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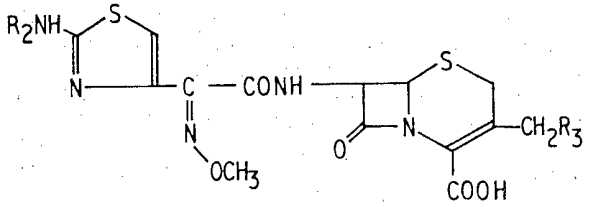
(54) NEW CEPHALOSPORINS

(71) We, TAKEDA YAKUHIN KOGYO KABUSHIKI KAISHA also known as TAKEDA CHEMICAL INDUSTRIES LTD., a body corporate organised under the laws of Japan of 27 Doshomachi 2-chome, Higashi-ku, Osaka, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

This invention relates to novel cephalosporin derivatives having a novel 7-acyl group and to processes for the production thereof. More particularly, this invention relates to 7-[2-(2-aminothiazol-4-yl)- 2-(*syn*)-methoxyiminoacetamido] -cephalosporin derivatives of the formula (I):

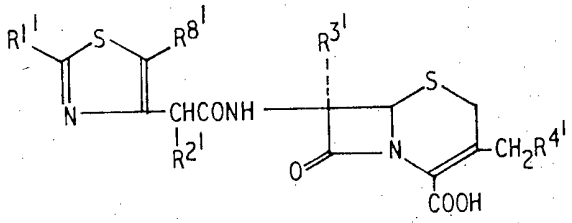


(1)

wherein R_3 is hydrogen or a residue of a nucleophilic compound; and R_2NH is an amino group which may optionally be protected,
and pharmaceutically acceptable salts or esters thereof, and also relates to processes for the production of the compounds (I) and their pharmaceutically acceptable salts or esters.

Heretofore, studies on synthetic cephalosporin derivatives have been directed to the conversion of 7-aminocephalosporanic acid into various acyl derivatives at the 7-position, or to derivatives at the 3-position, in order to synthesize compounds having a broad anti-bacterial spectrum or a specific anti-bacterial spectrum. However, known cephalosporin derivatives are not satisfactory in their anti-bacterial activity against a wide variety of micro-organisms.

Under these circumstances, we had found certain cephalosporin derivatives represented by the following formula:



wherein $R^{1'}$ represents an amino or hydroxyl group which may be protected; $R^{2'}$ represents an amino or hydroxyl group or a group convertible into one or the other of these groups; $R^{3'}$ represents hydrogen or a methoxy group or a group convertible into the methoxy group, $R^{4'}$ represents hydrogen or a residue of a nucleophilic compound and $R^{8'}$ represents hydrogen or halogen or pharmaceutically acceptable salts or esters thereof.

We have further found that compounds of the formula (I) are highly active against a broad spectrum of gram-positive and gram-negative bacteria including *Serratia marcescens, Proteus morganii*, and also that the compounds (I) are effective against β-lactamase-producing bacteria. This invention have accomplished on the basis of these findings.

