.66[1] s, 7.36[4] s, 4.50[2] s, 4.30[2] q, J = 7 Hz, 1.25[3] t, J = 7 Hz ppm.

calculated: C 54.4 H 4.2 Cl 24.7

found: C 54.0 H 4.2 Cl 24.8

Example 8

2-(2-Aminothiazol-4-yl)-3-(4-chlorophenyl)-propenoic acid ethyl ester



10.5 g of the substance prepared according to Example 7 and 2.8 g of thiourea are dissolved in 275 ml of ethanol and the solution is warmed to 50° for 2 hours. After the solvent has been evaporated off, ethyl acetate and water are added to the oil which remains and the solution is adjusted to pH 1 with hydrochloric acid. The ethyl acetate is separated off and dried over magnesium sulphate and the solvent is evaporated off. The viscous oil which remains consists of impure product. The acid aqueous phase is adjusted to pH 11 with concentrated

ammonia solution and is then extracted three times with chloroform. After the mixture has been dried over magnesium sulphate and the chloroform has been evaporated off, the pure E-isomer of the product can be crystallized with ethanol. Further E-isomer and also Z-isomer of the title compound can be isolated, in each case in a pure form, by medium pressure chromatography of the mother liquor.

a.) E-isomer:

Melting point: 119-21° (decomposition)

IR (Nujol): 3350, 3240, 3080, 1695, 1630, 1620, 1530, 1490, 1270, 1205, 1182, 1098 cm⁻¹.

NMR (CDCl₃): α = 7.88[1] s, 7.26[4] m, 6.42[4] s, 5.50[2] s broad, 4.33[2] q, J = 7 Hz, 1.33[3] t, J = 7 Hz ppm.

calculated: C 54.5 H 4.2 N 9.1 S 10.4 Cl 11.5

found: C 53.4 H 4.5 N 9.2 S 10.8 Cl 11.4

b.) Z-isomer:

Melting point: 114-16° (decomposition)

IR (Nujol): 3360, 3250, 3100, 1698, 1630, 1535, 1222, 1100, 1030, 1010 cm⁻¹.

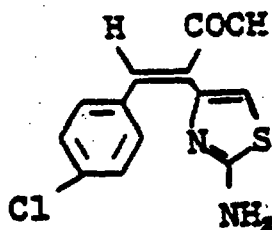
NMR (CDCl₃): δ = 7.45[1] s, 7.26[4] m, 6.55[1] s, 5.20[2] s, broad, 4.25[2] q, J = 7 Hz, 1.18[3] t, J = 7 Hz ppm.

calculated: C 54.5 H 4.2 N 9.1 S 10.4 Cl 11.5

found: C 53.5 H 4.3 N 8.6 S 9.8 Cl 11.8

Example 9

2-(2-Aminothiazol-4-yl)-3-(4-chlorophenyl)-propenoic acid (E-isomer)



10 g of the pure E-isomer prepared according to Example 8 are dissolved in a mixture of 50 ml of methanol and 20 ml of water. 20 ml of 2N sodium hydroxide solution are added to the solution and the mixture is stirred at room temperature overnight. The methanol is stripped off, the aqueous phase is adjusted to pH 3 with 2N hydrochloric

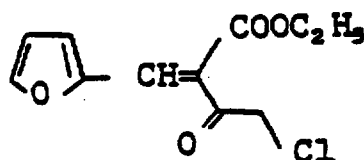
acid and the product which has precipitated is filtered off. It is recrystallized from ethanol. Yield: 66.6%, melting point: 225° (decomposition).

IR (Nujol): 1650, 1620, 1585, 1338 cm⁻¹.

5 NMR (DMSO): α = 7.72[1] s, 7.33[4] m, 7.0-7.8[3] broad, 6.40[1] s ppm.

Example 10

2-(2-Furylidene)-3-oxo-4-chlorobutyric acid ethyl ester



10 200 g of 4-chloroacetoacetic acid ethyl ester, 125.6 g of freshly distilled fururol, 2.6 ml of piperidine and 7 ml of glacial acetic acid are dissolved in 120 ml of benzene and the solution is boiled for 5 hours, using a water separator. 1 L of ether is added to the cooled
15 solution and the mixture is then extracted in each case once by shaking with saturated sodium bicarbonate solution, water, 2M citric acid solution and again with water. After the extract has been dried over magnesium sulphate and concentrated, an oil is obtained and is subjected to
20 incipient distillation under a high vacuum. The product remains as a viscous oil and the E/Z isomer ratio is 4:1. Yield: 86.8%.

IR (Nujol): 1720, 1678, 1620, 1450, 1415, 1355, 1303 cm⁻¹.

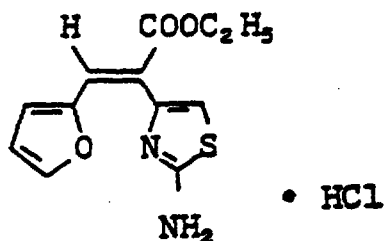
25 NMR (CDCl₃): signals of equivalent protons from isomeric compounds are separated by a /
 α = 7.50[2] m, 7.03/6.89[1] d, J = 7 Hz, 6.57[1] m, 4.48/4.50[2] s, 4.43/4.32[2] q, J = 7 Hz, 1.40/1.34[3] t, J = 7 Hz ppm.

calculated: C 54.4 H 4.6 Cl 14.6

30 found: C 54.3 H 4.5 Cl 14.8

Example 11

2-(2-Aminothiazol-4-yl)-3-(2-furyl)-propenoic acid ethyl ester hydrochloride (E-isomer)



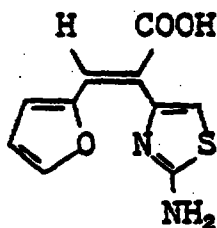
32.2 g of the isomer mixture prepared according to Example 10 and 10 g of thiourea are dissolved in 850 ml of ethanol. The solution is heated to 50° for 4 hours and is then left to stand at room temperature for 16 hours. The product which has precipitated is filtered off. Further product of the same purity can be obtained by concentrating the mother liquor. After recrystallization of the product from ethanol, the E-isomer, containing about 10% of the Z-isomer, is obtained. Yield: 65.4%, melting point: > 250°. The E-isomer can be obtained in a pure form by repeated crystallization from ethanol. IR (Nujol): 1679, 1620, 1300, 1270, 1222, 1156, 1080, 1050, 1025 cm⁻¹.

NMR (DMSO): δ = 6.6-8.2[1] broad, NH, 7.86[1] d, J = 2 Hz, 7.75[1] s, 7.0[1] d, J = 4 Hz, 6.90[1] s, 6.66[1] dd, J = 2 Hz, J = 4 Hz, 4.20[2] q, J = 7 Hz, 1.25[3] t, J = 7 Hz ppm.

calculated:	C 47.9	H 4.4	N 9.3	S 10.7	Cl 11.8
found:	C 47.8	H 4.5	N 9.1	S 10.2	Cl 11.7

Example 12

2-(2-Aminothiazol-4-yl)-3-(2-furyl)-propenoic acid
(E-isomer)



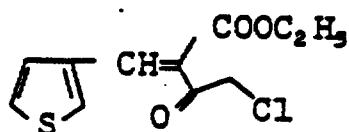
8.5 g of the product prepared according to Example 11 are dissolved in a mixture of 50 ml of methanol and 50 ml of water. The solution is brought to pH 13 with 2N sodium hydroxide solution and is stirred at room temperature for 5 hours. The methanol is then stripped off and

the aqueous solution is adjusted to pH 7.5 with 2n hydrochloric acid and extracted twice with ethyl acetate. The extract is adjusted to pH 3 and the product is filtered off and recrystallized from ethanol. Yield: 64.3%, melting point: 201° (decomposition).

5 IR (Nujol): 1630, 1598, 1570, 1540, 1330, 1280 cm^{-1} .
NMR (DMSO): δ = 7.84[1] d, J = 1.5 Hz, 7.64[1] s, 7.50[3] s broad, 6.65[1] s, 6.61[2] s, broadened ppm.
calculated: C 50.8 H 3.4 N 11.9 S 13.5
found: C 50.4 H 3.4 N 11.6 S 12.8

10 Example 13

2-(3-Thienylidene)-3-oxo-4-chlorobutyric acid ethyl ester



55.3 g of 4-chloroacetoacetic acid ethyl ester, 41 g of thiophene-3-aldehyde, 3.8 ml of glacial acetic acid and 1.5 ml of piperidine are dissolved in 30 ml of benzene. The solution is boiled for 7 hours, using a water separator, and, after the solution has been cooled, 400 ml of ether are added and the mixture is extracted three times with water. After the extract has been dried over sodium sulphate and the solvent has been evaporated off, the crude product is subjected to incipient distillation and the residue is then purified over a short silica gel column (70-230 times).

(Mobile phase: petroleum ether/ether 8/2). The E/Z mixture is obtained as an oil. Yield: 63%.

IR (film): 1720, 1690, 1609, 1265, 1240 cm^{-1} .

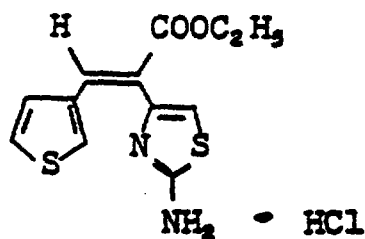
NMR (CDCl_3): δ = 7.54-7.83[2] m, 6.95-7.50[2] m, 4.52/4.45[2] s, 4.35/4.26[2] q, J = 7 Hz, 1.27/1.32[3] t, J = 7 Hz ppm. The signals which arise from isomeric compounds and correspond to one another are separated by a /.

calculated: C 51.1 H 4.3 S 12.4 Cl 13.7

found: C 51.7 H 4.5 S 12.4 Cl 12.6

Example 14

2-(2-Aminothiazol-4-yl)-3-(3-thienyl)-propenoic acid ethyl ester hydrochloride (E-isomer)



22 g of the E/Z mixture prepared in Example 13 and 6.5 g of thiourea, dissolved in 100 ml of ethanol, are heated to 50° for 2.5 hours. The solution is evaporated, a little water and ethyl acetate are added to the residue and the product is filtered off. Yield: 22%, melting point: 213-15° (decomposition).

IR (Nujol): 1685, 1620, 1278 cm⁻¹.

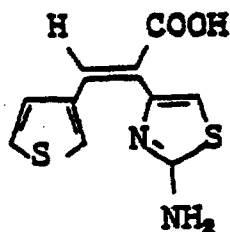
NMR (CD₃OD): δ = 8.18[1] s, 7.87[1] dd, J = 2 Hz, J = 4 Hz, 7.53[1] dd, J = 4 Hz, J = 6 Hz, 6.95[1] dd, J = 2 Hz, J = 6 Hz, 6.86[1] s, 4.32[2] q, J = 7 Hz, 1.32[3] t, J = 7 Hz ppm.

calculated: C 45.5 H 4.1 N 8.8 S 20.2 Cl 11.2

found: C 45.1 H 4.4 N 8.5 S 19.5 Cl 10.9

Example 15

2-(2-Aminothiazol-4-yl)-3-(3-thienyl)-propenoic acid (E-isomer)



8 ml of 2N sodium hydroxide solution are added to 3.3 g of the product prepared according to Example 14, dissolved in 10 ml of methanol. The solution is left to stand overnight at room temperature and the methanol is then stripped off and the residue is dissolved in water. The pH is adjusted to 8 with 2N hydrochloric acid and the aqueous solution is extracted three times with acetic acid. The product is then precipitated by adjusting the pH to 3 and is filtered off. Yield: 50.5%, melting point: 172-75° (decomposition).

IR (KBr): 1628, 1367, 1262, 1028 cm⁻¹.

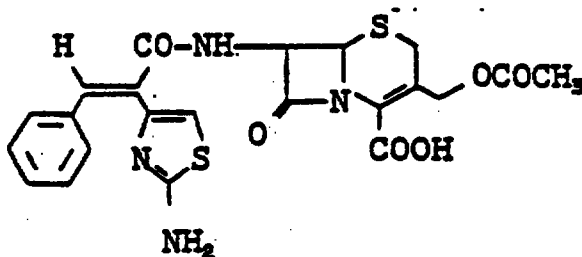
NMR (DMF): α = 8.5, N-H, very broad, 7.93[1] s, broadened, 7.86[1] dd, J_1 = 1.5 Hz, J_2 = 3 Hz, 7.54[1] ddd, J_3 = 1 Hz, J_4 = 6 Hz, 6.91[1] dd, J_4 = 6 Hz, J_1 = 1.5 Hz, 6.70[1] s ppm.

5 calculated: C 47.6 H 3.2 N 11.1 S 25.4
found: C 47.2 H 3.1 N 11.4 S 25.3

Example 16

Sodium E-7-[2-(2-aminothiazol-4-yl)-2-benzylideneacetamido]-3-acetoxymethyl-3-cephem-4-carboxylate

10



15

20

25

30

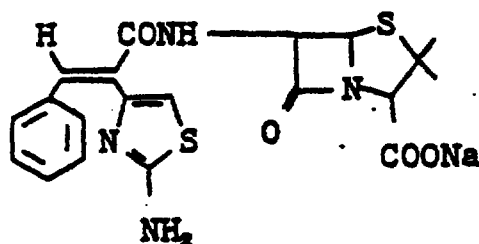
A suspension of 4.9 g of the product prepared according to Example 3 in 200 ml of ethyl acetate is cooled to 0-5° and 3.8 g of phosphorus oxychloride are added. After 30 minutes, 3.3 g of trimethylsilylacetamide, dissolved in 5 ml of ethyl acetate, are added, and a further 3.8 g of phosphorus oxychloride are then added. The mixture is subsequently stirred at 0° for 15 minutes and 1.8 ml of dimethylformamide are then added. After a further 40 minutes, the mixture is cooled to -10° and added dropwise to a solution, which had been cooled to -5°, of 5.44 g of 7-aminocephalosporanic acid and 4 g of sodium bicarbonate in a mixture of 100 ml of water and 75 ml of acetone. The mixture is subsequently stirred for 2 hours, during which the pH value is kept at 6 with saturated sodium bicarbonate solution. The solution is filtered, the aqueous phase is separated off and washed once with ethyl acetate, ethyl acetate is added and the mixture is adjusted to pH 3.5. The ethyl acetate is separated off and the aqueous phase is extracted twice more with ethyl acetate. Water is added to the combined ethyl acetate phases and the mixture is brought to pH 7. The aqueous phase is separated off and lyophilized to give 2.0 g of the product.

IR (Nujol): 1750 cm⁻¹.

NMR (CD₃OD): δ = 7.78[1] s, 7.29[5] s, 6.32[1] s, 5.82[1] s, J = 5 Hz, 5.09[1] d, J = 5 Hz, 5.06[1] d, J = 14 Hz, 4.83[1] d, J = 14 Hz, 3.60[1] d, J = 18 Hz, 3.29[1] d, J = 18 Hz, -2.03[3] s ppm.

5 Example 17

Sodium E-6-[2-(2-aminothiazol-4-yl)-2-benzylideneacetamido]-penam-3-carboxylate



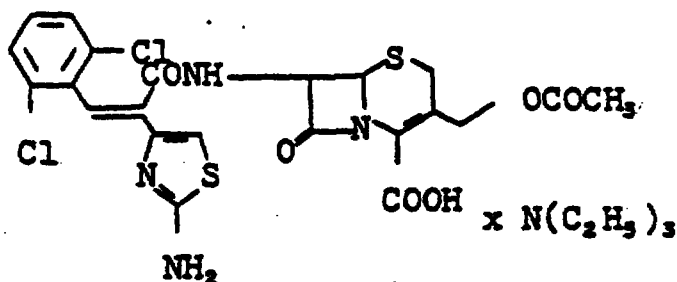
1.9 g of the product from Example 3 are reacted, according to the instructions in Example 16, with 6-aminopenicillanic acid instead of 7-aminocephalosporanic acid. 1.4 g of the lyophilized sodium salt are obtained. Melting point: 250°.

IR (KBr): 1761, 1607, 1508 cm⁻¹.

NMR (CD₃OD): 7.78[1] s, 7.25[5] s, 6.33[1] s, 5.62[2] s, 4.25[1] s, 1.58[6] s ppm.

