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ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ
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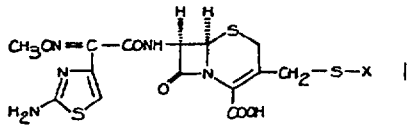
(54) 7-[2-(2-amino-4-thiazolyl)-2-methoxyimino-acetamido]-3-heterocyclyl(thiomethyl)-cephems

(57) Compounds of the general formula



(I)

[wherein X represents the 1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-as-triazin-3-yl group, the 2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl group of the 1,4,5,6-tetrahydro-4-methyl-5,6-dioxo-as-triazin-3-yl group] and readily hydrolysable esters, readily hydrolysable ethers and salts thereof and hydrates of these compounds have broad-spectrum anti-bacterial activity.

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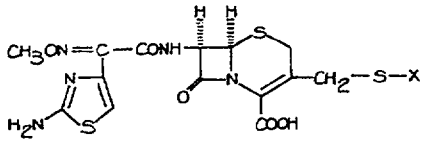
SPECIFICATION

Acyl derivatives

The present invention relates to acyl derivatives. More particularly, the invention is concerned with cephalosporin derivatives, a process for the manufacture thereof and pharmaceutical preparations containing same. The invention is further concerned with the use of said cephalosporin derivatives.

The cephalosporin derivatives provided by the present invention are compounds of the general formula



I

wherein X represents the 1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-as-triazin-3-yl group or the corresponding tautomeric form thereof, the 2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl group, or the 1,4,5,6-tetrahydro-4-methyl-5,6-dioxo-as-triazin-3-yl group,

as well as readily hydrolysable esters, readily hydrolysable ethers and salts of these compounds and hydrates of the compounds of formula I or of their esters, ethers and salts.

As readily hydrolysable ester of the compounds of formula I there are to be understood compounds of formula I in which the carboxy group is present in the form of a readily hydrolysable ester group. Examples of such esters, which can be of the conventional type, are the lower alkanoyloxyalkyl esters (e.g. the acetoxymethyl, pivaloyloxymethyl, 1-acetoxyethyl and 1-pivaloyloxyethyl ester), the lower alkoxycarbonyloxyalkyl esters (e.g. the methoxycarbonylmethyl, 1-ethoxycarbonyloxyethyl and 1-isopropoxycarbonyloxyethyl ester), the lactonyl esters (e.g. the phthalidyl and thiophthalidyl ester), the lower alkoxymethyl esters (e.g. the methoxymethyl ester) and the lower alkanoylaminomethyl esters (e.g. the acetamidomethyl ester). Other esters (e.g. the benzyl and cyanomethyl esters) can also be used.

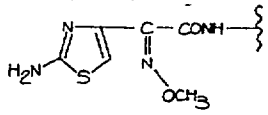
As readily hydrolysable ethers of the compounds of formula I there are to be understood compounds of formula I wherein X represents the 2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl group in which the enolic OH group is present in the form of a readily hydrolysable ether group. Possible ether groups are the same ether groups which have already been mentioned earlier in connection with the readily hydrolysable ester groups. Examples of such ethers are the lower alkanoyloxyalkyl ethers (e.g. the acetoxymethyl, pivaloyloxymethyl, 1-acetoxyethyl and 1-pivaloyloxyethyl ether), the lower alkoxycarbonyloxyalkyl ethers (e.g. the methoxycarbonyloxymethyl, 1-ethoxycarbonyloxyethyl and 1-isopropoxycarbonyloxyethyl ether), the lactonyl ethers (e.g. the phthalidyl and thiophthalidyl ether), the lower alkoxymethyl ethers (e.g. the methoxymethyl ether) and the lower alkanoylaminomethyl ethers (e.g. the acetamidomethyl ether).

Examples of salts of compounds of formula I are alkali metal salts such as the sodium salt and the potassium salt, the ammonium salt, alkaline earth metal salts such as the calcium salt, salts with organic bases such as salts with amines (e.g. salts with N-ethyl-piperidine, procaine, dibenzylamine, N,N'-dibenzylethylethylenediamine, alkylamines or dialkylamines), and salts with amino acids (e.g. salts with arginine or lysine). The salts can be mono-salts or di-salts. The second salt formation can occur in compounds with the hydroxy moiety of the 2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl group.

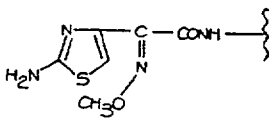
The compounds of formula I also form acid addition salts with organic or inorganic acids. Examples of such salts are hydrohalides (e.g. hydrochlorides, hydrobromides and hydroiodides), other mineral acid salts such as sulphates, nitrates, phosphates and the like, alkylsulphonates and monoarylsulphonates such as ethanesulphonates, toluenesulphonates, benzenesulphonates and the like and other organic acid salts such as acetates, tartrates, maleates, citrates, benzoates, salicylates, ascorbates and the like.

The compounds of formula I and their salts, readily hydrolysable esters and readily hydrolysable ethers can be hydrated. The hydration can be effected in the course of the manufacturing process or can occur gradually as a result of the hygroscopic properties of an initially anhydrous product.

The cephalosporin derivatives provided by the present invention can exist in the syn-isomeric form



or in the anti-isomeric form



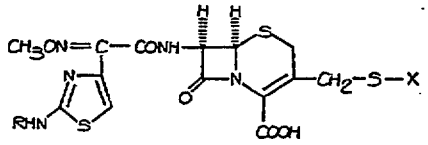
or as mixtures of these two forms. The syn-isomeric form is preferred, as are mixtures in which the syn-isomeric form predominates.