In the compounds of formula (I), R_3 is hydrogen or a residue of a nucleophilic compound. As examples of residues of nucleophilic compounds which are represented by R_3 we may mention hydroxy; mercapto; acyloxy derived from lower aliphatic carboxylic acid having 2 to 4 carbon atoms, which may optionally be substituted by oxo, carboxy or ethoxycarbamoyl (e.g. acetyloxy, propionyloxy, 3-oxobutyryloxy, 3-carboxypropionyloxy, 3-ethoxycarbamoylpropionyloxy or 4-carboxybutyryloxy); acyloxy derived from aromatic carboxylic acid, which may optionally be substituted by hydroxy, carboxy, carboethoxycarbamoyl or carboethoxysulfamoyl, (e.g. mandelyloxy, 2-carboxybenzoyloxy, 2-(carboethoxycarbamoyl)-benzoyloxy, 2-(carboethoxysulfamoyl)- benzoyloxy); carbamoyloxy; cyano; azido; amino; carbamoylthio; thiocarbamoyloxy; carbamoyloxy whose amino group is protected by a conventional protecting group for the amino function (e.g. N-mono-, di- and trihalogenoacetylcarbamoyloxy groups such as e.g. N-chloroacetylcarbamoyloxy, N-dichloroacetylcarbamoyloxy, N-trichloroacetylcarbamoyloxy, N-chlorosulfonylcarbamoyloxy or N-trimethylsilylcarbamoyloxy); and phenylglycyloxy. These residues of a nucleophilic compound may be substituted, the number of substituents being normally from 1 to 2. Thus, the substituents on the residues which have been mentioned above may, for example, be alkyls (such as lower alkyls of 1 to 3 carbon atoms, e.g. methyl, ethyl or propyl and acyl groups (such as acyls derived from lower aliphatic carboxylic acid having 2 to 4 carbon atoms, e.g. acetyl, propionyl or butyryl; acyls derived from aromatic carboxylic acids, e.g. benzoyl, *p*-chlorobenzoyl, *p*-methylbenzoyl or mandeloyl. The residue of a nucleophilic compound represented by R_3 may alternatively be a quaternary ammonium group. The residue represented by R_3 may further be a heterocyclic ring attached through S (sulphur atom), i.e. a heterocyclic ring thio group represented by the formula -S-heterocyclic ring. The heterocyclic ring mentioned above is a five- or six-membered ring including 1 to 4 hetero-atoms consisting of oxygen, sulphur or nitrogen atoms, and the nitrogen atom or atoms may be in oxide form. It follows, therefore, that the heterocyclic group (i.e. the group derived from the heterocyclic compound corresponding to the heterocyclic ring) may usually be one of the following and other groups: pyridyl; N-oxidopyridyl; pyrimidyl; pyridazinyl, N-oxidopyridazinyl; pyrazolyl; diazolyl such as pyrazolyl, imidazolyl; thiazolyl such as 1,2-thiazolyl, 1,3-thiazolyl; thiadiazolyl such as 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl; oxadiazolyl such as 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl; triazolyl such as 1,2,3-triazolyl, 1,2,4-triazolyl; tetrazolyl such as 1H-tetrazolyl, and 2H-tetrazolyl. Such hetero groups may each carry substituents such as lower alkyls of 1 to 3 carbon atoms (e.g. methyl, ethyl, *i*-propyl or allyl), lower alkoxy groups of 1 to 3 carbon atoms (e.g. methoxy, ethoxy or propoxy), halogens (e.g. chlorine or bromine), trihalogeno-lower alkyls (e.g. trifluoromethyl or trichloroethyl), hydroxyl, mercapto, amino, carboxyl, carbamoyl or di-lower alkyl (having 1 to 3 carbon atoms) amino lower alkyl of 1 to 3 carbon atoms (e.g. dimethylaminoethyl or dimethylaminomethyl), carboxymethyl, carbamoylmethyl, carboxymethylthio, sulfomethyl or methoxycarbonylamino.

The number of such substituents that may occur on the heterocyclic group is normally in the range of 1 to 2. The quaternary ammonium group represented by R_3 may, for example, by pyridinium which may optionally be substituted by one of methyl, halogen, carbamoyl, N-hydroxymethylcarbamoyl, carbomethoxycarbamoyl, cyanocarbamoyl, carboxymethyl, hydroxymethyl or trifluoromethyl, e.g. pyridinium, 3-methylpyridinium, 4-methylpyridinium, 3-chloropyridinium, 3-bromopyridinium, 3-iodopyridinium, 4-carbamoylpyridinium, 4-(N-hydroxymethylcarbamoyl)-pyridinium, 4-(N-carbomethoxycarbamoyl)-pyridinium, 4-(N-cyanocarbamoyl)-pyridinium, 4-(carboxymethyl)-pyridinium, 4-(hydroxymethyl)-pyridinium, 4-(trifluoromethyl)-pyridinium; quinolinium; picolinium and lutidinium.

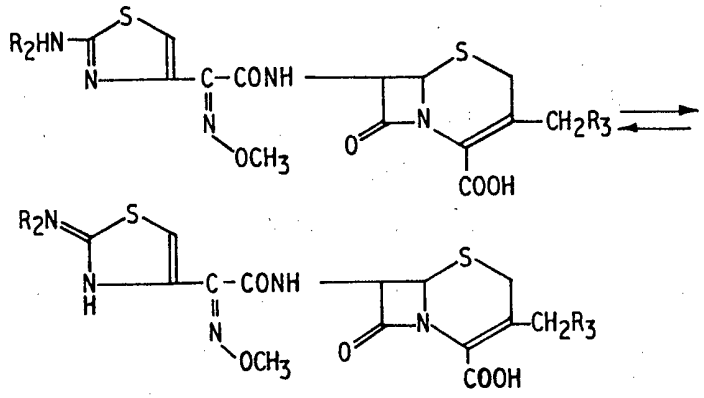
Referring to compounds of the formula (I), the group represented by R_3 is preferably hydrogen, carbamoyloxy, acyloxy derived from lower aliphatic carboxylic acid having 2 to 4 carbon atoms such as acetyloxy, or the heterocyclic-thio group whose heterocyclic group is unsubstituted or substituted.

The preferred substituents of the heterocyclic group of the heterocyclic-thio group are one or two members of lower alkyl (C_{1-4}), di-lower alkyl (C_{1-4}) amino-substituted lower alkyl

(C_{1-4}), carboxymethyl, amino, methoxycarbonylamino, carbamoylmethyl, carboxymethylthio or sulfomethyl. Among them the preferred R^3 groups are carbamoyloxy, 1-methyl-1H-tetrazol-5-ylthio, 2-methyl-1,3,4- thiadiazol-5-ylthio or 1,2-dimethyl-1,3,4- triazol-5-ylthio.