Example 18

Triethylammonium Z-7-[2-(2-aminothiazol-4-yl)-2-(2,6-dichlorobenzylidene)acetamido]-3-acetoxymethyl-3-cephem-4-carboxylate



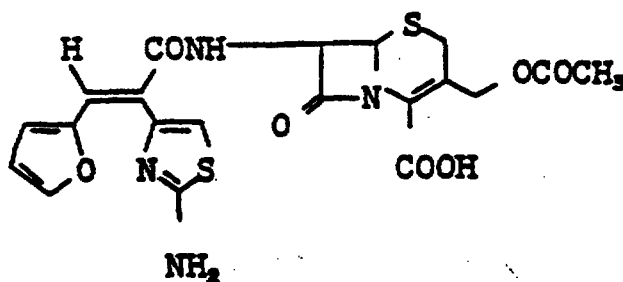
0.68 g of 1-hydroxybentriazole and 1.03 g of N,N'-dicyclohexylcarbodiimide are added to a solution of 2.1 g of the product from Example 6 in 15 ml of absolute dimethylformamide and the mixture is stirred at room temperature for 5 hours. The mixture is filtered and a solution of 1.36 g of 7-aminocephalosporanic acid and 2.0 ml of triethylamine in 25 ml of methylene chloride is

added dropwise to the mother liquor. The reaction solution is stirred overnight at room temperature and is then evaporated to dryness. The residue is dissolved in a little water and the solution is filtered at pH 7 and then washed several times with ethyl acetate. The aqueous solution is adjusted to pH 4.5 with 2N hydrochloric acid, and the product which has precipitated is filtered off, washed with water and dried over potassium hydroxide. The crude product is stirred with ethyl acetate for 1 hour and filtered off, the residue is stirred with methanol for 1 hour and filtered off again and the filtrate is evaporated to dryness in the cold. The residue is dried over potassium hydroxide. 0.6 g of the desired product is obtained.

IR (KBr): 1775, 1735, 1675, 1620 cm^{-1} .
NMR (CD_3OD): δ = 7.2-7.44[4] m, 6.78[1] s, 5.71[1] d, J = 6 Hz, 5.07[1] d, J = 12 Hz, 5.05[1] d, J = 6 Hz, 4.82[1] d, J = 12 Hz, 3.60[1] d, J = 18 Hz, 3.38[1] d, J = 18 Hz, 2.07[3] s; 3.23[6] q, J = 7 Hz and 1.32[9] t, J = 7 Hz, ppm.

Example 19

E-7-[2-(2-Aminothiazol-4-yl)-2-(2-furylidene)acetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid



2.0 g of the product prepared according to Example 12 are dissolved in 30 ml of absolute dimethylformamide over nitrogen in a previously thoroughly heated flask. 1.12 g of 1-hydroxybenzotriazole and 1.7 g of N,N'-dicyclohexylcarbodiimide are added to the solution and the mixture is stirred at room temperature for 6 hours. After the dicyclohexylurea has been filtered off, a solution of 2.2 g of 7-aminocephalosporanic acid and 3.4 ml of triethylamine in 20 ml of methylene chloride are added

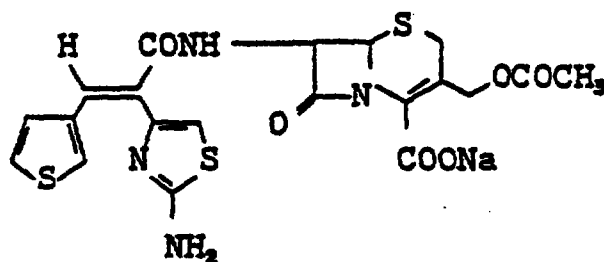
dropwise to the filtrate. The mixture is stirred overnight and then evaporated to dryness and the residue is dissolved at pH 7. After the aqueous solution has been extracted several times with ethyl acetate, it is adjusted to pH 2.5 with 2N HCl and stirred for 30 minutes. The product is filtered off and dried over KOH. This crude product is stirred with ethyl acetate for 1 hour, filtered off and then dissolved in cold methanol. The product is isolated by filtration and evaporation of the solution.

IR (KBr); 1759, 1612, 1514, 1397, 1249 cm^{-1} .

NMR (CD_3OD): δ = 7.54[1] s, 7.52[1] s, 6.60[1] s, 6.44[2] m, 5.76[1] d, J = 5 Hz, 5.04[1] d, J = 5 Hz, 4.98[1] d, J = 11 Hz, 4.80[1] d, J = 11 Hz, 3.58[1] d, J = 17 Hz, 3.30[1] d, J = 17 Hz, 2.01[3] ppm.

Example 20

Sodium E-7-[2-(2-aminothiazol-4-yl)-2-(3-thienylidene)-acetamido]-3-acetoxymethyl-3-cephem-4-carboxylate

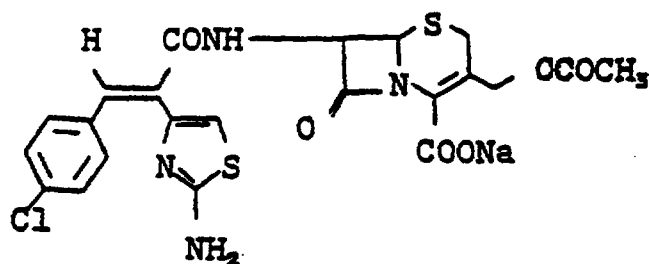


1.0 g of the product prepared according to Example 15 is reacted according to Example 18. The free acid precipitated at pH 4.5 is dissolved in water with 2N sodium hydroxide solution at pH 6.5 and the solution is then lyophilized. 0.7 g of the desired compound is obtained.

IR (Nujol): 1758, 1605, 1412, 1220 cm^{-1} .
NMR (CD_3OD): δ = 7.76[1] s, 7.52[1] d, J = 2 Hz, 7.29[1] dd, J = 2 Hz, J = 6 Hz, 6.79[1] d, J = 6 Hz, 5.79[1] d, J = 5 Hz, 5.08[1] d, J = 5 Hz, 5.00[1] d, J = 11 Hz, 4.82[1] d, J = 11 Hz, 3.60[1] d, J = 18 Hz, 3.32[1] d, J = 18 Hz, 2.04[3] s ppm.

Example 21

Sodium E-7-[2-(2-aminothiazol-4-yl)-2-(4-chlorobenzylidene)-acetamido]-3-acetoxymethyl-3-cephem-4-carboxylate



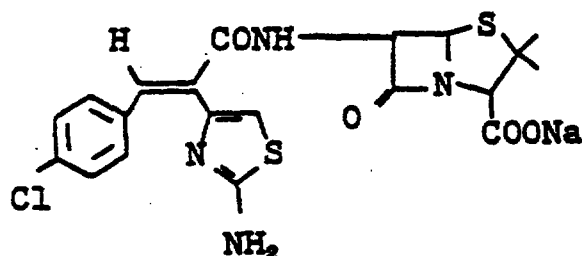
2.0 g of the compound prepared according to Example 9 are reacted according to Example 19. The crude product which has been filtered off at pH 2.5 is dissolved in cold methanol and the solution is filtered and evaporated to dryness. The residue is dissolved in water with 2N sodium hydroxide solution at pH 6.8. 0.9 g of the desired product is isolated by lyophilization of the aqueous solution.

IR (Nujol): 1759, 1610, 1515 cm^{-1} .

NMR (CD_3OD): δ = 7.67[1] s, 7.25[4] m, 6.35[1] s, 5.82[1] d, J = 5 Hz, 5.10[1] d, J = 5 Hz, 5.02[1] d, J = 12 Hz, 4.85[1] d, J = 12 Hz, 3.61[1] d, J = 17 Hz, 3.33[1] d, J = 17 Hz, 2.06[3] s ppm.

Example 22

Sodium E-7-[2-(2-aminothiazol-4-yl)-2-(4-chlorobenzylidene)-acetamido]-penam-3-carboxylate



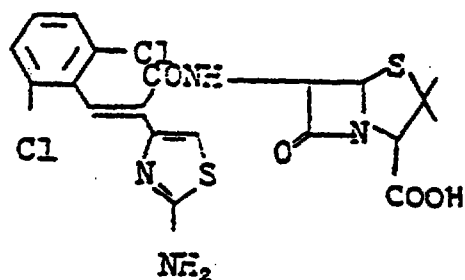
2.3 g of the product from Example 9 are reacted according to Example 17. 1.0 g of the lyophilized sodium salt is obtained.

IR (Nujol): 1755, 1600 cm^{-1} .

NMR (CD_3OD): δ 7.71[1] s, 7.24[4] m, 6.36[1] s, 5.59[2] s, 4.20[1] s, 1.55[3] s, 1.54[3] s ppm.

Example 23

Z-6-[2-(2-Aminothiazol-4-yl)-2-(2,6-dichlorobenzylidene)-acetamido]-penam-3-carboxylic acid



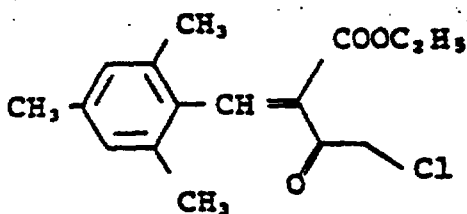
0.9 g of the product from Example 6 are dissolved in 15 ml of absolute dimethylformamide. 0.3 g of hydroxybenzotriazole and 0.44 g of dicyclohexylcarbodiimide are added and the mixture is stirred at room temperature for 5 hours. The mixture is filtered and the mother liquor is added dropwise to a solution of 0.4 g of 6-aminopenicillanic acid and 0.9 ml of triethylamine in 25 ml of methylene chloride. After the mixture has been stirred at room temperature overnight, it is evaporated, water and ethyl acetate are added to the residue and the mixture is adjusted to pH 6.5. The mixture is filtered, the organic phase is separated off and the aqueous phase is washed once more with ethyl acetate. The product phase is then adjusted to pH 2.8 and filtered. 0.5 g of product are thus obtained.

IR (KBr): 1770 (shoulder), 1728, 1637 cm^{-1} .

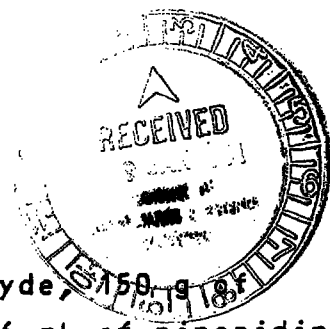
NMR (CD_3OD): δ 7.1[4] m, 6.74[1] s, 5.52[1] d, J = 6 Hz, 5.45[1] d, J = 6 Hz, 4.31[1] s, 1.49[3] s, 1.47[3] s ppm.

Example 24

2-(2,4,6-Trimethylbenzylidene)-3-oxo-4-chlorobutyric acid ethyl ester



90 g of 2,4,6-trimethylbenzaldehyde, 150 g of 4-chloroacetoacetic acid ethyl ester, 2.6 ml of piperidine and 7 ml of glacial acetic acid are dissolved in 60 ml of benzene and the solution is boiled for 6 hours using a



water separator. 200 ml of ethyl acetate are added to the cooled solution, the solution is extracted in each case once with saturated sodium bicarbonate solution, water and 1M citric acid solution and the extract is dried over magnesium sulphate and evaporated. The crude product is subjected to incipient distillation under a high vacuum in order to free it from excess 4-chloroacetoacetic acid ethyl ester. After chromatography of the product on silica gel 60 (Merck, 70-230 mesh), 21 g of the E-isomer can be crystallized with isopropanol and a 3:1 Z/E mixture remains as the mother liquor in the form of an oil. Total yield: 39%.

E-isomer: melting point 85°.

IR (Nujol): ~ 1700, 1610, 1310, 1250, 1175, 1135, 1095, 1030, 970 cm⁻¹.

NMR (CDCl₃): δ = 8.02[1] s, 6.90[2] s, 4.37[2] q, J = 7 Hz, 4.04[2] s, 2.32[3] s, 2.20[6] s, 1.38[3] t, J = 7 Hz ppm.

calculated: C 65.2 H 6.5 Cl 12.0

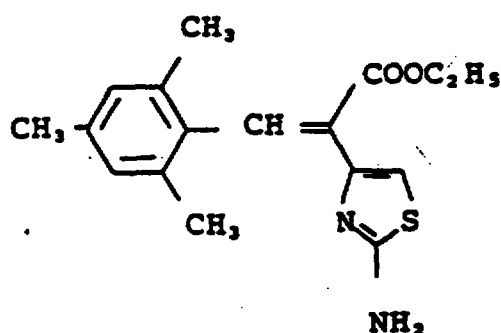
found: C 65.1 H 6.8 Cl 12.0

Z-isomer:

NMR (CDCl₃): δ = 7.98[1] s, 6.84[2] s, 4.56[2] s, 4.06[2] q, J = 7 Hz, 2.32[3] s, 2.20[6] s, 0.91[3] t, J = 7 Hz ppm.

25 Example 25

2-(2-Aminothiazol-4-yl)-3-(2,4,6-trimethylphenyl)-propenoic acid ethyl ester (Z-isomer)



A solution of 32 g of the Z/E mixture prepared in Example 24, 9 g of sodium acetate and 8.8 g of thiourea in 210 ml of tetrahydrofuran and 90 ml of water is stirred at room temperature for 48 hours. The tetrahydrofuran is

stripped off and the aqueous phase is adjusted to pH 8 and extracted three times with ethyl acetate. The organic phase is washed with water, dried and evaporated. Crystallization with dioxane gives 8.5 g of the pure Z-isomer, containing 1/2 mol of dioxane, of melting point 122-124°. A second fraction can be obtained from the mother liquor by chromatography.

IR (Nujol): 3600, 3210, 1710, 1640, 1540, 1465, 1285, 1230, 1210, 1140, 1110, 1080, 1040 cm^{-1} .

NMR (DMF): δ = 7.56[1] s, 7.30[2] s, 6.91[2] s, 6.30[1] s, 3.99[2] q, J = 7 Hz, 2.23[3] s, 2.16[6] s, 0.86[3] t, J = 7 Hz ppm.

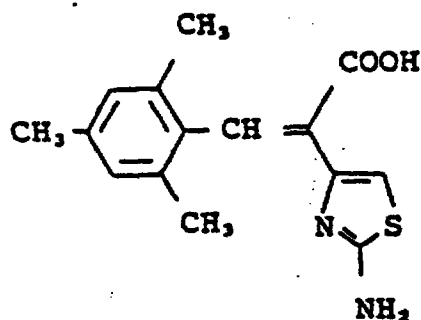
calculated for 1 mol of product + 1/2 mol of dioxane:

C 63.2 H 6.7 N 7.8 S 8.9

found: C 63.0 H 6.8 N 7.7 S 9.0

Example 26

2-(2-Aminothiazol-4-yl)-3-(2,4,6-trimethylphenyl)-propenoic acid (Z-isomer).



6.1 g of the product from Example 26 are dissolved in a mixture of 150 ml of dioxane and 45 ml of 1.5N sodium hydroxide solution. The solution is boiled under reflux overnight and the dioxane is then stripped off, the residue is diluted with 50 ml of water and the mixture is filtered. The filtrate is adjusted to pH 5 with dilute hydrochloric acid and is filtered off again after 10 minutes. Recrystallization of the residue from methanol gives the desired product in a yield of 72%. Melting point: > 200°.

IR (KBr): 1675, 1565, 1473, 1393, 1307, 1242, 1199, 1171 cm^{-1} .

NMR (DMF): δ = 7.52[1] s, 7.20[2] s, 6.91[2] s, 6.75[1] s,

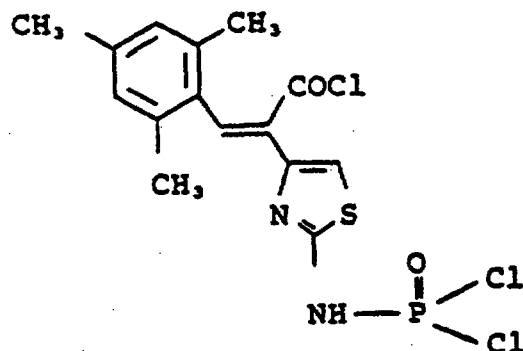
2.23[9] s ppm.

calculated: C 62.5 H 5.6 N 9.7 S 11.1

found: C 62.0 H 6.0 N 9.8 S 11.2

Example 27.

- 5 2-(2-Dichlorophosphorylaminothiazol-4-yl)-3-(2,4,6-trimethylphenyl)-propenoic acid chloride (Z-isomer)

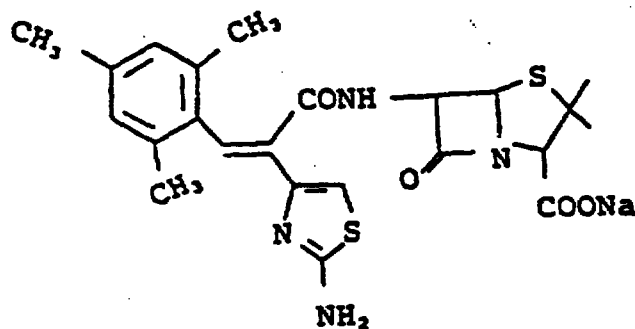


- 2 g of the carboxylic acid from Example 26 are suspended in 50 ml of methylene chloride under a nitrogen atmosphere. 3 g of phosphorus pentachloride are added at 0° and the mixture is then stirred at room temperature for 4 hours. After filtration, the filtrate is evaporated and the oil which remains is crystallized with ether. Yield: 1 g. Melting point: 161-2° (decomposition).
- 10 IR (Nujol): 1760, 1570, 1360, 1310, 1275, 1235, 1175, 1060, 1010, 910 cm⁻¹.