Preferred cephalosporin derivatives provided by the present invention are:

(6R,7R)-7-[2-(2-Amino-4-thiazolyl)-2-(Z-methoxyimino)acetamido]-3-/[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl/-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid and salts thereof as well as the corresponding hydrates.

According to the process provided by the present invention, the cephalosporin derivatives aforesaid are manufactured by

(a) cleaving off the protecting group R (and, if desired, also a carboxy protecting group which may be present) in a compound of the general formula



II,

wherein X has the significance given earlier, R represents a cleavable protecting group and the carboxy group can be present in protected form,

or

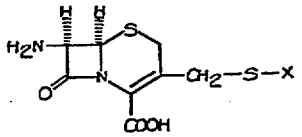
(b) for the manufacture of a readily hydrolysable ester or ether of a compound of formula I, subjecting a carboxylic acid or an enol of formula I to a corresponding esterification or etherification,

or

(c) for the manufacture of salts or hydrates of a compound of formula I or hydrates of said salts, converting a compound of formula I into a salt or hydrate or into a hydrate of said salt.

If desired, the carboxy group present in the starting materials of formula II can be protected; for example, by esterification to form readily cleavable ester such as a silyl ester (e.g. the trimethylsilyl ester). The carboxy group can also be protected in the form of one of the aforementioned readily hydrolysable esters. Furthermore, the carboxy group can be protected by salt formation with an inorganic or tertiary organic base such as triethylamine. Possible protecting groups denoted by R are, for example, protecting groups which are cleavable by acid hydrolysis (e.g. the tert.butoxycarbonyl or trityl groups) or by basic hydrolysis (e.g. the trifluoroacetyl group). Preferred protecting groups denoted by R are the chloroacetyl, bromoacetyl and iodoacetyl groups, especially the chloroacetyl group. These last-mentioned protecting groups can be cleaved off by treatment with thiourea.

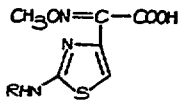
The starting materials of formula II hereinbefore can be prepared, for example, by N-acylating a corresponding 7-amino compound, namely by reacting a compound of the general formula



III,

wherein X has the significance given earlier and the carboxy group and/or the amino group can be present in protected form,

with an acid of the general formula



IV,

wherein R has the significance given earlier,

or with a reactive functional derivative of this acid and, if desired, cleaving off a carboxy protecting group which may be present.

If desired, the carboxy group present in the 7-amino compounds of formula III can be protected in the same manner as mentioned hereinbefore in connection with the starting materials of formula II. The amino group in the compounds of formula III can be protected, for example, by a silyl protecting group such as the trimethylsilyl group.

Examples of reactive functional derivatives of acids of formula IV are halides (i.e. chlorides, bromides and fluorides), azides, anhydrides, especially mixed anhydrides with strong acids, reactive esters (e.g. N-hydroxysuccinimide esters) and amides (e.g. imidazolides).

The reaction of a 7-amino compound of formula III with an acid of formula IV or a reactive functional derivative thereof can be carried out in a manner known per se. Thus, for example, a free acid of formula IV can be reacted with an aforementioned ester of a compound of formula III in the presence of a carbodiimide such as dicyclohexylcarbodiimide in an inert solvent such as ethyl acetate, acetonitrile, dioxan, chloroform, methylene chloride, benzene or dimethylformamide and subsequently

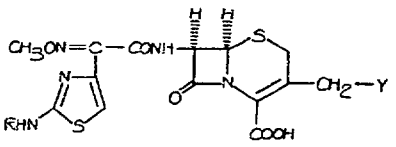
the ester group can be cleaved off. Oxazolium salts (e.g. N-ethyl-5-phenyl-isoxazolium 3'-sulphonate) can be used in place of carbodiimides in the foregoing reaction.

According to another embodiment, a salt of an acid of formula III (e.g. a trialkylammonium salt such as the triethylammonium salt) is reacted with a reactive functional derivative of an acid of formula IV as mentioned earlier in an inert solvent (e.g. one of the aforementioned solvents).

According to a further embodiment, an acid halide, preferably the chloride, of an acid of formula IV is reacted with an amine of formula III. The reaction is preferably carried out in the presence of an acid-binding agent, for example in the presence of aqueous alkali, preferably sodium hydroxide, or in the presence of an alkali metal carbonate such as potassium carbonate or in the presence of a lower alkylamine such as triethylamine. As the solvent there is preferably used water, optionally in admixture with an inert organic solvent such as tetrahydrofuran or dioxan. The reaction can also be carried out in an aprotic organic solvent such as dimethylformamide, dimethyl sulphoxide or hexamethylphosphoric acid triamide. When a silylated compound of formula III is used, the reaction is carried out in an anhydrous medium.

The reaction of a 7-amino compound of formula III with an acid of formula IV or a reactive functional derivative thereof can conveniently be carried out at a temperature between about —40°C and room temperature, for example at about 0°—10°C.

The starting materials of formula II hereinbefore can also be prepared by thiolation, namely by reacting a compound of the general formula



V,

wherein R has the significance given earlier, Y represents a leaving atom or group and the carboxy group can be present in protected form,

with a thiol of the general formula

HS—X VI,

wherein X has the significance given earlier,

and, if desired, cleaving off a carboxy protecting group which may be present.