NMR (CDCl₃): δ = ~14.5-15.5[1] very broad, 7.82[1] s, 6.95[2] s, 6.64[1] d, J = 2 Hz, 2.35[3] s, 2.30[6] s ppm.

Example 28

- 20 A) Sodium Z-6-[2-(2-aminothiazol-4-yl)-2-(2,4,6-trimethylbenzylidene)-acetamido]-penam-3-carboxylate



1 g of the product from Example 26 are reacted according to Example 23. The acid precipitated at pH 2.5

is suspended in ethyl acetate/water and dissolved at pH 7 by adding 2N sodium hydroxide solution. After the ethyl acetate has been separated off, the aqueous phase is lyophilized. 0.8 g of the sodium salt, which still contains residues of 1-hydroxybenzotriazole, is obtained.

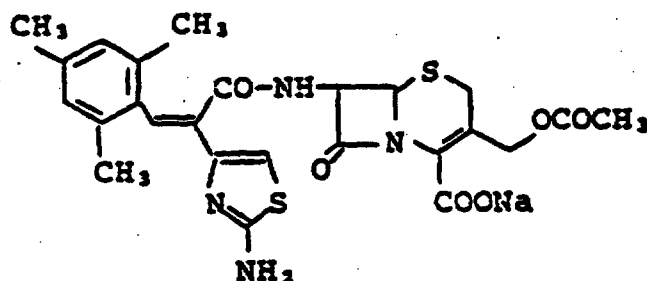
IR (Nujol): 1750, 1600 cm^{-1} .

NMR (CD_3OD): δ = 7.44[1] s, 6.82[2] s, 6.65[1] s, 5.45[1] d, J = 5 Hz, 5.37[1] d, J = 5 Hz, 4.07[1] s, 2.22[9] s, 1.49[3] s, 1.43[3] s.

B) 0.43 g of 6-aminopenicillanic acid are dissolved in 20 ml of 80 per cent strength aqueous tetrahydrofuran at pH 7-8 with triethylamine. The product from Example 27 is introduced at 0°, during which the pH is kept at 7.5 by addition of triethylamine. The mixture is subsequently stirred at room temperature for two hours and the tetrahydrofuran is then stripped off and the aqueous solution is extracted twice with ethyl acetate. The aqueous phase is freed from residual ethyl acetate and is then adjusted to pH 2.0 with 2N hydrochloric acid. The product which has precipitated is filtered off and suspended in 10 ml of water and the suspension is stirred at 50° and at pH 3 for 3 hours. It is filtered off again and the residue is converted into the lyophilized sodium salt as described. Yield: 0.7 g.

Example 29

Sodium Z-7-[2-(2-aminothiazol-4-yl)-2-(2,4,6-trimethylbenzylidene)-acetamido]-3-acetoxymethyl-3-cephem-4-carboxylate

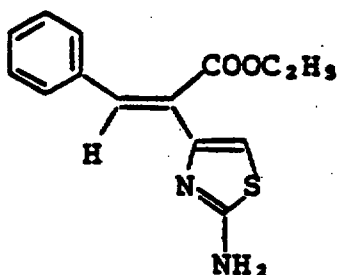


1 g of the product from Example 26 is reacted according to Example 19. The carboxylic acid precipitated at pH 2.5 is converted into the sodium salt in accordance with Example 28. Yield: 1.2 g. IR (Nujol): 1750, 1600, 1520 cm^{-1} .

NMR (CD₃OD): δ 7.35[1] s, 6.80[2] s, 6.60[1] s, 5.59[1] d, J = 5 Hz, 4.99[1] d, J = 12 Hz, 4.93[1] d, J = 5 Hz, 4.81[1] d, J = 12 Hz, 3.50[1] d, J = 17 Hz, 3.21[1] d, J = 17 Hz, 2.24[6] s, 2.22[3] s, 2.04[3] s ppm.

5 Example 30

2-(2-Aminothiazol-4-yl)-3-phenylpropenoic acid ethyl ester (Z-isomer)

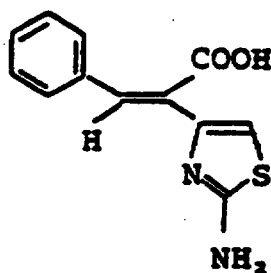


209.2 g of 2-benzylidene-3-oxo-4-chlorobutyric acid ethyl ester (described in J. Amer. Chem. Soc. 66, 1933 (1944)), 63.2 g of thiourea and 104.6 g of sodium acetate are dissolved in a mixture of 1,460 ml of tetrahydrofuran and 630 ml of water. The solution is stirred overnight at room temperature and the tetrahydrofuran is then evaporated off. The aqueous phase is adjusted to pH 8 and extracted three times with ethyl acetate. Drying and evaporation of the organic phase gives a viscous oil, which chiefly consists of the desired Z-isomer. The product is further processed in the crude form. Yield: 222 g.

20 IR (CHCl₃): 1710, 1610, 1525, 1380 cm⁻¹.
NMR (CDCl₃): δ 7.46[1] s, 7.24[5] s, 6.45[1] s, 4.18[2] q, J = 7 Hz, 1.10[3] t, J = 7 Hz ppm.

Example 31

2-(2-Aminothiazol-4-yl)-3-phenylpropenoic acid (Z-isomer)



25 216 g of the crude product from Example 30 are dissolved in a mixture of 1.2 l of dioxane and 800 ml of

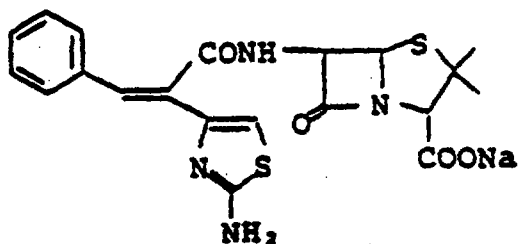
12 per cent strength sodium hydroxide solution. The solution is boiled under reflux for 15 hours and the dioxane is then stripped off and the residue is adjusted to pH 8 with 2N hydrochloric acid. The mixture is extracted three times with ethyl acetate, the aqueous solution is adjusted to pH 3-4 and the product which has precipitated is filtered off. 20 g of the desired product, of melting point 138°, can be obtained directly by recrystallization from methanol. The mother liquor consists of an E/Z mixture, which cannot be separated by crystallization.

IR (KBr); 1650, 1599, 1579, 1564, 1425, 1344, 1304 cm⁻¹.

NMR (CDCl₃ + DMSO): δ = 7.54[1] s, 7.32[5] m, 6.50[1] s ppm.

Example 32

15 Sodium Z-6-[2-(2-aminothiazol-4-yl)-2-benzylideneacetamido]-penam-3-carboxylate



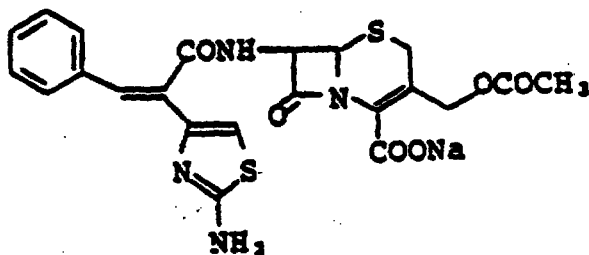
20 2 g of the product from Example 31 are reacted according to Example 28 A. 2.6 g of the sodium salt are obtained.

IR (Nujol): 1750, 1600 cm⁻¹.

NMR (CD₃OD): δ 7.25[1] s, 7.20[5] m, 6.50[1] s, 5.57[1] d, J = 5 Hz, 5.49[1] d, J = 5 Hz, 4.08[1] s, 1.47[6] s ppm.

Example 33

25 Sodium Z-7-[2-(2-aminothiazol-4-yl)-2-benzylideneacetamido]-3-acetoxymethyl-3-cephem-4-carboxylate



2 g of the product from Example 31 are reacted according to Example 29. 2.8 g of the sodium salt are

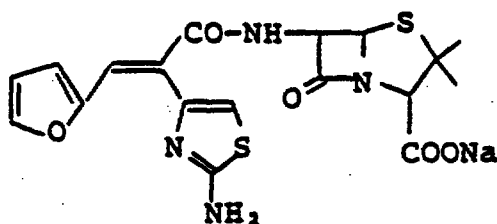
obtained.

IR (Nujol): 1755, 1600 cm^{-1} .

NMR (CD_3OD): δ = 7.26[1] s, 7.20[5] m, 6.48[1] s,
5.76[1] d, J = 5 Hz, 5.05[1] d, J = 5 Hz, 4.93[1] d, J =
5 12.5 Hz, 4.75[1] d, J = 12.5 Hz, 3.52[1] d, J = 18 Hz,
3.24[1] d, J = 18 Hz, 1.98[3] s ppm.

Example 34

E-6-[2-(2-Aminothiazol-4-yl)-2-(2-furylidene)-acetamido]-
penam-3-carboxylate



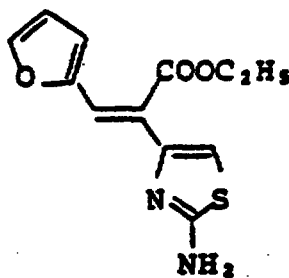
4 g of the product prepared according to Example
12 are reacted according to Example 28 A. 3.5 g of the
sodium salt are obtained.

IR (Nujol); 1750, 1595 cm^{-1} .

15 NMR (CD_3OD): δ = 7.62[1] s, 7.56[1] s, broad, 6.64[1] s,
6.48[2] m, 5.62[2] s, 4.22[1] s, 1.55[3] s, 1.53[3] s ppm.

Example 35

2-(2-Aminothiazol-4-yl)-3-(2-furyl)-propenoic acid ethyl
ester (Z-isomer)



200 g of the isomer mixture prepared according to
Example 10, 68 g of thiourea and 68 g of sodium acetate
are dissolved in a mixture of 1 l of tetrahydrofuran and
250 ml of water. The solution is stirred at room tem-
25 perature for 24 hours, the tetrahydrofuran is stripped
off and the aqueous phase is adjusted to pH 8. The
aqueous phase is extracted three times with ethyl acetate
and the combined ethyl acetate phases are washed once

with water, dried over magnesium sulphate and concentrated, whereupon a small amount of the E-isomer (4.7 g) can be crystallized. The mother liquor is evaporated completely and the oil which remains is crystallized with ethanol. 106 g of the pure Z-isomer of melting point 109-110° are obtained.

IR (Nujol): 1700, 1635, 1590, 1520, 1350, 1230, 1190, 1140, 1020 cm^{-1} .

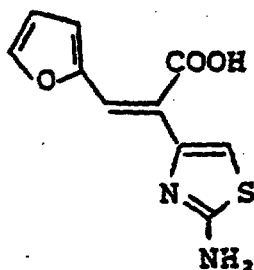
NMR (DMF): δ = 7.65[1] m, 7.18[3] s broadened, 6.50[3] m, 4.35[2] q, J = 7 Hz, 1.30[3] t, J = 7 Hz ppm.

calculated: C 54.5 H 4.6 N 10.6 S 12.1

found: C 53.9 H 4.6 N 10.5 S 11.2

Example 36

2-(2-Aminothiazol-4-yl)-3-(2-furyl)-propenoic acid
(Z-isomer)



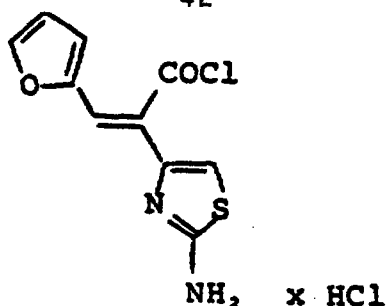
300 ml of 2N sodium hydroxide solution are added to a solution of 61 g of the product prepared according to Example 35 in 1 L of dioxane and the mixture is boiled under reflux for 7 hours. The dioxane is stripped off and the aqueous solution is adjusted to pH 9 with 2N hydrochloric acid and extracted three times with ethyl acetate. The product phase is then adjusted to pH 2.0 and filtered. Recrystallization of the residue from ethanol gives 41 g of the product of melting point 143° (decomposition).

IR (KBr): 1660, 1635, 1612, 1575, 1468, 1421, 1308 cm^{-1} .

NMR (DMSO): δ = 7.62[1] d, J = 2 Hz, 6.91[1] s, 6.53[2] m, 6.42[1] s ppm.

Example 37

2-(2-Aminothiazol-4-yl)-3-(2-furyl)-propenoic acid
chloride hydrochloride (Z-isomer)



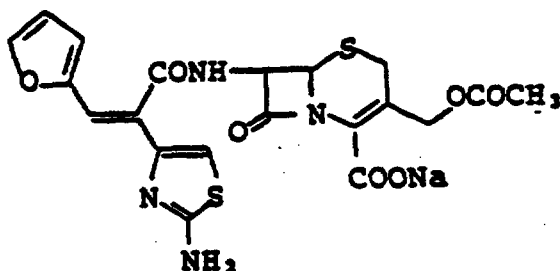
10 g of the dried product prepared according to Example 36 are suspended in 120 ml of absolute methylene chloride under a nitrogen atmosphere. 17.5 g of phosphorus pentachloride are added at 0° and the mixture is
5 allowed to come to room temperature and is subsequently stirred for 4.5 hours. The product is filtered off, yield: 6.3 g, melting point: 123° (decomposition).
IR (Nujol): 1779, 1622, 1295 cm⁻¹.

10 NMR (DMF): δ = 12.7[3] s very broad, 7.83[1] d, J = 2 Hz, 7.46[1] s, 6.96[1] s, 6.91[1] d, J = 4 Hz, 6.64[1] dd, J = 2 Hz, J = 4 Hz ppm.

MS: 192, 150

Example 38

15 Sodium Z-7-[2-(2-aminothiazol-4-yl)-2-(2-furylidene)-
acetamido]-3-acetoxymethyl-3-cephem-4-carboxylate



1 g of the product from Example 37 is added to a solution of 0.8 g of 7-aminocephalosporanic acid and 1.3 ml of triethylamine in 100 ml of absolute methylene chloride at 0°. The mixture is subsequently stirred at 0° for 30 minutes and at room temperature for 4 hours and is then poured onto water and adjusted to pH 6.5. After the organic solvent has been stripped off, the aqueous phase is extracted three times with ethyl acetate and then adjusted to pH 2.5. The mixture is filtered and the residue is converted into the sodium salt as described

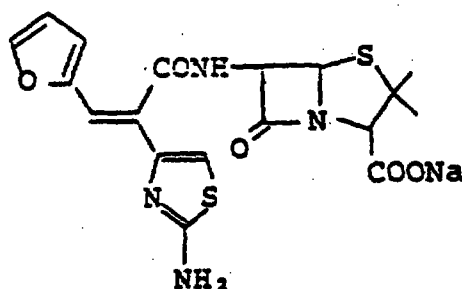
in Example 28. Yield: 1.1 g.

IR (Nujol): 1750, 1600, 1520, 1325, 1232, 1020 cm^{-1} .

NMR (CD_3OD): δ = 7.60[1] d, J = 1.5 Hz, 7.15[1] s, 6.61[1] d, J = 4 Hz, 6.56[1] s, 6.51[1] dd, J = 4 Hz, J = 1.5 Hz, 5.98[1] d, J = 5 Hz, 5.21[1] d, J = 5 Hz, 5.05[1] d, J = 13 Hz, 4.88[1] d, J = 13 Hz, 3.66[1] d, J = 18 Hz, 3.38[1] d, J = 18 Hz, 2.07[3] s ppm.

Example 39

Sodium Z-6-[2-(2-aminothiazol-4-yl)-2-(2-furylidene)-acetamido]-penam-4-carboxylate

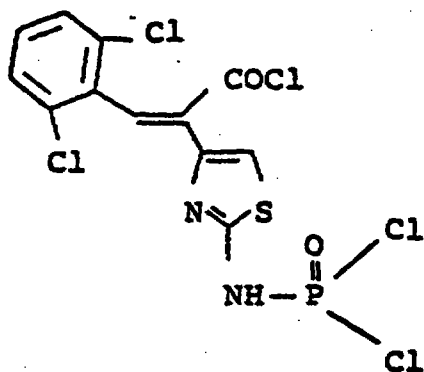


2 g of the acid chloride from Example 37 are reacted with 1.5 g of 6-aminopenicillanic acid analogously to Example 38. 2.4 g of the sodium salt are obtained.

IR (Nujol): 3300, 1750, 1600, 1510, 1310 cm^{-1} .
NMR (CD_3OD): δ = 7.57[1] d, J = 2 Hz, 7.13[1] s, 6.56[1] s, 6.56[1] d, J = 3 Hz, 6.49[1] dd, J = 2 Hz, J = 3 Hz, 5.79[1] d, J = 5 Hz, 5.69[1] d, J = 5 Hz, 4.24[1] s, 1.26[3] s, 1.22[3] s ppm.

Example 40

2-(2-Dichlorophosphorylaminothiazol-4-yl)-3-(2,6-dichlorophenyl)-propenoic acid chloride (Z-isomer)



26.2 g of phosphorus pentachloride are introduced in portions into a suspension of 20 g of the product

prepared according to Example 6 in 200 ml of absolute methylene chloride at 0° under a nitrogen atmosphere. The mixture is subsequently stirred until a clear solution has formed, and this solution is then evaporated. The residue is stirred with ether and the product is filtered off, washed thoroughly with ether and recrystallized from acetonitrile. Yield: 10 g, melting point: 174-6° (decomposition).

IR (Nujol): 1760, 1570, 1545, 1235, 1000 cm⁻¹.

10 NMR (acetone-d₆): δ = 7.80[1] s, 7.58[3] s, 7.43[1] d, J = 2 Hz ppm.

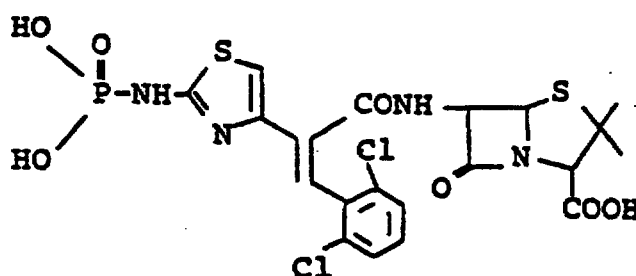
MS: 448, 413, 377, 117, 82, 66, 47, 36.

calculated: C 32.0 H 1.3 N 6.2 S 7.1 Cl 39.4 P 6.9

found: C 32.1 H 1.7 N 5.8 S 7.4 Cl 39.2 P 7.2

15 Example 41

Z-6-[2-(2-Dihydroxyphosphorylaminothiazol-4-yl)-2-(2,6-dichlorobenzylidene)-acetamido]-penam-3-carboxylic acid



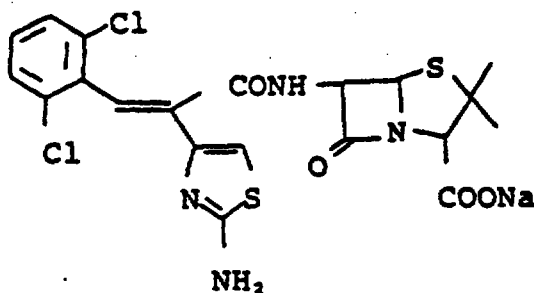
3 g of 6-aminopenicillanic acid are dissolved in 100 ml of 80 per cent strength aqueous tetrahydrofuran with one equivalent of triethylamine. The solution is cooled to 0° and 5 g of the product from Example 40 are introduced, during which the pH of the solution is kept at 7.5 by addition of triethylamine. The mixture is subsequently stirred for 30 minutes and the tetrahydrofuran is then stripped and the aqueous solution is adjusted to pH 1.8 with 2N hydrochloric acid. The solution is stirred at this pH for one hour and is then adjusted to pH 6.5 with 2N sodium hydroxide solution and extracted three times with ethyl acetate. The aqueous phase is again adjusted to pH 1.8 and the product is filtered off, washed with water and dried. It contains one mol of triethylamine. Yield: 7.5 g.

IR (Nujol): 1775, 1740, 1665, 1570, 1550, 1495, 1290, 1080 cm^{-1} .

NMR ($\text{CD}_3\text{OD}/\text{DMF}$): δ = 7.50[4] m, 7.25[1] s, 5.71[1] d, J = 4 Hz, 5.62[1] d, J = 4 Hz, 4.45[1] s, 1.65[3] s, 1.58[3] s ppm.

Example 42

Sodium Z-6-[2-(2-aminothiazol-4-yl)-2-(2,6-dichlorobenzylidene) acetamido]penam-3-carboxylate

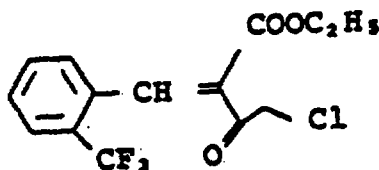


A suspension of 4 g of the product from Example 41 in 20 ml of water is warmed to 50° at pH 3 for 3 hours, with stirring. The mixture is filtered and the residue is washed with water and converted into the sodium salt in accordance with Example 28. Yield 2.4 g.

IR (Nujol): 1755, 1600, 1500, 1300, 1090 cm^{-1} .
NMR (CD_3OD): δ = 7.45[3] m, 7.36[1] s, 6.85[1] s, 5.55[1] d, J = 4 Hz, 5.51[1] d, J = 4 Hz, 4.20[1] s, 1.40[3] s, 1.38[3] s ppm.

Example 43

2-(2-Trifluoromethylbenzylidene)-3-oxo-4-chlorobutyric acid ethyl ester



226.2 g of 2-trifluoromethylbenzaldehyde, 235 g of 4-chloroacetoacetic acid ethyl ester, 4.2 ml of glacial acetic acid and 2.1 ml of piperidine are dissolved in 500 ml of benzene and the solution is boiled for 8 hours using a water separator. 1 l of ethyl acetate is added and the mixture is extracted twice with sodium bicarbonate, once with citric acid and once more with water,

dried and evaporated. The crude product is subjected to incipient distillation up to 130° under a high vacuum and the product remains as the residue in the form of a chromatographically pure 2:1 isomer mixture. Yield: 234 g.

5 IR (film): 1720, 1620, 1575, 1490, 1450, 1400, 1375, 1320, 1300, 1260, 1175, 1130, 1062, 1040 cm⁻¹.

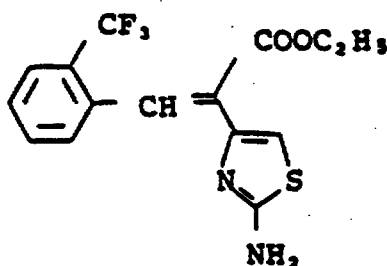
NMR (CDCl₃): δ = 8.20[1] m, 7.3-7.8[4]m, 4.59/4.40[2] s, 4.38/4.10[2] q, J = 7 Hz, 1.32/1.00[3] t, J = 7 Hz ppm.

calculated: C 52.4 H 3.8 Cl 11.1 F 17.8

10 found; C 51.5 H 3.7 Cl 11.3 F 17.3

Example 44

2-(2-Aminothiazol-4-yl)-3-(2-trifluoromethylphenyl)-propenoic acid ethyl ester



15 A solution of 234 g of the product from Example 43 and 55.5 g of thiourea in 500 ml of ethanol is stirred at 50° for 3 hours and is then evaporated. The residue is taken up in water/ethyl acetate, the mixture is adjusted to pH 8 and the aqueous phase is extracted three times
20 with ethyl acetate. The combined ethyl acetate extracts are washed once with water, dried over magnesium sulphate and concentrated to about 300 ml. After the concentrate has been left to stand overnight, it is filtered and the residue is washed with ether. 44.8 g of the E-isomer are
25 thus obtained. Melting point: 145-7°.

68 g of the pure Z-isomer can be obtained from the evaporated mother liquor by fractional crystallization from toluene. Melting point: 97-8°.

E-isomer:

30 IR (Nujol): 3350, 1690, 1635, 1625, 1520, 1310, 1260, 1150, 1120, 1035 cm⁻¹.

NMR (CDCl₃): δ = 8.0[1] m, 7.0-7.8[4] m, 6.16[1] s, 5.24[2] s, broad, 4.30[2] q, J = 7 Hz, 1.30[3] t,

J = 7 hz ppm.

calculated: C 52.6 H 3.8 N 8.2 S 9.4 F 16.6

found: C 51.6 H 3.9 N 7.9 S 9.3 F 16.7

Z-isomer:

5 IR (Nujol): 3350, 3220, 3100, 1700, 1623, 1530, 1350, 1310, 1260, 1230, 1170, 1110, 1060, 1025 cm^{-1} .

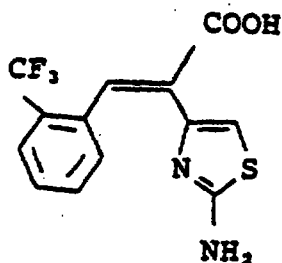
NMR (DMSO): δ = 7.3-7.9[5] m, 7.23[2] s, broad, 6.65[1] s, 4.06[2] q, J = 7 Hz, 0.95[3] t, J = 7 Hz ppm.

calculated: C 52.6 H 3.8 N 8.2 S 9.4 F 16.6

10 found: C 52.1 H 4.1 N 7.9 S 9.5 F 17.2

Example 45

2-(2-Aminothiazol-4-yl)-3-(2-trifluoromethylphenyl)-propenoic acid (E-isomer)



15 44 g of the E-isomer prepared according to Example 44 are reacted according to Example 15. The product is recrystallized from methanol. Yield: 33.5 g, melting point: 222-3° (decomposition).

20 IR (Nujol): 1650 (shoulder), 1620, 1590, 1520, 1315, 1180, 1120, 1095, 1060, 1030 cm^{-1} .

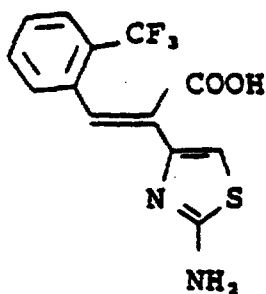
NMR (DMSO): δ = 7.1-8.0[5] m, 7.06[2] s broad, 6.23[1] s, ppm.

calculated: C 49.7 H 2.9 N 8.9 S 10.2 F 18.1

found: C 49.1 H 3.2 N 8.9 S 10.0 F 18.3

25 Example 46

2-(2-Aminothiazol-4-yl)-3-(2-trifluoromethylphenyl)-propenoic acid (Z-isomer)



66.5 g of the Z-isomer prepared according to Example 44 are reacted according to Example 36. Recrystallization from methanol gives 43.4 g of the product of melting point 205-7° (decomposition).

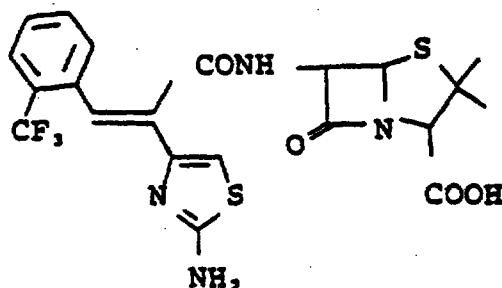
5 IR (Nujol): 1625, 1400, 1310, 1260, 1170, 1108 cm^{-1} .
NMR (DMSO): δ = 7.3-7.8[4] m, 7.53[1] s, 7.14[2] s broad, 6.57[1] s ppm.

calculated: C 49.7 H 2.9 N 8.9 S 10.2 F 18.1

found: C 49.5 H 3.5 N 8.6 S 10.0 F 18.2

10 Example 47

Z-6-[2-(2-Aminothiazol-4-yl)-2-(2-trifluoromethylbenzylidene) acetamidolpenam-3-carboxylic acid



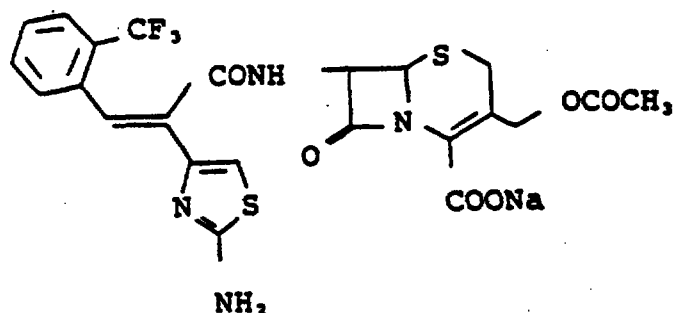
15 4.7 g of the product prepared according to Example 46 are reacted according to Example 23 and 4.2 g of product are obtained.

IR (Nujol): 1750, 1715, 1650, 1600, 1310 cm^{-1} .

NMR (CD_3OD): δ = 7.3-7.8[5] m, 6.67[1] s, 5.56[1] d, J = 4 Hz, 5.480 d, J = 4 Hz, 4.160 s, 1.50[3] s, 1.47[3] s, ppm.

Example 48

Sodium Z-7-[2-(2-aminothiazol-4-yl)-2-(2-trifluoromethylbenzylidene)acetamido]-3-acetoxymethyl-3-cephem-4-carboxylate



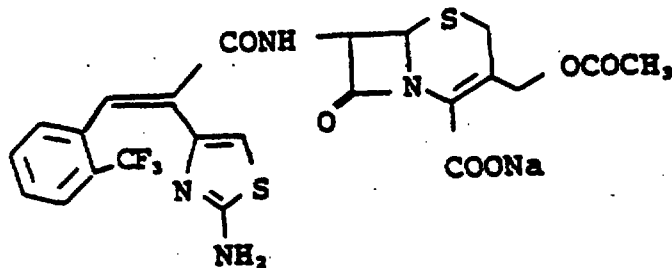
4.7 g of the product from Example 46 are reacted according to Example 29 and 5.2 g of the sodium salt are obtained:

IR (Nujol): 1750, 1600, 1520, 1310 cm^{-1} .

NMR (CD_3OD): δ = 7.7[3] m, 7.53[1] t, J = 6 Hz, 7.41[1] t, J = 6 Hz, 6.65[1] s, 5.74[1] d, J = 4 Hz, 5.02[1] d, J = 4 Hz, 4.99[1] d, J = 12 Hz, 4.85[1] d, J = 12 Hz, 3.52[1] d, J = 18 Hz, 3.26[1] d, J = 18 Hz, 2.00[3] s, ppm.

Example 49

Sodium E-7-[2-(2-aminothiazol-4-yl)-2-(2-trifluoromethylbenzylidene)acetamido]-3-acetoxymethyl-3-cephem-4-carboxylate



4.7 g of the product prepared according to Example

45 are reacted according to Example 29 and 4.5 g of the sodium salt are obtained.

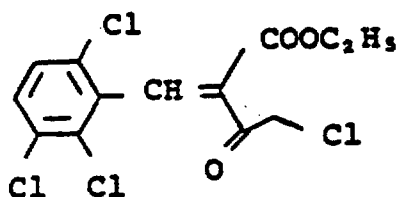
IR (Nujol); 1750, 1600, 1310, 1100 cm^{-1} .

NMR (CD_3OD): δ = 7.95[1] s, 7.68[1] m, 7.40[2] m,

5 7.18[1] m, 5.91[1] s, 5.87[1] d, J = 4 Hz, 5.11[1] d, J = 4 Hz, 5.03[1] d, J = 12 Hz, 4.87[1] d, J = 12 Hz, 3.60[1] d, J = 17 Hz, 3.35[1] d, J = 17 Hz, 2.02[3] s ppm.

Example 50

2-(2,3,6-Trichlorobenzylidene)-3-oxo-4-chlorobutyric acid ethyl ester
10 ethyl ester

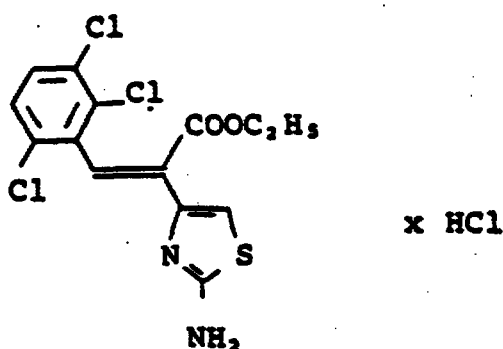


210 g of 2,3,6-trichlorobenzaldehyde are reacted with 4-chloroacetoacetic acid ethyl ester according to Example 43. 213 g of a 3:1 isomer mixture are obtained as an oily crude product.