Examples of leaving atoms and groups denoted by Y in a compound of formula V are halogen atoms (e.g. a chlorine, bromine or iodine atom), acyloxy groups (e.g. lower alkanoyloxy groups such as the acetoxy group), lower alkylsulphonyloxy or arylsulphonyloxy groups (e.g. the mesyloxy or tosyloxy groups) and the azido group. The compound of formula V can be protected at the carboxy group in the same manner as described earlier in connection with the starting materials of formula II.

The reaction of a compound of formula V with a thiol of formula VI can be carried out in a manner known per se; for example, at a temperature between about 40°C and 80°C, conveniently at about 60°C, in a polar solvent, for example in an alcohol such as a lower alkanol (e.g. ethanol, propanol and the like), dimethylformamide or dimethyl sulphoxide, preferably in water or in a buffer solution having a pH of about 6 to 7, preferably 6.5.

In accordance with embodiment (a) of the process provided by the present invention, the amino protecting group denoted by R in a compound of formula II is cleaved off. Protecting groups which are cleavable by acid hydrolysis are preferably removed with the aid of a lower alkanecarboxylic acid which may be halogenated. In particular, formic acid or trifluoroacetic acid is used. The acid hydrolysis is generally carried out at room temperature, although it can be carried out at a slightly elevated or slightly reduced temperature, for example a temperature in the range of about 0°C to +40°C. Protecting groups which are cleavable under alkaline conditions are generally hydrolysed with a dilute aqueous alkali metal hydroxide solution at 0°C to 30°C. The chloroacetyl, bromoacetyl and iodoacetyl protecting groups can be cleaved off by means of thiourea in an acid, neutral or alkaline medium at about 0°C—30°C. Hydrogenolytic cleavage (e.g. cleavage of the benzyl group) is unsuitable in this case, since the oxime group is reduced to the amino group during the hydrogenolysis.

After carrying out embodiment (a) of the process, a carboxy protecting group present in the resulting product can be cleaved off if desired. When the protecting group is a silyl group (silyl ester), this group can be cleaved off especially readily by treatment with water. Lower alkanoyloxyalkyl, alkoxycarbonyloxyalkyl, lactonyl, alkoxymethyl and alkanoylaminomethyl esters are preferably cleaved enzymatically with the aid of a suitable esterase at about 20°C—40°C. When the carboxy group is protected by salt formation (e.g. with triethylamine), then the cleavage of this salt-forming protecting group can be carried out by treatment with an acid. Acids which can be used for this purpose are, for example, hydrochloric acid, sulphuric acid, phosphoric acid or citric acid.

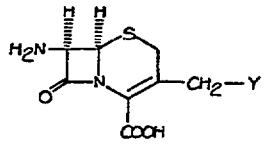
The carboxy protecting group can be cleaved off in the same manner as just described also prior to the cleavage of the protecting group denoted by R.

In order to manufacture a readily hydrolysable ester of a carboxylic acid of formula I in accordance with embodiment (b) of the process provided by the present invention, a carboxylic acid of formula I is preferably reacted with a corresponding halide, preferably an iodide, containing the desired ester group. The reaction can be accelerated with the aid of a base such as an alkali metal hydroxide, an alkali metal carbonate or an organic amine (e.g. triethylamine). If the 2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl group with its enolic function is present, this is etherified with the formation of a corresponding readily hydrolysable ether. In this case there is preferably used an excess of the corresponding halide. The esterification/etherification is preferably carried out in an inert organic solvent such as dimethylacetamide, hexamethylphosphoric acid triamide, dimethyl sulphoxide or, especially, dimethylformamide. The reaction is preferably carried out at a temperature in the range of about 0°—40°C.

The manufacture of the salts and hydrates of compounds of formula I or the hydrates of said salts in accordance with embodiment (c) of the process provided by the present invention can be carried out in a manner known per se; for example, by reacting a carboxylic acid of formula I with an equivalent amount of the desired base, conveniently in a solvent such as water or an organic solvent (e.g. ethanol, methanol, acetone and the like). When a second equivalent of base is used, salt formation also takes place on a tautomeric enol form which may be present (2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl group X), whereby a di-salt is formed. The temperature at which the salt formation is carried out is not critical. The salt formation is generally carried out at room temperature, but it can be carried out at a temperature slightly above or below room temperature, for example in the range of 0°C to +50°C.

The manufacture of the hydrates usually takes place automatically in the course of the manufacturing process or as a result of the hygroscopic properties of an initially anhydrous product. For the controlled manufacture of a hydrate, a completely or partially anhydrous carboxylic acid of formula I or ester, ether or salt thereof can be exposed to a moist atmosphere, e.g. at about +10°C to +40°C.

The 7-amino compounds of formula III hereinbefore can be prepared by reacting a compound of the general formula



VII,

wherein Y represents a leaving atom or group and the carboxy group can be present in protected form,

with a thiol of formula VI hereinbefore. The reaction of a compound of formula VII with a thiol of formula VI can be carried out under the same conditions as those described earlier in connection with the reaction of a compound of formula V with a compound of formula VI.

The compounds of formula V hereinbefore can be prepared from a compound of formula VII and an acid of formula IV or a reactive functional derivative thereof under the same conditions as those described earlier in connection with the reaction of a 7-amino compound of formula III with an acid of formula IV or a reactive functional derivative thereof.

A syn/anti mixture of a compound of formula I which may be obtained can be separated into the corresponding syn and anti forms in the customary manner, for example by recrystallisation or by chromatographical methods using a suitable solvent or solvent mixture.