15 NMR (DMSO): δ = 7.5-8.0[3] m, 5.02/4.80[2] s, 4.10/4.30 [2] q, J = 7 Hz, 1.33/0.96[3] t, J = 7 Hz ppm.

Example 51

2-(2-Aminothiazol-4-yl)-3-(2,3,6-trichlorophenyl)-propenoic acid ethyl ester hydrochloride
20 acid ethyl ester hydrochloride



213 g of the product from Example 50 and 30 g of thiourea, dissolved in 500 ml of ethanol, are stirred at 15° for 15 hours. The mixture is evaporated and the residue is crystallized with acetone. After recrystallization of the product from acetone, 35 g of the Z-isomer of melting point 178° are thus obtained.

Evaporation of the mother liquor gives 166 g of the E/Z mixture as a viscous oil which, after being converted into the free base, can be separated by chromatography (mobile phase: methylene chloride/methanol = 95/5).

5 Z-isomer: (hydrochloride)

IR (Nujol): 1700, 1620, 1550, 1295, 1235, 1175, 1140, 1030 cm^{-1} .

NMR (DMSO): δ = 9.10[3] s broad, 7.71[1] s, 7.76[1] d, J = 9 Hz, 7.60[1] d, J = 9 Hz, 7.20[1] s, 4.05[2] q, J = 7 Hz, 0.90[3] t, J = 7 Hz ppm.

calculated: C 40.6 H 2.9 N 6.8 S 7.7 Cl 34.2

found: C 40.7 H 2.9 N 6.6 S 7.5 Cl 33.0

E-isomer: (free base)

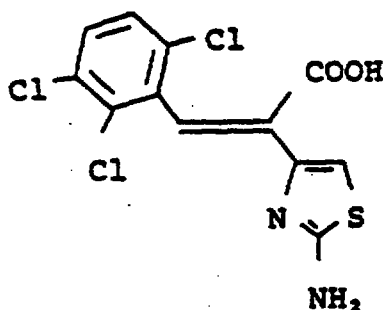
Melting point: 172°.

15 IR (Nujol): 1690, 1625, 1525, 1275, 1245 cm^{-1} .

NMR (DMSO): δ = 7.62[1] d, J = 9 Hz, 7.48[1] d, J = 9 Hz, 7.26[1] s, 6.72[2] s broad, 6.48[1] s, 4.28[2] q, J = 7 Hz, 1.30[3] t, J = 7 Hz ppm.

Example 52

20 2-(2-Aminothiazol-4-yl)-3-(2,3,6-trichlorophenyl)propenoic acid (Z-isomer)



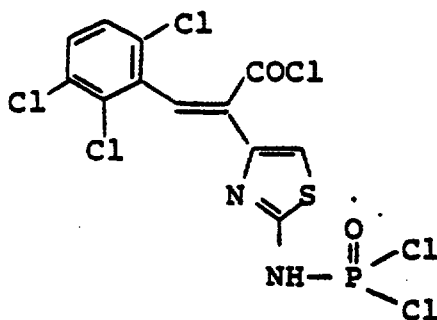
25 g of the Z-isomer from Example 51 and 100 ml of 2N NaOH, dissolved in 500 ml of dioxane, are boiled under reflux for 5 hours. Working up according to Example 36 gives 18.5 g of product of melting point: > 210°.

IR (Nujol): 1600, 1565, 1300, 1225, 1170, 1090 cm^{-1} .

NMR (DMSO): δ = 7.63[1] d, J = 9 Hz, 7.50[1] d, J = 9 Hz, 7.46[1] s, 6.92[1] s ppm.

30 Example 53

2-(2-Dichlorophosphorylaminothiazol-4-yl)-3-(2,3,6-trichlorophenyl)propenoic acid chloride (Z-isomer)

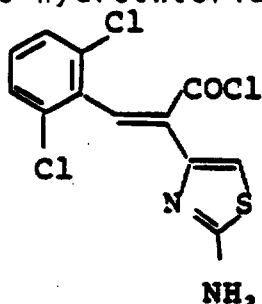


3.5 g of the product from Example 52 are reacted according to Example 40. 2.8 g of crystalline product of melting point 200° (decomposition) are obtained from ether.

NMR (CDCl_3): δ = 7.70[1] s, 7.53[1] s, 7.48[1] s, 7.36[1] s, 6.98[1] d, J = 2 Hz, ppm.

Example 54

2-(2-Aminothiazol-4-yl)-3-(2,6-dichlorophenylpropenoic acid chloride hydrochloride (Z-isomer)



x HCl
x $\frac{1}{2}$ CH_2Cl_2

30 μl of water are added to a suspension of 1 g of the product from Example 6 in 30 ml of methylene chloride, and 1.3 g of phosphorus pentachloride are then added at 0° . The mixture is stirred at room temperature for 3 hours and the product is then filtered off; washed with methylene chloride and dried. Yield: 1.1 g, melting point: 234° (decomposition).

IR (Nujol): 3210, 1760, 1630, 1570, 1550, 1300, 1255, 1195, 1180, 1090, 1030 cm^{-1} .

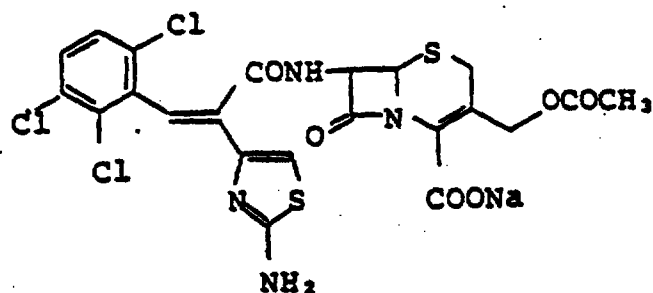
NMR ($\text{THF}-d_8$): δ = 7.86[1] s, 7.36[3] m, 6.85[1] s ppm.

calculated: C 36.3 H 2.2 N 6.8 S 7.7 Cl 43.0

found: C 35.9 H 2.0 N 6.7 S 7.7 Cl 41.1

Example 55

Sodium Z-7-[2-(2-aminothiazol-4-yl)-2-(2,3,6-trichlorobenzylidene)acetamido]-3-acetoxymethyl-3-cephem-4-carboxylate

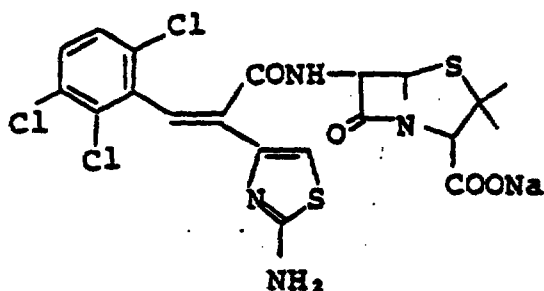


4 g of the product from Example 52 are reacted according to Example 29 and 6 g of the sodium salt are obtained.

5 IR (Nujol): 1755, 1650, 1600, 1510, 1230 cm^{-1} .
 NMR (CD_3OD): δ = 7.44[1] d, J = 8 Hz, 7.36[1] d, J = 8 Hz, 7.24[1] s, 6.76[1] s, 5.65[1] d, J = 5 Hz, 4.98[1] d, J = 12 Hz, 4.96[1] d, J = 5 Hz, 4.80[1] d, J = 12 Hz, 3.53[1] d, J = 18 Hz, 3.25[1] d, J = 18 Hz, 2.02[3] s ppm.

Example 56

Sodium Z-6-[2-(2-aminothiazol-4-yl)-2-(2,3,6-trichlorobenzylidene)acetamidopenam-4-carboxylate

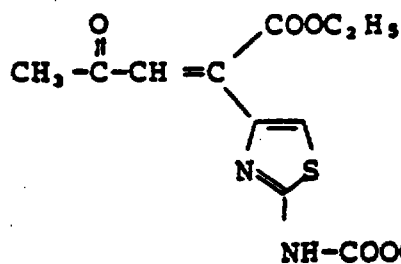


15 4 g of the product from Example 52 are reacted according to Example 28 and 3.3 g of the sodium salt are obtained.

IR (Nujol): 1750, 1600, 1190, 1170, 1095 cm^{-1} .
 NMR (CD_3OD): δ = 7.45[1] d, J = 8 Hz, 7.37[1] d, J = 8 Hz, 7.28[1] s, 6.79[1] s, 5.47[2] m, 4.15[1] s, 1.55[3] s, 1.51[3] s ppm.

Example 57

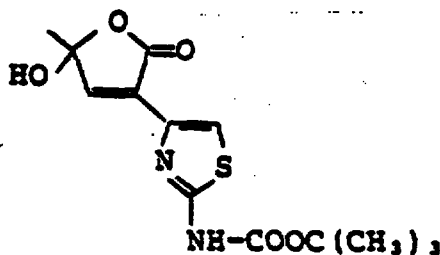
2-(2-tert.-Butoxycarbonylaminothiazol-4-yl)-4-oxo-2-pentenoic acid ethyl ester



3.5 g of sodium hydride are suspended in 100 ml of absolute dimethoxyethane (DME) in a thoroughly heated flask under nitrogen. 20 g of diethyl-2-oxo-propyl-phosphonate, dissolved in 100 ml of DME, are added dropwise at room temperature. The mixture is subsequently stirred for one hour and a solution of 30 g of 2-(2-tert.-butoxycarbonylaminothiazol-4-yl)-glyoxylic acid ethyl ester in 100 ml of DME is then added dropwise. After the mixture has been stirred overnight, hydrolysis is carried out with ice and 1N citric acid solution and the mixture is adjusted to pH 6. The DME is stripped off and the aqueous phase is extracted three times with ethyl acetate. The combined ethyl acetate phases are dried and concentrated. The oil which remains is crystallized with ether/petroleum ether and this crude product (yield: 62%, melting point: 107-8°) is recrystallized from cyclohexane. Yield: 44%, melting point: 108-110°. A pure isomer is obtained. IR (KBr); 3284 (broad), 3085, 1717, 1700 (shoulder), 1686, 1591, 1550, 1246, 1150 cm⁻¹. NMR (CDCl₃): δ = 7.10[1] s, 6.96[1] s, 4.42[2] q, J = 7 Hz, 2.28[3] s, 1.54[9] s, 1.38[3] t, J = 7 Hz ppm. calculated: C 52.9 H 5.9 N 8.2 S 9.4 found: C 52.1 H 5.9 N 7.4 S 8.5

25 Example 58

2-(2-tert.-Butoxycarbonylaminothiazol-4-yl)-4-hydroxy-4-methylbutenolide



A suspension of 15 g of the product prepared in Example 57 in a mixture of 100 ml of methanol and 20 ml of water is adjusted to pH 13 with 2N sodium hydroxide solution and is stirred at room temperature until the pH remains constant (2-3 hours). The pH is adjusted to 7, the methanol is stripped off, the mixture is filtered and the filtrate is washed twice with ethyl acetate. The aqueous phase is then adjusted to pH 1.8 and extracted three times with ethyl acetate. The combined ethyl acetate phases are dried and evaporated and the product is obtained as a yellow hard foam. Yield: 88%.

IR (KBr): 3399, 1769, 1727, 1543, 1443, 1371, 1208, 1154 cm^{-1} .

NMR (CDCl_3): δ = 7.70[1] s, 7.35[1] s, 6.80[2] s very broad, 1.76[3] s, 1.57[9] s ppm.

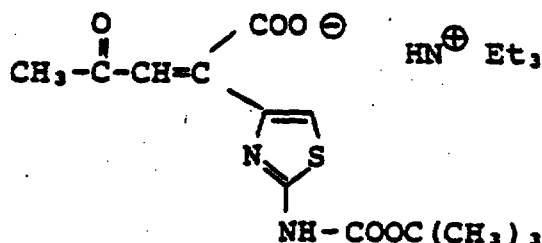
MS: 312, 256, 212, 197, 195, 169, 151, 125, 57.

calculated: C 50.0 H 5.2 N 9.0 S 10.3

found: C 49.2 H 5.3 N 8.5 S 9.9

Example 59

Triethylammonium 2-(2-tert.-butoxycarbonylaminothiazol-4-yl)-3-oxo-pentenoate



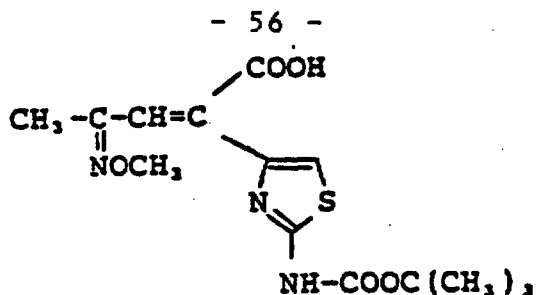
The product prepared in Example 58 is dissolved in ethyl acetate, and water is added to the solution. The pH is adjusted to 7 with triethylamine, the ethyl acetate is separated off and the aqueous phase is lyophilized.

IR (KBr): 1608, 1527, 1370, 1239 (all broad), 1140 cm^{-1} .

NMR (D_2O): δ = 7.34[1] s, 6.77[1] s, 3.21[6] q, J = 7 Hz, 2.33[3] s, 1.52[9] s, 1.29[9] t, J = 7 Hz ppm.

Example 60

2-(2-tert.-Butoxycarbonylaminothiazol-4-yl)-4-methoxy-imino-2-pentenoic acid



A solution of 12.75 g of the product from Example 58, 3.6 g of hydroxylamine methylether hydrochloride and 12.5 ml of triethylamine in 150 ml of ethanol is stirred at room temperature for 24 hours. The ethanol is stripped off, the residue is taken up in ethyl acetate and the mixture is extracted three times with 2N hydrochloric acid and once with water. After the mixture has been dried and evaporated, the oil which remains is crystallized from acetonitrile or carbon tetrachloride. Yield: 7.7 g, melting point: 165° (decomposition). IR (Nujol): 3150, 1700, 1550, 1300, 1250, 1180, 1155, 1080, 1055 cm⁻¹.

NMR (DMSO): δ = 7.08[1] s, 6.83[1] s, 3.87[3] s, 1.98[3] s, 1.50[9] s ppm.

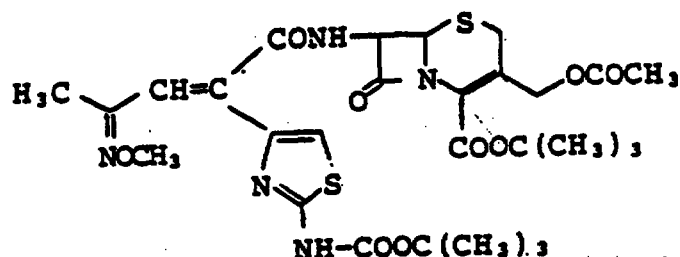
MS: 341, 295, 285, 241, 222

calculated(->x1/3CCl₄); C 43.8 H 4.8 N 10.7 S 8.1

found: C 44.3 H 5.1 N 10.4 S 8.0

Example 61

tert.-Butyl-7-[2-(2-tert.-butoxycarbonylaminothiazol-4-yl)-4-methoxyimino-pent-2-enoyl]amino-3-acetoxymethyl-3-cephem-4-carboxylate



0.4 g of 1-hydroxybenzotriazole and 0.6 g of dicyclohexylcarbodiimide are added to a solution of 1 g of the product from Example 60 in 30 ml of absolute tetrahydrofuran. The mixture is stirred at room temperature for 5 hours, a solution of 1 g of 7-amino-cephalosporanic

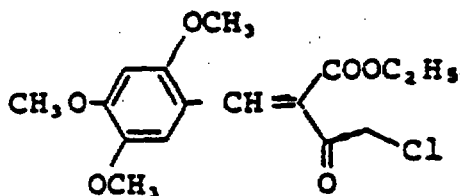
acid tert.-butyl ester in 20 ml of tetrahydrofuran is then added and the mixture is stirred overnight at room temperature. The dicyclohexylurea is filtered off, the filtrate is evaporated and the residue is dissolved in ethyl acetate. The solution is extracted three times with sodium bicarbonate solution and once with water, dried and evaporated. Titration of the residue with ether, filtration of the mixture and evaporation of the filtrate gives 1.2 g of a crude product which is purified by chromatography on silica gel (mobile phase: toluene/ethyl acetate 4:1). Yield: 320 mg.

IR (KBr): 3284, 2979, 2932, 1787, 1725, 1679, 1551, 1453, 1370, 1245, 1154, 1105, 1052 cm^{-1} .

NMR (CDCl_3): δ = 8.70[1] s broad, 7.46[1] d, J = 9 Hz, 7.20[1] s, 7.03[1] s, 5.89[1] dd, J = 9 Hz, J = 5 Hz, 5.10[1] d, J = 13 Hz, 5.01[1] d, J = 5 Hz, 4.79[1] d, J = 13 Hz, 3.88[3] s, 3.55[1] d, J = 18 Hz, 3.36[1] d, J = 18 Hz, 2.08[3] s, 2.07[3] s, 1.52[18] s ppm.