The compounds of formulae I and II as well as the corresponding readily hydrolysable esters, readily hydrolysable ethers and salts and the hydrates of same have antibiotic, especially bactericidal, activity. They possess a broad spectrum of activity against gram-positive and gram-negative microorganisms, including β-lactamase-forming Staphylococci and various β-lactamase-forming gram-negative bacteria such as, for example, Pseudomonas aeruginosa, Haemophilus influenzae, Escherichia coli, Serratia marcescens and Proteus and Klebsiella species.

The compounds of formulae I and II as well as the corresponding readily hydrolysable esters, readily hydrolysable ethers and salts and the hydrates of same can be used for the treatment and prophylaxis of infectious diseases. A daily dosage of about 0.1 g to about 2 g is envisaged for adults. The parenteral administration of the compounds provided by the present invention is especially preferred.

In order to demonstrate the antimicrobial activity of the compounds provided by the present invention, the following representatives were tested:

Compound A: (6R,7R)-7-[2-(2-Amino-4-thiazolyl)-2-(Z-methoxyimino)acetamido]-3-/[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl/-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Compound B: (6R,7R)-7-[2-[2-(2-Chloroacetamido)-4-thiazolyl]-2-(Z-methoxyimino)acetamido]-3-[[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Activity in vitro: Minimum inhibitory concentration (μg/ml)

		A	B
Haemophilus influenzae	strain 1	0.08	1.2
	strain 2	0.005	0.3
	strain 3	0.005	0.16
	strain 4	0.005	0.16
	strain 5	0.0025	0.08
	strain 6	0.0025	0.16
	strain 7	0.0025	0.16
Klebsiella pneumoniae		1.2	10
Escherichia coli	strain 1	0.02	0.16
	strain 2	0.6	5
Proteus mirabilis	strain 1	≤0.01	0.08
	strain 2	≤0.01	0.16
Proteus vulgaris		≤0.01	0.16
Proteus rettgeri		≤0.01	0.16
Staphylococcus aureus	strain ATCC 6538	2.5	2.5
Penicillin-resistant strain		2.5	5
Pseudomonas aeruginosa	strain 1	0.3	1.2
	strain 2	10	>80
	strain 3	2.5	40
	strain 4	5	80
	strain 5	5	80
	strain 6	10	80
	strain 7	5	80
Serratia marcescens		0.08	2.5

Activity in vivo

Groups of 5 mice are infected intraperitoneally with an aqueous suspension of Escherichia coli. The test substance is administered subcutaneously in physiological sodium chloride solution three times, i.e. 1 hour, 2.5 hours and 4 hours, after the infection. The number of surviving animals is determined on the fourth day. Various dosages are administered and the dosage at which 50% of the test animals survive (CD_{50}, mg/kg) is determined by interpolation.

Test substance	A	B
CD_{50}, mg/kg	≤0.005	0.16

Toxicity

Test substance		A	B
LD_{50}, mg/kg	i.v.	250—500	250—500
	s.c.	>4000	2000—4000
	p.o.	>5000	>5000

The cephalosporin derivatives provided by the present invention can be used as medicaments, for example in the form of pharmaceutical preparations which contain them in association with a compatible carrier material. This carrier material can be an organic or inorganic inert carrier material which is suitable for enteral or parenteral administration such as, for example, water, gelatin, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkyleneglycols, petroleum jelly etc. The pharmaceutical preparations can be made up in solid form (e.g. as tablets, dragées, suppositories or capsules) or in liquid form (e.g. as solutions, suspensions or emulsions). The pharmaceutical preparations may be sterilised and/or may contain adjuvants such as preserving, stabilising, wetting or emulsifying agents, salts for varying the osmotic pressure, anaesthetics or buffers. The pharmaceutical preparations can also contain other therapeutically valuable substances. The compounds of formula I and their salts and hydrates are especially suitable for parenteral administration and for this purpose they are preferably made up in the form of lyophilisates or dry powders for dilution with custmoary agents such as water or isotonic sodium chloride solution. The readily hydrolysable esters and readily hydrolysable ethers of the compounds of formula I and their salts or hydrates are also suitable for enteral administration.

The following Examples illustrate the process provided by the present invention:

EXAMPLE 1

Manufacture of the disodium salt of (6R,7R)-7-2-[2-(2-amino-4-thiazolyl)-2-(Z-methoxyimino)acetamido]-3-/[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl/-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