Example 62

2-(2,4,5-Trimethoxybenzylidene)-3-oxo-4-chlorobutyric acid ethyl ester



42 g of 4-chloroacetoacetic acid ethyl ester, 50 g of 2,4,5-trimethoxybenzaldehyde, 2.5 ml of glacial acetic acid and 1 ml of piperidine are dissolved in 60 ml of benzene and the solution is boiled for two hours using a water separator. Although conversion is not yet complete, the mixture is worked up. It is diluted with 200 ml of ethyl acetate, extracted in each case three times with saturated sodium bicarbonate solution, water, 1M citric acid solution and again with water, dried and evaporated. On fractional crystallization of the residue from methanol, first 20 g of pure product, as the E/Z mixture, and then 10.5 g of unreacted aldehyde can be

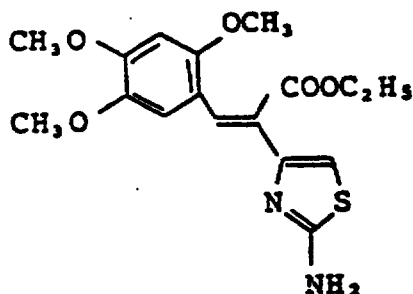
crystallized. In addition to a large amount of product, the mother liquor still contains only a little aldehyde and, after preliminary purification by chromatography on silica gel, can likewise be crystallized. A further 25 g of product are obtained.

IR (Nujol): 1715, 1680, 1595, 1505, 1405, 1370, 1340, 1270, 1210, 1165, 1120, 1020 cm^{-1} .

NMR (CDCl_3): δ = 8.09[1] s, 7.00/6.80[1] s, 6.71[1] s, 4.50/4.41[2] s, 4.33[2] q, J = 7 Hz, 3.98[3] s, 3.88[3] s, 3.83[3] s, 1.36/1.32[3] t, J = 7 Hz ppm.

Example 63

2-(2-Aminothiazol-4-yl)-3-(2,4,5-trimethoxyphenyl)-propenoic acid ethyl ester (Z-isomer)



54.8 g of the E/Z mixture from Example 62 are reacted according to Example 25. After the tetrahydrofuran has been stripped off and the aqueous phase has been adjusted to pH 8, some of the pure Z-isomer crystallizes and is recrystallized from acetone, giving a yield of 12.5 g with a melting point of 194° . Extraction of the aqueous phase with ethyl acetate and drying and evaporation of the organic phase give 44 g of the E/Z mixture as a dark-coloured oil.

IR (Nujol): 3320, 1700, 1635, 1600, 1510, 1395, 1320, 1290, 1270, 1230, 1200, 1150, 1110, 1025 cm^{-1} .

NMR (DMSO): δ = 7.62[1] s, 7.22[2] s broadened, 6.91[1] s, 6.82[1] s, 6.51[1] s, 4.33[2] q, J = 7 Hz, 3.93[6] s, 3.78[3] s, 1.25[3] t, J = 7 Hz ppm.

calculated: C 55.9 H 5.8 N 7.7 S 8.8

found: C 55.7 H 5.8 N 7.5 S 8.8

Example 64

2-(2-Aminothiazol-4-yl)-3-(2,4,5-trimethoxyphenyl)-propenoic acid ethyl ester hydrochloride (E-isomer)

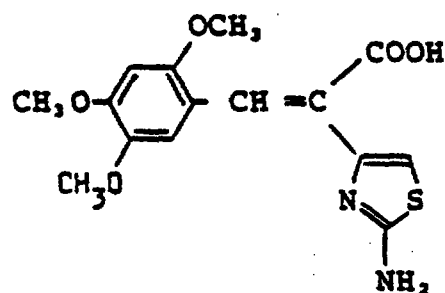
5 g of the E/Z mixture from Example 62 and 1.1 g of thiourea are stirred 100 ml of ethanol at room temperature overnight and the mixture is then warmed to 50° for 6 hours. After the mixture has been cooled, the product is filtered off, and a second fraction of the same purity can be obtained by concentration of the mother liquor and renewed filtration. Yield: 4.4 g, melting point: 200° (decomposition).

IR (Nujol): 3220, 1680, 1625, 1595, 1575, 1490, 1400, 1340, 1285, 1255, 1210, 1120, 1040 cm⁻¹.

NMR (DMSO): δ = 8.17[1] s, 6.75[2] s, 6.60[1] s, 4.23[2] q, J = 7 Hz, 3.90[6] s, 3.53[3] s, 1.25[3] t, J = 7 Hz ppm.

Example 65

2-(2-Aminothiazol-4-yl)-3-(2,4,5-trimethoxyphenyl)-propenoic acid



5.5 g of the product from Example 63 are suspended in 200 ml of dioxane and, after the addition of 24 ml of 2N sodium hydroxide solution and 10 ml of water, the suspension is boiled under reflux for 12 hours. The dioxane is stripped off and the aqueous phase is extracted twice with ethyl acetate and adjusted to pH 2.5. The product is filtered off and dried. Yield: 3.4 g of an E/Z mixture.

IR (Nujol): 1650, 1600, 1495, 1330, 1290, 1260, 1206, 1120, 1020 cm⁻¹.

E-isomer

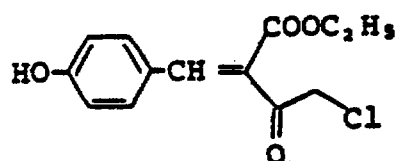
NMR (DMSO): δ = 7.90[1] s, 6.86[2] s broadened, 6.62[1] s, 6.58[1] s, 6.30[1] s, 3.82[3] s, 3.80[3] s, 3.43[3] s ppm.

Z-isomer

NMR (DMSO): δ = 7.39[1] s, 6.98[2] s broadened, 6.66[1] s, 6.55[1] s, 6.34[1] s, 3.80[6] s, 3.63[3] s ppm.

Example 66

2-(4-Hydroxybenzylidene)-3-oxo-4-chlorobutyric acid ethyl ester



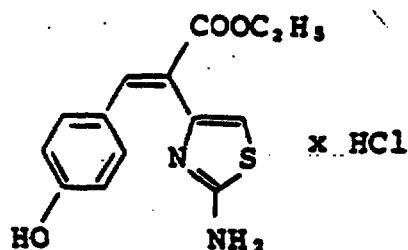
5 122 g of 4-hydroxybenzaldehyde are reacted, and the mixture is worked up, according to Example 24. After unreacted 4-chloroacetoacetic acid ethyl ester has been distilled off, the crude product is left to stand over-
10 mixture of 200 ml of toluene and 50 ml of cyclohexane, and 21 g of p-hydroxybenzaldehyde are filtered off. The mother liquor is evaporated again and the residue is left to stand for several days to crystallize. After treatment with toluene, 85 g of an E/Z mixture of melting point
15 92-95° are obtained.

IR (Nujol): 3310, 1700, 1665, 1600, 1570, 1505, 1400, 1310, 1285, 1210, 1160, 1010 cm^{-1} .

NMR (DMSO): δ = 10.40[1] s broad, 7.76/7.72[1] s, 7.45/7.33[2] d, J = 7 Hz, 6.91/6.88[1] d, J = 7 Hz, 4.96/4.68
20 [2] s, 4.32/4.23[2] q, J = 7 Hz, 1.25[3] t, J = 7 Hz ppm.
calculated: C 58.1 H 4.9 Cl 13.2 O 23.8
found: C 58.2 H 4.9 Cl 13.1 O 24.1

Example 67

25 2-(2-Aminothiazol-4-yl)-3-(4-hydroxyphenyl)-propenoic acid ethyl ester hydrochloride (E-isomer)



83.2 g of the product from Example 66 and 23.6 g of thiourea, dissolved in 500 ml of ethanol, are boiled under reflux for 5 hours. The mixture is evaporated, the
30 residue is mixed thoroughly with a mixture of 200 ml of

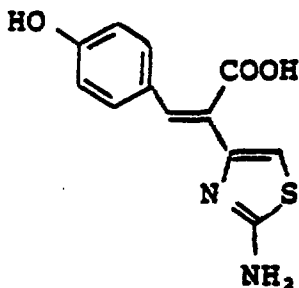
ethyl acetate and 30 ml of water and the mixture is filtered. Recrystallization of the residue from methanol gives 32 g of the pure E-isomer as the hydrochloride. Melting point: 195-7° (decomposition). The solution in ethyl acetate/water is adjusted to pH 8 with 2N sodium hydroxide solution, the ethyl acetate phase is separated off and the aqueous solution is extracted twice more with ethyl acetate. Drying and evaporation of the organic phase gives an oil from which 8.2 g of the E-isomer can be crystallized as the free base by means of ethanol. An impure E/Z mixture remains as the mother liquor in the form of an oil.

IR (Nujol): 1695, 1620, 1590, 1505, 1310, 1270, 1250, 1200, 1160, 1130, 1035 cm^{-1} .

NMR (DMSO): δ = 7.93[1] s, 7.27[2] d, J = 8 Hz, 6.93[2] d, J = 8 Hz, 6.86[1] s, 4.26[2] q, J = 7 Hz, 1.26[3] t, J = 7 Hz ppm.

Example 68

2-(2-Aminothiazol-4-yl)-3-(4-hydroxyphenyl)-propenoic acid
(Z-isomer)



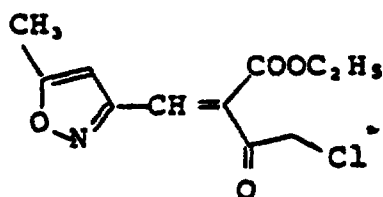
120 ml of a 2N sodium hydroxide solution are added to a solution of 21 g of the product from Example 67 in 300 ml of dioxane and the mixture is warmed to 50-60° for 5 hours and then left to stand at room temperature for 3 days. Working up according to Example 26 gives 13 g of product. Melting point: 178° (decomposition).

IR (Nujol): 1630, 1580, 1510, 1420, 1335, 1305, 1280, 1240, 1170 cm^{-1} .

NMR (DMF): δ = 7.39[2] d, J = 8 Hz, 7.07[1] s, 6.78[2] d, J = 8 Hz, 6.45[1] s ppm.

Example 69

2-(5-Methylisoxazol-3-ylidene)-3-oxo-4-chlorobutyric acid ethyl ester



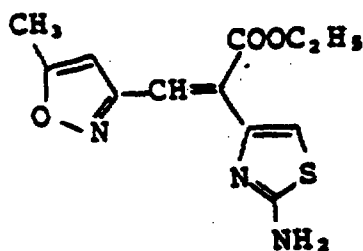
5 79.5 g of 5-methylisoxazole-3-aldehyde are reacted with 4-chloroacetoacetic acid ethyl ester according to Example 24. A crude product, which is chromatographically pure, is obtained. The isomer ratio is 2:1.

IR (film): 2950, 1720, 1590, 1420, 1255, 1225, 1020 cm^{-1} .

10 NMR (CDCl_3); δ = 7.64/7.61[1] s, 6.21/6.08[1] s, 4.47[2] s, 4.40/4.32[2] q, J = 7 Hz, 2.43[3] s, 1.32[2] t, J = 7 Hz ppm.

Example 70

15 2-(2-Aminothiazol-4-yl)-3-(5-methylisoxazol-3-yl)-propenoic acid ethyl ester



20 79.5 g of the product from Example 69 are reacted according to Example 25. The crude product is purified by chromatography on silica gel (mobile phase: methylene chloride/methanol 95:5). 74.5 g of the isomer mixture are obtained.

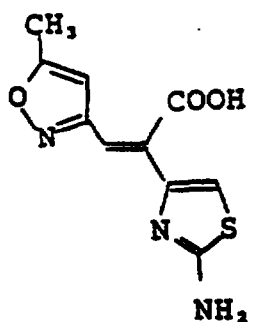
Isomer A

IR (Nujol): 3350, 3250, 3100, 1700, 1625, 1590, 1540, 1250, 1210, 1160, 1040, 1020 cm^{-1} .

25 NMR (DMSO): δ = 7.25[2] s broad, 7.20[1] s, 6.70[1] s, 6.21[1] s, 4.38[2] q, J = 7 Hz, 2.41[3] s, 1.25[3] t, J = 7 Hz ppm.

Example 71

30 2-(2-Aminothiazol-4-yl)-3-(5-methylisoxazol-3-yl)-propenoic acid (Z-isomer)



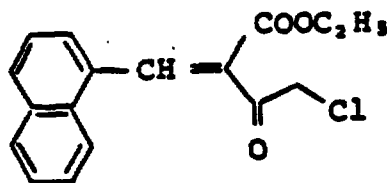
50 g of the isomer mixture prepared according to Example 70 are dissolved in 200 ml of ethanol. The solution is adjusted to pH 13.5 by the addition of 2N sodium hydroxide solution and is left to stand at pH 13.5 and at room temperature for 24 hours. The ethanol is then stripped off, 100 ml of water are added, the pH is adjusted to 8 and the mixture is extracted three times with ethyl acetate. Evaporation of the organic phase gives 20 g of crude product, which are dissolved in a mixture of 70 ml of dioxane and 70 ml of 2N sodium hydroxide solution. The solution is boiled under reflux for 5 hours and is then worked up according to Example 31, and the crude product is recrystallized from acetone/methanol 1:3. Yield: 7 g, melting point: 180-2° (decomposition).

IR (Nujol): 1600, 1460, 1400, 1290 cm^{-1} .

NMR (DMSO): δ = 7.02[1] s, 6.63[1] s, 6.26[1] s, 2.41[3] s, ppm.

20 Example 72

2-Naphthylidene-3-oxo-4-chlorobutyric acid ethyl ester

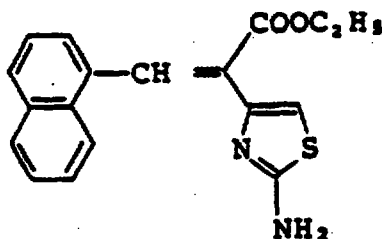


9.85 g of 1-naphthaldehyde are reacted with 15.2 g of 4-chloroacetoacetic acid ethyl ester in the course of 10 hours according to Example 24. After incipient distillation under a high vacuum has been carried out, a 2:1 isomer mixture which still contains traces of aldehyde remains as the residue.

NMR (CDCl₃): δ = 8.12/8.06[1] s, 7.33-8.0[7] m, 7.26/7.20[1] s, 4.55/4.05[2] s, 4.39/4.10[2] q, J = 7 Hz, 1.33/0.90[3] t, J = 7 Hz ppm.

Example 73.

- 5 2-(2-Aminothiazol-4-yl)-3-naphthylpropenoic acid ethyl ester



18 g of the crude product prepared according to Example 72 are stirred with 4.6 g of thiourea in 100 ml of ethanol at 50° for 3 hours. Working up according to Example 44 gives a crude product, from which 6.3 g of the E-isomer of melting point 155-7° can be crystallized with ether. An E/Z mixture remains in the mother liquor.

E-isomer

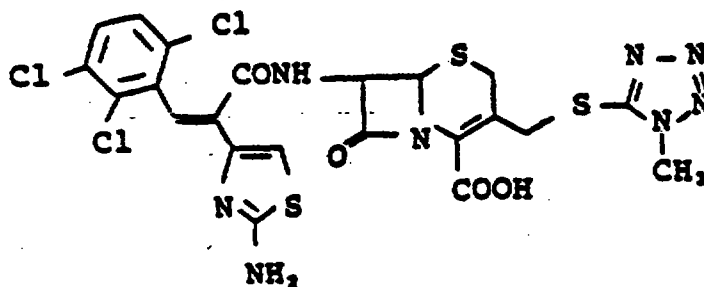
- 15 NMR (DMSO): δ = 8.18[1] s, 7.1-8.1[7] m, 6.85[2] s broadened, 6.20[1] s, 4.26[2] q, J = 7 Hz, 1.28[3] t, J = 7 Hz ppm.

Z-isomer

- 20 NMR (DMSO): δ = 8.06[1] s, 7.1-8.1[7] m, 7.26[2] s broadened, 6.70[1] s, 4.08[2] q, J = 7 Hz, 0.90[3] t, J = 7 Hz ppm.

Example 74

- 25 7-[2-(2-Aminothiazol-4-yl)-2-(2,3,6-trichlorobenzylidene)-acetamido]-3-(1-methyl-1-H-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid (Z-isomer)



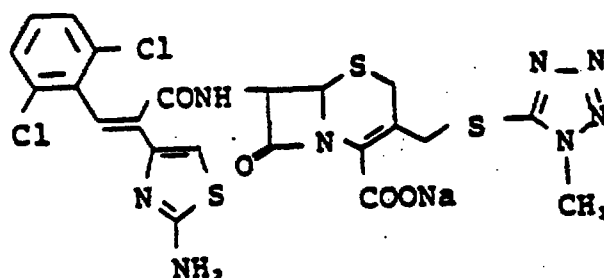
0.7 g of 7-amino-3-(1-methyl-1-H-tetrazol-5-yl)-thiomethyl-3-cephem-4-carboxylic acid are dissolved at

pH 7-8 in a mixture of 20 ml of THF and 20 ml of water through addition of triethylamine. At 0°, 1 g of product from Example 53 is added, and the solution is then stirred for 3 hours at room temperature, the pH being kept at 7.5 by addition of triethylamine. After stripping off the THF, the pH is adjusted to 3.0, and the aqueous suspension is warmed at 50° for 5 hours.

The supernatant is decanted from any viscous residue which has deposited, and the aqueous phase is adjusted to pH 2.8 and filtered under suction. Yield 0.4 g.
 IR (KBr): 1785, 1630, 1517, 1436, 1385, 1235, 1178 cm⁻¹.
 NMR (CD₃OD): δ = 7.52[1] d, J = 8 Hz, 7.42[1] d, J = 8 Hz, 7.16[1] s, 7.10[1] s, 5.69[1] d, J = 5 Hz, 5.03[1] d, J = 5 Hz, 4.31[2] s broad, 4.01[3] s, 3.78[1] d, J = 18 Hz, 3.65[1] d, J = 18 Hz ppm.

Example 75

Sodium 7-[2-(2-aminothiazol-4-yl)-2-(2,6-dichlorobenzylidene)acetamido]-3-(1-methyl-1-H-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylate (Z-isomer)



2 g of the product from Example 54 are reacted analogously to Example 38 with 1.8 g of 7-amino-3-(1-methyl-1-H-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid.

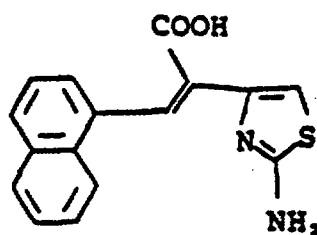
1.6 of the sodium salt are obtained.

IR (Nujol): 1750, 1595 cm⁻¹.

NMR (CD₃OD): δ = 7.34[1] s, 7.27[3] m, 6.73[1] s, 5.62[1] d, J = 5 Hz, 4.95[1] d, J = 5 Hz, 4.39[1] d, J = 13 Hz, 4.29[1] d, J = 13 Hz, 3.97[3] s, 3.66[1] d, J = 18 Hz, 3.42[1] d, J = 18 Hz ppm.

Example 76

2-(2-Aminothiazol-4-yl)-3-naphthylpropenoic acid (Z-isomer)

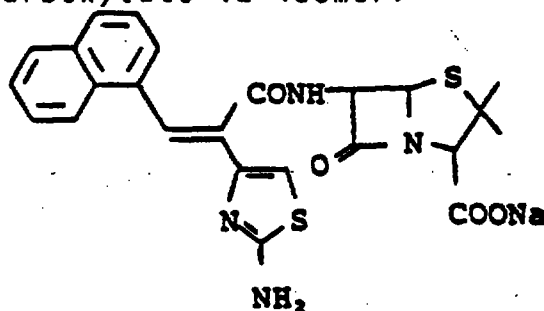


A solution of 10 g of the isomer mixture from Example 73 in 50 ml of ethanol is adjusted to pH 13.5 using 2N sodium hydroxide solution, and the mixture is stirred at room temperature for 10 hours. The alcohol is stripped off, water and 2N hydrochloric acid are added to pH 8, and the mixture is extracted three times with ethyl acetate. The combined extracts are washed once with water and evaporated. The residue is taken up in 100 ml of dioxane, 30 ml of concentrated sodium hydroxide solution are added to the solution, and the mixture is refluxed for 15 hours. After the solution has been concentrated, the pH is adjusted to 10 using 15 per cent hydrochloric acid with cooling, and the aqueous solution is extracted three times with ethyl acetate. The aqueous phase is subsequently acidified to pH 2.8, and the precipitated product is filtered off under suction. Recrystallization from methanol/acetone gives 2.5 g of pure Z-isomer, melting point: $> 220^{\circ}$.

IR (Nujol): 1620, 1595, 1560, 1420, 1300, 1208 cm^{-1} .
NMR (DMSO): $\delta = 7.40-8.18[8] \text{ m}$, 7.17[2] s broad, 6.62[1] s ppm.

Example 77

Sodium 7-[2-(2-aminothiazol-4-yl)-2-naphthylideneacetamido]penam-4-carboxylate (Z-isomer)



24 μl of water and subsequently 1.1 g of phosphorus pentachloride are added at 0° to a suspension of 0.8 g of the product from Example 76 in 20 ml of absolute methylene chloride. The mixture is stirred at room

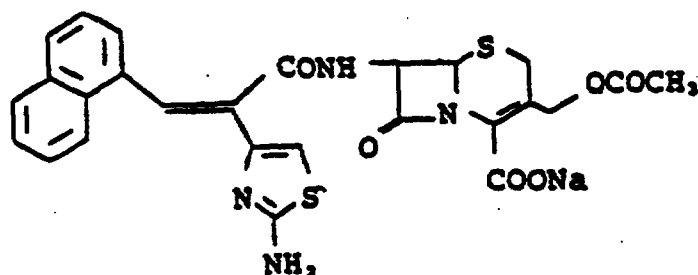
temperature for 2 1/2 hours and filtered under suction, and the residue is washed again with methylene chloride. This residue is added to a solution, cooled to 0°, of 310 mg of 6-aminopenicillanic acid and 600 µl of triethylamine in 60 ml of absolute methylene chloride. The mixture is stirred for 30 minutes at 0° and then for 3 1/2 hours at room temperature, and worked up analogously to Example 38.

Yield: 0.8 g of the sodium salt.

- 10 IR(Nujol): 1755, 1600 cm⁻¹.
NMR (CD₃OD): δ = 8.04[1] m, 7.88[1] s, 7.68-7.80[2] m, 7.26-7.54[4] m, 6.53[1] s, 5.34[1] d, J = 5 Hz, 5.28[1] d, J = 5 Hz, 3.91[1] s, 1.32[3] s, 1.22[3] s ppm.

Example 78

- 15 Sodium 7-[2-(2-aminothiazol-4-yl)-2-naphthylideneacetamido]-3-acetoxymethyl-3-cephem-4-carboxylate (Z-isomer)

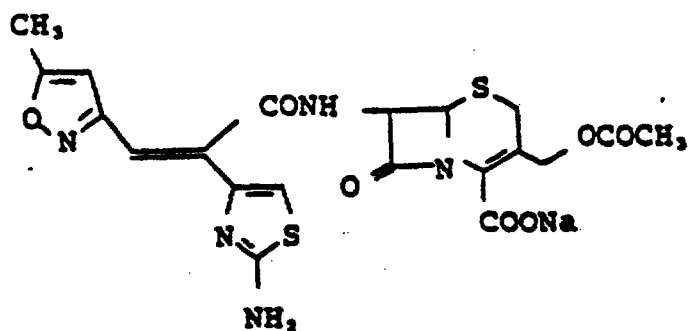


1 g of the product from Example 76 is reacted analogously to Example 29, and 0.8 of the sodium salt is obtained.

- 20 IR (Nujol): 1745, 1600 cm⁻¹.
NMR (CD₃OD): δ = 8.20[1] m, 8.06[1] s, 7.38-7.95 [6] m, 6.66[1] s, 5.74[1] d, J = 5 Hz, 4.99[1] d, J = 5 Hz, 4.97[1] d, J = 13 Hz, 4.78[1] d, J = 13 Hz, 3.46[1] d, J = 17 Hz, 3.11[1] d, J = 17 Hz, 2.01[3] s ppm.

Example 79

Sodium 7-[2-(2-aminothiazol-4-yl)-2-(5-methylisoxazol-3-ylidene)acetamido]-3-acetoxymethyl-3-cephem-4-carboxylate (Z-isomer)

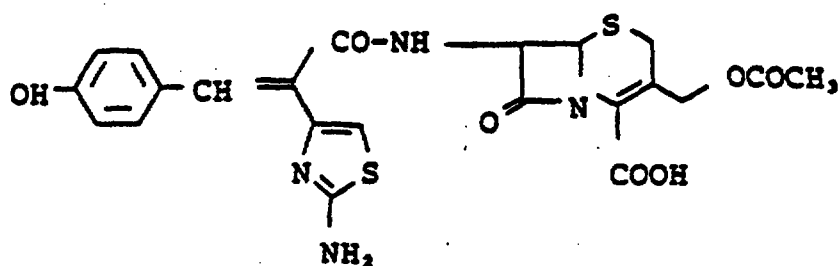


1 g of the product from Example 71 is reacted analogously to Example 29. Yield 1.5 g of the sodium salt.

5 IR (Nujol): 1755, 1600, 1520, 1230 cm^{-1} .
 NMR (CD_3OD): δ = 7.21[1] s, 6.70[1] s, 6.30[1] s, 5.91[1] d, J = 5 Hz, 5.16[1] d, J = 5 Hz, 5.00[1] d, J = 12 Hz, 4.81[1] d, J = 12 Hz, 3.61[1] d, J = 18 Hz, 3.34[1] d, J = 18 Hz, 2.41[3] s, 2.03[3] s ppm.

10 Example 80

7-[2-(2-Aminothiazol-4-yl)-2-(4-hydroxybenzylidene)acetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid



3 g of the product from Example 68 are reacted analogously to Example 29. 4.5 g of an E/Z mixture are obtained. 1 g of this mixture is suspended in 25 ml of methylene chloride, 500 μl of triethylamine are added, and the mixture is stirred overnight at room temperature. The mixture is filtered under suction, the residue is suspended in 20 ml of water, and the pH is adjusted to 3.0 using 2N hydrochloric acid. The product is filtered off under suction and dried. Yield 0.6 g.

IR (Nujol): 1765, 1720, 1650, 1590, 1500, 1225, 1165 cm^{-1} .

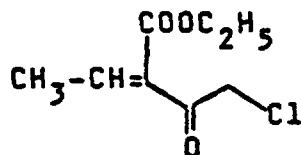
25 NMR (DMSO): δ = 8.56/8.15[1] d, J = 8 Hz, 7.0-7.8[5] m, 6.72[1] t, J = 7 Hz, 6.40/6.29[1] s, 5.84[1] m, 5.21/5.15[1] d, J = 5 Hz, 5.02[1] d, J = 12 Hz, 4.68[1] d, J =

12 Hz, 3.66[1] d, J = 17 Hz, 3.49[1] d, J = 17 Hz,
2.05[3] s ppm.

Example 81

Ethyl 2-ethylidene-3-oxo-4-chlorobutyrate

5



10

1 g of piperidine was added dropwise to a stirred mixture of 82 g of 4-chloroacetoacetic acid and 24 g of acetaldehyde at -20°C. When the mixture had been stirred for 7 hours at -10 to -20°C, 100 ml of ethyl acetate were added. The solution was then extracted three times with ice-cold 1 normal hydrochloric acid and with water. The organic phase was dried over magnesium sulphate and concentrated. The oil remaining was subjected to bulb-tube distillation under a high vacuum.

15

Yield 37 g.

Boiling point: 110°C/0.05

The product obtained was a Z/E mixture.

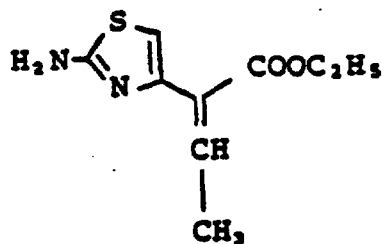
IR (CHCl₃); 1700, 1620, 1445, 1375, 1260 cm⁻¹.

20

NMR (CDCl₃): δ = 7.30/7.20[1] q, J = 8 Hz, 4.45/4.43[2] s, 4.36/4.30[2] q, J = 7 Hz, 2.10/1.96[3] d, J = 8 Hz, 1.35/1.30[3] t, J = 7 Hz ppm.

Example 82

Ethyl 1-(2-aminothiazol-4-yl)-1-propenecarboxylate



25

A solution of 82 g of sodium acetate in 150 ml of water and then 76 g of thiourea are added consecutively to a solution of 190 g of the product from Example 81 in 400 ml of tetrahydrofuran. The mixture is stirred at room temperature for 20 hours, the THF is then stripped off, and ethyl acetate is added to the residue.

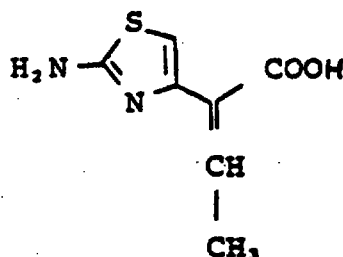
30

After the water has been removed, the organic

phase is extracted twice with water, once with 1M citric acid solution and once with water, dried and evaporated. The product is purified by chromatography on silica gel (mobile phase methylene chloride). Yield 10.3 g.

5 Example 83

1-(2-Aminothiazol-4-yl)-1-propenecarboxylic acid



10 The product from Example 82 is dissolved in a mixture of 20 ml of methanol and 5 ml of 2N sodium hydroxide solution.

The solution is refluxed for 6 hours and then worked up as in Example 15. Yield 2.2 g.

E-isomer:

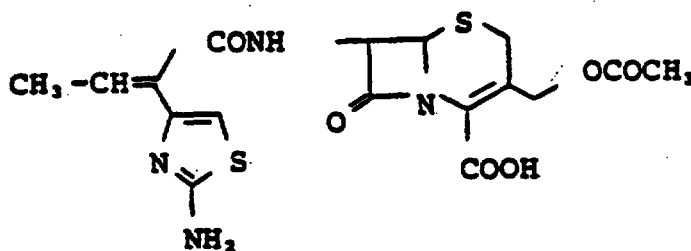
15 NMR (DMSO): δ = 7.04[2] s broadened, 6.89[1] q, J = 7 Hz, 6.48[1] s, 1.88[6] d, J = 7 Hz ppm.

Z-isomer:

NMR (DMSO): δ = 6.54[1] q, J = 7 Hz, 6.48[1] s, 1.81[6] d, J = 7 Hz ppm.

Example 84

20 7-[1-(2-Aminothiazol-4-yl)-1-propenecarbamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid



Z-isomer

25 1 g of the Z-isomer from Example 83 is reacted analogously to Example 19, and 0.6 g of product is obtained.

NMR (DMSO): δ = 9.39[1] d, J = 7 Hz, 7.10[2] s broad, 6.33[1] q, J = 7 Hz, 6.24[1] s, 5.82[1] dd, J = 4 Hz, J = 7 Hz, 5.20[1] d, J = 4 Hz, 5.01[1] d, J = 13 Hz, 30 4.71[1] d, J = 13 Hz, 5.66[1] d, J = 18 Hz, 3.52[1] d,

J = 18 Hz, 2.06[3] s, 1.84[6] d, J = 7 Hz ppm.

E-isomer

1 g of the F-isomer from Example 83 is reacted analogously to Example 19, and 0.6 g of product is obtained.

NMR (DMSO): δ = 9.20[1]d, J = 9 Hz, 7.90[2] s, very broad, 6.87[1] q, J = 7 Hz, 6.64[1] s, 5.81[1] dd, J = 9 Hz, J = 5 Hz, 5.15[1] d, J = 5 Hz, 5.02[1] d, J = 13 Hz, 4.67[1] d, J = 13 Hz, 3.65[1] d, J = 18 Hz, 3.50[1] d, J = 18 Hz, 2.03[3] s, 1.90[6] d, J = 7 Hz ppm.

The following was prepared in the same way as the product from Example 84:

7-[1-(2-Aminothiazol-4-yl)-1-butenecarbamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid

Z-isomer

NMR (DMSO): δ = 9.25[1] d, J = 7 Hz, 7.00[2] s, broad, 6.23[1] t, J = 7 Hz, 6.19[1] s, 5.79[1] dd, J = 7 Hz, J = 6 Hz, 5.17[1] d, J = 6 Hz, 4.98[1] d, J = 12 Hz, 4.67[1] d, J = 12 Hz, 3.62[1] d, J = 18 Hz, 3.50[1] d, J = 18 Hz, 2.18[2]dq, J = 7 Hz, J = 7 Hz, 2.04[3] s, 1.01[3] t, J = 7 Hz ppm.