15.3 g of (6R,7R)-7-/2-[2-(2-chloroacetamido)-4-thiazolyl]-2-(Z-methoxyimino)acetamido/-3-/[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl/-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (fraction I, see hereinafter) are suspended in 150 ml of water together with 5 g of thiourea. While gassing well with nitrogen and stirring thoroughly the pH is adjusted to 6.8—7.0 with saturated sodium hydrogen carbonate solution, there being obtained an orange coloured solution. The pH of the solution is kept constant at 6.8 for 6 hours by adding sodium hydrogen carbonate solution by means of an autotitrator. Thereafter, a further 2.5 g of thiourea are added and the solution is stirred for a further 3 hours, the pH being kept at 6.8 by adding saturated sodium hydrogen carbonate solution. Thereafter, the red solution is stored overnight in a refrigerator, whereby it becomes darker. The pH of this solution is adjusted to 2.0—2.5 by adding 100% formic acid, whereby the substance separates out. The precipitate is filtered off under suction and washed with 100 ml of 10% formic acid. The mother liquor is discarded. The brownish material on the suction filter is suspended in 200 ml of water and the pH is adjusted to 7 with triethylamine, a brown solution being obtained. This solution is stirred with 2 g of active carbon for 30 minutes, the carbon is filtered off and the filtrate, which is still brown, is adjusted to pH 3.5 with 100% formic acid while stirring well. The substance which thereby precipitates out is filtered off under suction, washed with 50 ml of 10% formic acid and discarded. The dark yellow filtrate is adjusted to pH 2—2.5 with 100% formic acid, whereby the substance precipitates out. This precipitate is filtered off under suction, washed with ice-water and dried. For conversion into the disodium salt, the cephalosporin acid obtained is suspended in a mixture of 40 ml of acetone and 40 ml of water and treated with 20 ml of a 2-N solution of the sodium salt of 2-ethylcaproic acid in ethyl acetate. 50 ml of acetone are added to the thus-obtained orange coloured solution, whereby there separates out a brown resin which is separated off by filtration. The yellow filtrate is stirred for 30 minutes, whereby the disodium salt crystallises. The mixture is treated portionwise with 50 ml of acetone and stored overnight in a refrigerator. The crystallite is filtered off under suction, washed successively with an acetone/water mixture (85:15), pure acetone and low-boiling petroleum ether and dried overnight at 40°C in vacuo. The title substance is obtained in the form of beige crystals; $[\alpha]_D^{20} = -144°$ (c = 0.5 in water). The nuclear magnetic resonance spectrum and the microanalysis correspond to the structure indicated.

The (6R,7R)-7-/2-[2-(2-chloroacetamido)-4-thiazolyl]-2-(Z-methoxyimino)acetamido/-3-/[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl/-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid used as the starting material can be prepared as follows:

22.24 g of 2-(2-chloroacetamido-thiazol-4-yl)-2-(Z-methoxyimino)-acetic acid are suspended in

240 ml of methylene chloride. 13.39 ml of triethylamine are added to this suspension, a light brown solution being obtained. This solution is cooled to 0°—5°C and treated with 16.72 g of phosphorus pentachloride. The mixture is stirred for 5 minutes at 0°—5°C and for 20 minutes without cooling. The resulting yellow solution is evaporated at 35°C in vacuo. The evaporation residue is shaken twice with n-heptane and the latter is decanted off. The resinous residue is treated with 240 ml of tetrahydrofuran and the undissolved triethylamine hydrochloride is filtered off. The yellow filtrate contains the acid chloride.

22 g of (7R)-7-amino-3-desacetoxy-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]-cephalosporanic acid are suspended in a mixture of 300 ml of water and 150 ml of tetrahydrofuran. 2-N sodium hydroxide is added dropwise to the suspension with the aid of an autotitrator while gassing well with nitrogen until a brown-red solution having a pH of 8 is obtained. This solution is cooled to 0°—5°C and treated dropwise during 15 minutes with the solution of the acid chloride in tetrahydrofuran prepared as described in the preceding paragraph. Thereafter, the mixture is stirred at 25°C for 2.5 hours. The pH of the mixture is held constant at 8 by adding 2-N sodium hydroxide. The almost black solution is freed from tetrahydrofuran at 40°C in vacuo. 100 ml of 2-N sulphuric acid are now added. The substance which thereby precipitates out is filtered off under suction, washed with water and filtered off well under suction. The moist brown material on the suction filter is dissolved in 1.5 litres of acetone. The dark solution is filtered off through Hyflo from a small amount of dark undissolved material, treated with carbon, stirred for 30 minutes and again filtered through Hyflo. The orange-red filtrate is dried over sodium sulphate, concentrated in vacuo and evaporated with ethyl acetate. A black resin thereby precipitates out. This resin is filtered off and discarded. The 2-phase filtrate which still contains water is subjected to azeotropic distillation three times with benzene at 40°C in vacuo. The substance which thereby precipitates out is filtered off under suction and dried at 40°C in vacuo. This substance is stirred up twice with 1 litre of acetone each time, there remaining a brown resin which is discarded. The combined orange coloured acetone extracts are concentrated to ca 150 ml at 40°C in vacuo, a brown resin being filtered off and discarded. The filtrate is treated with 1 litre of ethyl acetate and concentrated at 40°C in vacuo. The substance which thereby precipitates out is filtered off under suction, washed with ethyl acetate and then with ether [(6R,7R)-7-[2-[2-(2-chloroacetamido)-4-thiazolyl]-2-(Z-methoxyimino)acetamido]-3-[[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, fraction I; a beige, amorphous acid]. This fraction I can be used directly for the manufacture of the desired cephalosporin derivative.

The ethyl acetate mother liquor is concentrated extensively at 40°C in vacuo, diluted with ether and the precipitated substance is filtered off under suction [(6R,7R)-7-[2-[2-(2-chloroacetamido)-4-thiazolyl]-2-(Z-methoxyimino)acetamido]-3-[[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, fraction II; a light beigeamorphous acid, somewhat purer than fraction I according to thin-layer chromatography].

For the manufacture of the disodium salt, 3.5 g of the acid (fraction II) are dissolved in a mixture of 20 ml of acetone and 11 ml of water. The solution is treated with 7 ml of a 2-N solution of the sodium salt of 2-ethylcaproic acid in ethyl acetate, whereby the disodium salt crystallises. A further 25 ml of acetone are now added portionwise and the mixture is stored in a deep-freeze cabinet for 2 hours. Thereafter, the crystallisate is filtered off under suction, washed successively with 25 ml of an ice-cold acetone/water mixture (80:20), pure acetone and low-boiling petroleum ether and dried overnight at 40°C in a high vacuum. There is obtained the disodium salt of (6R,7R)-7-[2-[2-(2-chloroacetamido)-4-thiazolyl]-2-(Z-methoxyimino)acetamido]-3-[[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid in the form of light yellow crystals; $[\alpha]_D^{20} = -142.7°$ (c = 1 in water). The nuclear magnetic resonance spectrum and the microanalysis correspond to the structure indicated.

EXAMPLE 2

Manufacture of the sodium salt of (6R,7R)-7-[2-(2-amino-4-thiazolyl)-2-(methoxyimino)acetamido]-8-oxo-3-[[(1,4,5,6-tetrahydro-4-methyl-5,6-dioxo-as-triazin-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

19 g of (6R,7R)-7-[2-[2-(2-chloroacetamido)-4-thiazolyl]-2-(methoxyimino)acetamido]-8-oxo-3-[[(1,4,5,6-tetrahydro-4-methyl5,6-dioxo-as-triazin-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid are suspended in 150 ml of water together with 9.5 g of thiourea. The pH is adjusted to 6.8 with 5% sodium hydrogen carbonate solution while gassing with nitrogen and stirring, there being obtained a yellow-orange solution. The pH of the solution is held constant at 6.8—7.0 for 6 hours by adding sodium hydrogen carbonate solution by means of an autotitrator. 100% formic acid is added to the orange coloured solution until the pH is 3.5. The precipitated material is filtered off under suction and washed with 100 ml of 10% formic acid. This material is denoted as ①. The filtrate is adjusted to pH 2.5 by adding 100% formic acid, whereby additional substance precipitates out. The mixture is held in an ice-bath for 1 hour, the precipitated substance is then filtered off and washed with a small amount of ice-water. This material is denoted as fraction I. The aforementioned orange-brown material ① is suspended in 250 ml of water. The suspension is adjusted to pH 7 with 2-N sodium

hydroxide, there being obtained an orange-brown solution. Additional 100% formic acid is added to this solution until the pH is 3.5. The material which thereby precipitates out is filtered off under suction and discarded. The filtrate is adjusted to pH 2.5 with 100% formic acid, whereby additional substance precipitates out. The mixture is held in an ice-bath for 1 hour, the precipitated substance is then filtered off under suction and washed with a small amount of ice-water. This material is denoted as fraction II. Fractions I and II are suspended together in 500 ml of ethanol and evaporated in a rotary eveporator in order to remove water. After adding ether, the mixture is filtered under suction and the precipitate is washed successively with ether and low-boiling petroleum ether. There is thus obtained the title substance in the form of a yellowish solid material which is denoted as A.

The mother liquors and washings of fractions I and II are concentrated from a volume of ca 1.7 litres to 250 ml, the pH is adjusted to 2.5 with 100% formic acid and the solution is stored overnight in a refrigerator, whereby further substance crystallises. This is filtered off under suction and washed with a small amount of water. The residue on the suction filter is azeotropically distilled with ethanol. There is obtained solid, almost colourless title substance which is denoted as B. B is purer than A according to thin-layer chromatography.

In order to obtain pure title substance, the acid B is suspended in 150 ml of methanol and treated while stirring with 10 ml of a 2-N solution of the sodium salt of 2-ethylcaproic acid in ethyl acetate. After ca 10 minutes, there results a solution which is treated with 100 ml of ethanol. The mixture is extensively concentrated at 40°C in vacuo. The sodium salt precipitates out in amorphous form after adding ethanol. This salt is filtered off under suction, washed successively with ethanol and low-boiling petroleum ether and dried at 40°C in a high vacuum. There is obtained the title substance in the form of an almost colourless amorphous powder; $[\alpha]_D^{20} = -42.9°$ (c = 1 in water).

The title substance exists as a Z/E mixture (90:10) according to the nuclear magnetic resonance spectrum. The microanalysis likewise agrees with the structure indicated.

The (6R,7R)-7-[2-[2-(2-chloroacetamido)-4-thiazolyl]-2-(methoxyimino)acetamido]-8-oxo-3-[[(1,4,5,6-tetrahydro-4-methyl-5,6-dioxo-as-triazin-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid used as the starting material can be prepared as follows:

44 g of (7R)-7-amino-3-desacetoxy-3-[(1,4,5,6-tetrahydro-4-methyl-5,6-dioxo-as-triazin-3-yl)thio]-cephalosporanic acid are suspended in a mixture of 600 ml of water and 300 ml of tetrahydrofuran. 2-N sodium hydroxide is added dropwise to the suspension with the aid of an autotitrator while gassing well with nitrogen until a brown solution having a pH of 7.8 is obtained. This solution is cooled to 0°—5°C and treated dropwise during 15 minutes with a solution of 2-(2-chloroacetamido-thiazol-4-yl)-2-(Z-methoxyimino)-acetic acid chloride in tetrahydrofuran (prepared from 44.5 g of the corresponding acid in a manner analogous to that described in Example 1). Thereafter, the mixture is stirred at 25°C and pH 8 for 2.5 hours. The pH of the mixture is held constant at 7.8—8 by adding 2-N sodium hydroxide using an autotitrator. The dark solution is freed from tetrahydrofuran at 40°C in vacuo. Thereafter, the solution is diluted with water to a volume of 2 litres. The pH is adjusted to 2 with 2-N sulphuric acid. The substance which thereby precipitates out is filtered off under suction, washed with 1 litre of water and dried at 40°C in vacuo for 2 days. For purification, the dried substance is firstly dissolved in a mixture of 100 ml of water and 300 ml of acetone. The dark solution is diluted with acetone to a volume of 2 litres. The dark material which thereby precipitates out is filtered off and discarded. The filtrate is treated with 1 litre of ethyl acetate and 1 litre of solvent is evaporated off at 40°C in vacuo. The solution is now diluted with 2 litres of ethyl acetate. The beige-brown substance which thereby precipitates out is discarded. The filtrate is extensively concentrated at 40°C in vacuo. The acid which thereby crystallises out is filtered off under suction. For recrystallisation, the acid is firstly dissolved in 800 ml of methanol at reflux. The solution is cooled down to 25°C and filtered off from a small amount of orange coloured substance. The yellow filtrate is stirred in an ice-bath for 1.5 hours, whereby the acid crystallises. The acid is filtered off under suction, washed successively with methanol and low-boiling petroleum ether and dried at 25°C in vacuo. There is thus obtained the desired starting material in the form of beige crystals. The starting material exists as a Z/E mixture (75:25) according to the nuclear magnetic resonance spectrum. $[\alpha]_D^{20} = -127.9°$ (c = 1 in dimethylformamide).

EXAMPLE 3

Manufacture of methylene-(6R,7R)-7-[2-(2-amino-4-thiazolyl)-2-(Z-methoxyimino)acetamido]-3-[[2,5-dihydro-2-methyl-5-oxo-6-[(pivaloyloxy)methoxy]-as-triazin-3-yl]thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate pivalate.

1.85 g of the cephalosporin disodium salt manufactured as described in Example 1 are suspended in 50 ml of dimethylformamide and treated with 1.35 g of pivaloyloxymethyl iodide at 0°—5°C while gassing with nitrogen. The mixture is stirred at 0°—5°C for 30 minutes and thereafter poured into 500 ml of ethyl acetate. The mixture is washed three times with water, twice with 5% sodium hydrogen carbonate solution and finally again with water. The solution is dried over sodium sulphate and extensively concentrated at 35°C in vacuo. The title substance precipitates out in amorphous form after adding ether. This substance is filtered off under suction, washed with ether and low-boiling petroleum ether and dried at 25°C overnight in a high vacuum. The title substance is obtained in the form of a

beige amorphous powder. The nuclear magnetic resonance spectrum and the microanalysis are in agreement with the structure indicated.

The following Examples illustrate pharmaceutical preparations containing the cephalosporin derivatives provided by the present invention:

EXAMPLE A

Manufacture of dry ampoules for intramuscular administration:

A lyophilisate of 1 g of the disodium salt of (6R,7R)-7-[2-(2-amino-4-thiazolyl)-2-(Z-methoxyimino)acetamido]-3-{[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid is prepared in the usual manner and filled into an ampoule. Prior to the administration, the lyophilisate is treated with 2.5 ml of a 2% aqueous lidocaine hydrochloride solution.

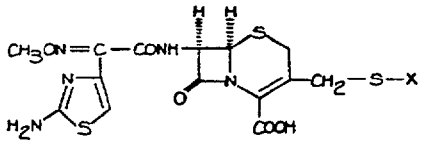
EXAMPLE B

Interlocking gelatin capsules each containing the folliwing ingredients are manufactured in the usual manner:

Methylene-(6R,7R)-7-[2-(2-amino-4-thiazolyl)-2-(Z-methoxyimino)acetamido]-3-{[(2,5-dihydro-2-methyl-5-oxo-6-[(pivaloyloxy)methoxy]-as-triazin-3-yl]thio}methyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylate pivalate	500 mg
Luviskol (water-soluble polyvinylpyrrolidone)	20 mg
Mannitol	20 mg
Talc	15 mg
Magnesium stearate	2 mg
	557 mg

CLAIMS

1. Compounds of the general formula



I,

in which X represents the 1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-as-triazin-3-yl group, the 2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl group or the 1,4,5,6-tetrahydro-4-methyl-5,6-dioxo-as-triazin-3-yl group,

as well as readily hydroylsable esters, readily hydrolysable ethers and salts of these compounds and hydrates of the compounds of formula I and of their esters, ethers and salts.

2. Compounds of formula I given in claim 1, wherein X represents the 1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-as-triazin-3-yl group or the 2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl group, as well as salts of these compounds and hydrates of these compounds and salts.

3. Compounds of formula I given in claim 1, wherein X represents the 1,4,5,6-tetrahydro-4-methyl-5,6-dioxo-as-triazin-3-yl group, as well as salts of these compounds and hydrates of these compounds and salts.

4. (6R,7R)-7-[2-(2-Amino-4-thiazolyl)-2-(Z-methoxyimino)acetamido]-3-{[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid as well as salts of this compound and hydrates of this compound and salts.

5. Readily hydrolysable esters of the compounds of formula I set forth in any one of claims 1 to 4 as well as salts of these esters and hydrates of these esters and salts.

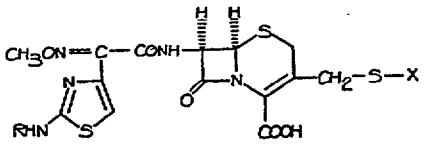
6. Readily hydrolysable ethers of the compounds of formula I set forth in any one of claims 1 to 4 as well as salts of these ethers and hydrates of these ethers and salts.