E-isomer

NMR (DMSO): δ = 9.08[1] d, J = 8 Hz, 8.0[2] s very broad, 6.77[1] t, J = 7 Hz, 6.63[1] s, 5.80[1] dd, J = 8 Hz, J = 5 Hz, 5.15[1] d, J = 5 Hz, 5.01[1] d, J = 13 Hz, 4.69[1] d, J = 13 Hz, 3.66[1] d, J = 18 Hz, 3.49[1] d, J = 18 Hz, 2.29[2] dq, J = 7 Hz, J = 7 Hz, 2.05[3] s, 1.02[3] t, J = 7 Hz ppm.

The following were prepared analogously:

7-[1-(2-aminothiazol-4-yl)-1-undecenecarbamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid

7-[1-(2-aminothiazol-4-yl)-3,3-dimethyl-1-butenecarbamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid

7-[1-(2-aminothiazol-4-yl)-3-methyl-1-butenecarbamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid

7-[1-(2-aminothiazol-4-yl)-2-cyclohexyl-1-ethenecarbamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid

7-[1-(2-aminothiazol-4-yl)-2-cyclopentyl-1-ethenecarbamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid

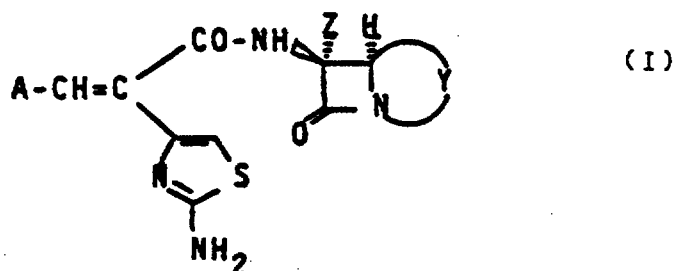
- 7-[1-(2-aminothiazol-4-yl)-2-cycloheptyl-1-carbamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid
- 7-[1-(2-aminothiazol-4-yl)-3-methoxy-1-propenecarbamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid
- 5 7-[1-(2-aminothiazol-4-yl)-3-ethoxy-1-propenecarbamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid
- 7-[1-(2-aminothiazol-4-yl)-4-dimethylamino-3,3-dimethyl-1-butenecarbamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid
- 10 7-[1-(2-aminothiazol-4-yl)-3-dimethylaminomethyl-3-methyl-1-hexenecarbamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid
- 6-[1-(2-aminothiazol-4-yl)-3,3-dimethyl-1-butenecarbamido]-penamcarboxylic acid
- 15 7-[1-(2-aminothiazol-4-yl)-3,3-dimethyl-1-butenecarbamido]-3-(1-methyl-1-H-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid
- 6-[1-(2-aminothiazol-4-yl)-1-propenecarbamido]-penamcarboxylic acid
- 20 7-[1-(2-aminothiazol-4-yl)-propenecarbamido]-3-(1-methyl-1-H-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid
- 7-[1-(2-aminothiazol-4-yl)-4-dimethylamino-3,3-dimethyl-1-butenecarbamido]-3-(1-methyl-1-H-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid
- 25 6-[1-(2-aminothiazol-4-yl)-4-dimethylamino-3,3-dimethyl-1-butenecarbamido]penamcarboxylic acid
- 6-[1-(2-aminothiazol-4-yl)-3-methoxy-1-propenecarbamido]-penamcarboxylic acid
- 7-[1-(2-aminothiazol-4-yl)-3-methoxy-1-propenecarbamido]-3-(1-methyl-1-H-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid
- 30 7-[1-(2-aminothiazol-4-yl)-1-pentenecarbamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid
- 7-[1-(2-aminothiazol-4-yl)-1-hexenecarbamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid
- 35 7-[1-(2-aminothiazol-4-yl)-1-heptenecarbamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid
- 7-[1-(2-aminothiazol-4-yl)-1-octenecarbamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid

7-[1-(2-aminothiazol-4-yl)-1-nonenecarbamido]-3-acetoxy-
methyl-3-cephem-4-carboxylic acid

7-[1-(2-aminothiazol-4-yl)-1-decencarbamido]-3-acetoxy-
methyl-3-cephem-4-carboxylic acid

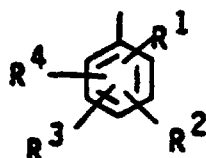
Patent claims

1. Compounds of the formula (I)



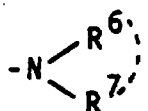
wherein

A denotes hydrogen, optionally cyclic, alkyl, alkenyl or alkynyl with up to 18 C atoms, any of which may be substituted by O, S or methoxyimino, or denotes a radical of the formula



wherein

R¹, R², R³ and R⁴ independently of one another denote hydrogen, halogen, alkyl with up to 6 carbon atoms, aryl, an -OCOR⁵ group, a



group, nitro, cyano, trifluoromethyl,

hydroxyl, alkoxy or alkylthio with up to 6 C atoms, hydroxycarbonyl, alkoxy carbonyl with up to 6 C atoms in the alkyl part, aminocarbonyloxy, sulphonyl or sulpho,

wherein

aryl in turn denotes a substituted or unsubstituted carbocyclic aromatic ring or 5-membered or 6-membered heterocyclic ring,

and wherein

R⁵ denotes optionally substituted and optionally cyclic alkyl, alkenyl or alkynyl with up to 6 C atoms,

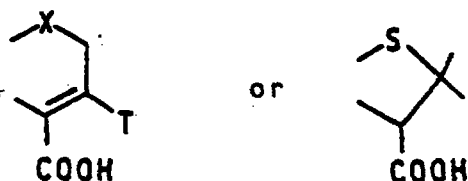
and wherein



R^6 and R^7 independently of one another denote hydrogen, optionally substituted and optionally cyclic alkyl, alkenyl or alkynyl with up to 6 C atoms or alkanoyl with up to 6 C atoms, or together denote alkyl or alkanoyl with up to 6 C atoms, or denotes naphthyl, 5-methylisoxazol-3-yl, furyl, thienyl or pyridinyl,

and wherein

Y in the form of the free acid represents a radical of the formula



wherein

X denotes sulphur or oxygen and

T is a conventional radical in cephalosporin chemistry,

and wherein

Z denotes H or methoxy.

2. Compounds according to Claim 1, characterized in that

T denotes hydrogen, C_1 - C_4 -alkyl, halogen, C_1 - C_4 -alkoxy, hydroxymethyl, formyloxymethyl, C_1 - C_4 -alkylcarbonyloxymethyl, aminocarbonyloxymethyl, pyridiniummethyl, 4-carbamoylpyridiniummethyl or heterocyclylthiomethyl,

wherein

heterocyclyl represents a radical of the formula



wherein

R^8 denotes hydrogen, methyl, 2-dimethylamino-ethyl, carboxymethyl or sulphomethyl and

R^9 denotes hydrogen or methyl.

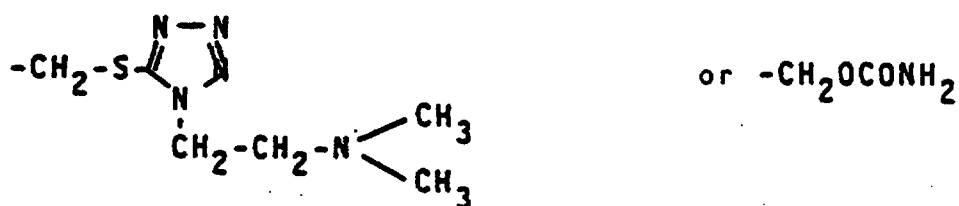
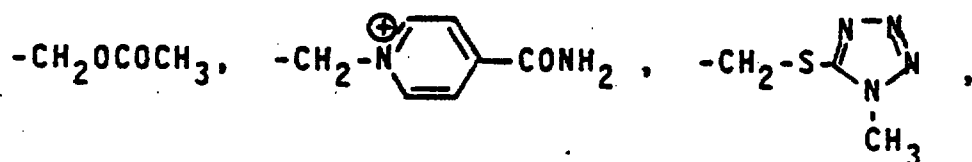


3. Compounds according to Claims 1 and 2, characterized in that

Z denotes hydrogen or methoxy,

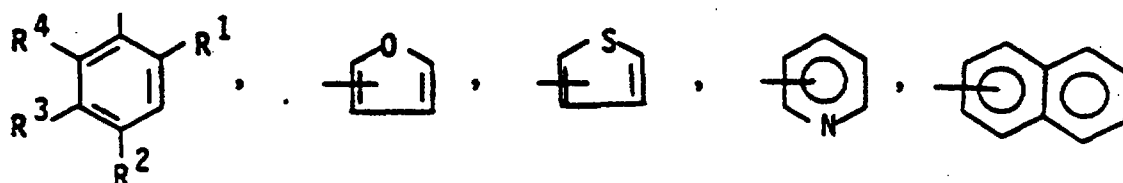
X denotes sulphur,

T denotes a radical



and

A denotes a radical of the formula



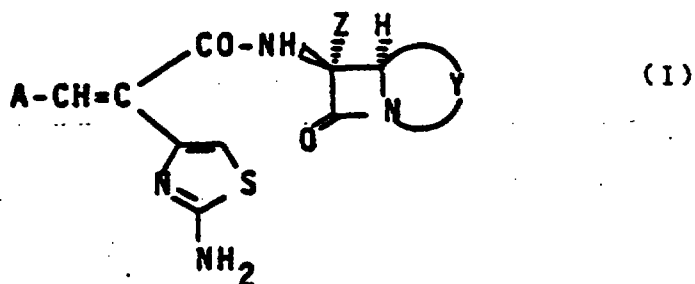
wherein

R¹ to R⁴ have the meaning given in Claim 1.

4. Pharmaceutically acceptable salts of the compounds according to Claims 1 to 3.

5. Compounds according to one of Claims 1 to 4 in the Z-configuration.

6. Process for the preparation of the compounds of the formula (I),

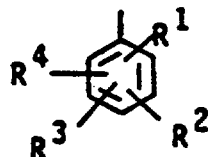


wherein

A denotes hydrogen, optionally cyclic, alkyl, alkenyl or alkynyl with up to 18 C atoms, any of

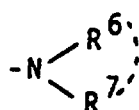


which may be substituted by O, S or methoxyimino,
or denotes a radical of the formula



wherein

R¹, R², R³ and R⁴ independently of one another denote hydrogen, halogen, alkyl with up to 6 carbon atoms, aryl, an -OCOR⁵ group, a



group, nitro, cyano, trifluoromethyl,

hydroxyl, alkoxy or alkylthio with up to 6 C atoms, hydroxycarbonyl, alkoxy carbonyl with up to 6 C atoms in the alkyl part, aminocarbonyloxy, sulphonyl or sulpho,

wherein

aryl in turn denotes a substituted or unsubstituted carbocyclic aromatic ring or 5-membered or 6-membered heterocyclic ring,

and wherein

R⁵ denotes optionally substituted and optionally cyclic alkyl, alkenyl or alkynyl with up to 6 C atoms,

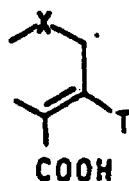
and wherein

R⁶ and R⁷ independently of one another denote hydrogen, optionally substituted and optionally cyclic alkyl, alkenyl or alkynyl with up to 6 C atoms or alkanoyl with up to 6 C atoms, or together denote alkyl or alkanoyl with up to 6 C atoms, or denotes naphthyl, 5-methylisoxazol-3-yl, furyl, thienyl or pyridinyl,

and wherein

Y in the form of the free acid represents a radical of the formula





or



wherein

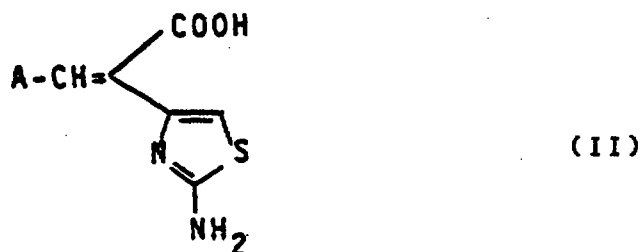
X denotes sulphur or oxygen and

T is a conventional radical in cephalosporin chemistry,

and wherein

Z denotes H or methoxy,

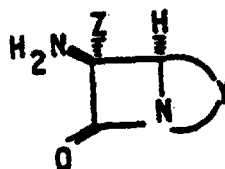
characterized in that compounds of the general formula (II)



wherein

A has the abovementioned meaning,

and in which the amino group can be in the protected or unprotected form, are reacted, after the carboxyl group has been activated by being converted into a mixed anhydride, or after being converted into the acid halide, or after being converted into an activated ester with compounds of the general formula III, if appropriate in the monosilyl or disilyl form or in the form of esters which can be split



(III)

wherein

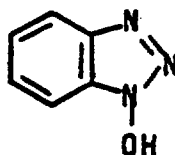
Y and Z have the abovementioned meaning,

and, if appropriate, the protective groups are then removed.

7. Process according to Claim 6, characterized in that compounds of the formula (II) are reacted, after the



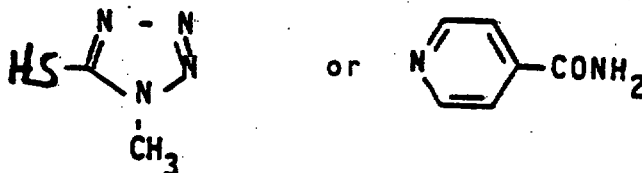
carboxyl group has been activated with phosphorus pentachloride or phosphorus oxychloride or in the form of esters with an alcohol of the formula (IV)



(IV)

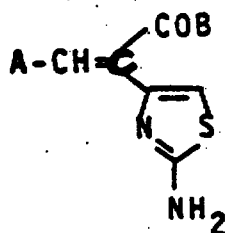
with a compound of the formula (III) without prior introduction of an amino-protective group.

8. Process for the preparation of compounds of the formula (I), characterized in that compounds of the formula (I) according to Claim 6, in which T denotes $-\text{CH}_2-\text{OCO}-$ C_1-C_4 -alkyl are reacted with nucleophiles, in particular



9. Process for the preparation of compounds of the formula (I), characterized in that compounds of the formula (I) according to Claim 6, in which T denotes $-\text{CH}_2\text{OH}$ are reacted with $\text{O}=\text{C}=\text{NSO}_2\text{Cl}$ or $\text{O}=\text{C}=\text{N}-\text{COCCl}_3$ and the $-\text{SO}_2\text{Cl}$ or $-\text{COCCl}_3$ group is then split off.

10. Compounds of the general formula

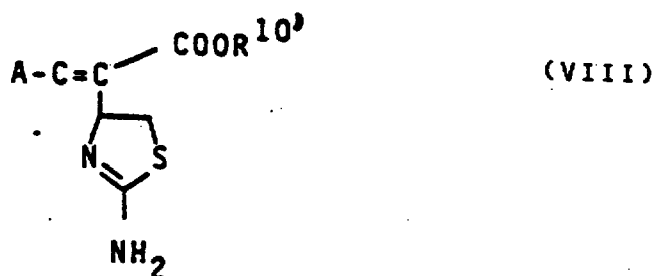


in which

A has the meaning given in Claim 1 and B represents OH, halogen, a grouping activating carboxyl groups or a C_1-C_4 -alkoxy group.

11. Process for the preparation of compounds of the formula (VIII)

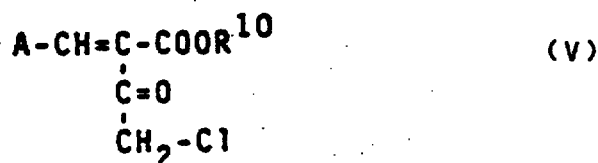




wherein

$\text{R}^{10'}$ denotes C_1 - C_4 -alkyl or H and

A has the meaning given in Claim 6, characterized in that a compound of the formula (V)



in which

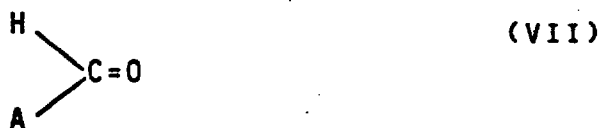
A has the abovementioned meaning and

R^{10} denotes C_1 - C_4 -lower alkyl, in particular ethyl, is prepared, in a first step, by condensation of a compound of the formula (VI)



in which

R^{10} has the abovementioned meaning, with a carbonyl compound of the formula (VII)



in which

A has the abovementioned meaning, and the compound of the formula (V) is then reacted with thiourea and a compound of the formula (VIII) is optionally hydrolysed to give the free carboxylic acid.

12. Process for the preparation of the compounds according to formula (VIII) according to Claim 11, wherein

$\text{R}^{10'}$ denotes ethyl,

characterized in that the condensation product IX of ethyl acetoacetate and a carbonyl compound of the formula (VII)