7. Pivaloyloxymethyl esters of the compounds of formula I set forth in any one of claims 1 to 4 as well as salts of these esters and hydrates of these esters and salts.

8. Methylene-(6R,7R)-7-[2-(2-amino-4-thiazolyl)-2-(Z-methoxyimino)acetamido]-3-{[(2,5-

dihydro-2-methyl-5-oxo-6-[(pivaloyloxy)methoxy]-as-triazin-3-yl]thio/methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate pivalate as well as salts of this compound and hydrates of this compound and salts.

9. Compounds of the general formula



II

in which X represents the 1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-as-triazin-3-yl group, the 2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl group or the 1,4,5,6-tetrahydro-4-methyl-5,6-dioxo-as-triazin-3-yl group, R represents a cleavable protecting group and the carboxy group can be present in protected form.

10. Compounds according to claim 9, wherein X represents the 1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-as-triazin-3-yl group or the 2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl group.

11. (6R,7R)-7-/2-[2-(2-Chloroacetamido)-4-thiazolyl]-2-(Z-methoxyimino)acetamido/-3-/[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl/-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

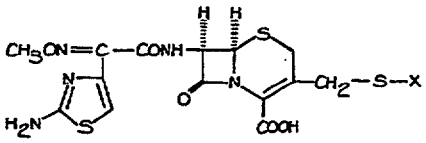
12. Compounds as set forth in any one of claims 1 to 8 as pharmaceutically active substances.

13. (6R,7R)-7-[2-(2-Amino-4-thiazolyl)-2-(Z-methoxyimino)acetamido]-3-/[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl/-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid as well as salts of this compound and hydrates of this compound and salts as pharmaceutically active substances.

14. Compounds as set forth in any one of claims 1 to 8 as pharmaceutically active substances for the treatment and prophylaxis of infectious diseases.

15. (6R,7R)-7-[2-(2-Amino-4-thiazolyl)-2-(Z-methoxyimino)acetamido]-3-/[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl/-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid as well as salts of this compound and hydrates of this compound and salts as pharmaceutically active substances for the treatment and prophylaxis of infectious diseases.

16. A pharmaceutical preparation which contains a compound of the general formula



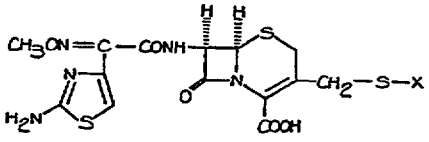
I,

wherein X represents the 1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-as-triazin-3-yl group, the 2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl group or the 1,4,5,6-tetrahydro-4-methyl-5,6-dioxo-as-triazin-3-yl group,

or a readily hydrolysable ester, readily hydrolysable ether or salt of such a compound or a hydrate of a compound of formula I or of an ester, ether or salt thereof.

17. A pharmaceutical preparation according to claim 16 which contains (6R,7R)-7-[2-(2-amino-4-thiazolyl)-2-(Z-methoxyimino)acetamido]-3-/[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl/-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid or a salt of this compound or a hydrate of this compound or of a salt thereof.

18. A pharmaceutical preparation for the treatment and prophylaxis of infectious diseases which contains a compound of the general formula



I,

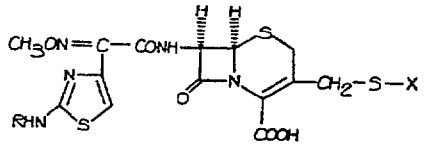
wherein X represents the 1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-as-triazin-3-yl group, the 2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl group or the 1,4,5,6-tetrahydro-4-methyl-5,6-dioxo-as-triazin-3-yl group,

or a readily hydrolysable ester, readily hydrolysable ether or salt of such a compound or a hydrate of a compound of formula I or of an ester, ether or salt thereof.

19. A pharmaceutical preparation according to claim 18 which contains (6R,7R)-7-[2-(2-amino-4-thiazolyl)-2-(Z-methoxyimino)acetamido]-3-/[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl/-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid or a salt of this compound or a hydrate of this compound or of a salt thereof.

20. A process for the manufacture of the cephalosporin derivatives set forth in any one of claims 1 to 8, which process comprises

(a) cleaving off the protecting group R (and, if desired, also a carboxy protecting group which may be present) in a compound of the general formula



II,

wherein X has the significance given in claim 1, R represents a cleavable protecting group and the carboxy group can be present in protected form,

or

(b) for the manufacture of a readily hydrolysable ester or ether of a compound of formula I, subjecting a carboxylic acid or an enol of formula I to a corresponding esterification or etherification,

or

(c) for the manufacture of salts or hydrates of a compound of formula I or hydrates of said salts, converting a compound of formula I into a salt or hydrate or into a hydrate of said salts.

21. The use of the compounds set forth in any one of claims 1 to 8 in the treatment or prophylaxis of diseases.

22. The use of (6R,7R)-7-[2-(2-amino-4-thiazolyl)-2-(Z-methoxyimino)acetamido]-3-/[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl/-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid as well as salts of this compound and hydrates of this compound and salts in accordance with claim 21.

23. The use of the compounds set forth in any one of claims 1 to 8 in the treatment or prophylaxis of infectious diseases.

24. The use of (6R,7R)-7-[2-(2-amino-4-thiazolyl)-2-(Z-methoxyimino)acetamido]-3-/[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl/-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid as well as salts of this compound and hydrates of this compound and salts in accordance with claim 23.

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