Where R_3 is a carbamoyloxy group whose amino group has been protected, e.g. N-chloroacetylcarbamoyloxy, N-dichloroacetylcarbamoyloxy or N-trichloroacetylcarbamoyloxy, such protective group for the amino group may be removed by a procedure similar to that used for removing the protective group from the protected amino group represented by R_2NH-, which is described hereinafter. Generally, the compound (I) is employed with its amino and carbamoyloxy group (where R_1 is carbamoyloxymethyl) being free and unprotected, as an active compound. An amino group which may optionally be protected is indicated by R_2NH. Therefore, R_2 means hydrogen or a protective group for the amino function, the latter being any of the *per se* known protective groups generally used for the protection of amino, i.e. conventional protective groups for the amino function. Thus, such protective groups include, among others, aromatic acyl groups such as phthaloyl, benzoyl, benzoyl substituted by halogen, nitro or a lower alkyl of 1 to 4 carbon atoms (e.g. chlorobenzoyl, *p*-nitrobenzoyl, *p*-tert-butylbenzoyl or toluoyl), naphthoyl; phenylacetyl; phenoxyacetyl; benzenesulfonyl; benzenesulfonyl substituted by a lower alkyl of 1 to 4 carbon atoms (e.g. *p*-tert-butylbenzenesulfonyl or toluenesulfonyl); acyl derived from aliphatic or halogenated aliphatic carboxylic acid such as acetyl, valeryl, caprylyl, *n*-decanoyl, acryloyl, pivaloyl or halogenoacetyl (e.g. monochloroacetyl, monobromoacetyl, dichloroacety or trichloroacetyl); camphorsulfonyl; methanesulfonyl; esterified carboxyl groups such as ethoxycarbonyl, tert-butyloxycarbonyl, isobornyloxycarbonyl, phenyloxycarbonyl, trichloroethoxycarbonyl or benzyloxycarbonyl; carbamoyl groups such as methylcarbamoyl, phenylcarbamoyl or naphthylcarbamoyl and the corresponding thiocarbamoyl groups.

The cephalosporin derivative of the formula (I) is thought to take a tautomeric form,i.e. a 2-aminothiazole compound and a 2-iminothiazoline compound, as shown below, although it is described as the thiazole compound throughout this specification:



While the carboxyl group in the 4-position of the compound of the formula (I) may be free, it may form a salt, for example with a non-toxic cation such as an alkali metal, e.g. sodium or potassium; a basic amino acid, e.g. arginine, ornithine, lysine or histidine; or a polyhydroxyalkylamine, e.g. N-methylglucamine, diethanolamine, triethanolamine or trishydroxymethylaminomethane. The compound (I) may form an acid salt with an inorganic acid such as hydrogen chloride or sulfuric acid, or with an organic acid such as toluenesulfonic acid or benzenesulfonic acid. The 4-carboxyl group may also be one of those biologically active ester forms which conduce, for example, to increase of blood levels and prolonged efficacy. Such ester residues include lower alkoxymethyl groups, e.g. methoxymethyl, ethoxymethyl, isopropoxymethyl, α-methoxyethyl or α-ethoxyethyl; α-lower alkoxy-α-substituted methyl groups such as α-lower alkoxy (C_{1-4}) ethyl (e.g. methoxyethyl, ethoxyethyl, propoxyethyl or i-propoxyethyl); lower alkylthiomethyl groups of 1 to 3 carbon atoms, e.g. methylthiomethyl, ethylthiomethyl or isopropylthiomethyl; acyloxymethyl groups, e.g. pivaloyloxy methyl or α-acetoxymethyl; ethoxycarbonyloxy-1-methylmethyl; or α-acyloxy-α- substituted methyl groups (e.g. α-acetoxy- α-methylmethyl). These salts and esters of compounds (I) also fall within the scope of the present invention.

As in the case of the known cephalosporins or penicillins, the compounds (I) according to this invention may be administered in such dosage forms as injections, capsules, tablets or granules. Thus, the compounds (I) are novel compounds which show high activity against a

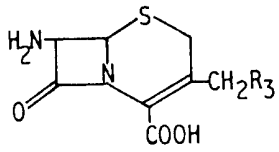
broad spectrum of bacteria including gram-negative bacteria, such as *Escherichia coli, Serratia marcescens, Proteus rettgeri, Enterobacter cloacae* and *Citrobacter freundii*, and are resistant to β-lactamase.

The compounds (I) may be used, for example as disinfectans for removing the aforesaid microorganisms from surgical instruments or as ant-infective agents. Where the compounds (I) are employed as anti-infective agents, for example for the treatment of intraperitoneal infections, respiratory organ infections, urinary tract infections and other infectious diseases caused by the aforementioned microorganisms, they may be safely administered to mammals including humans, mice and rats at a daily dose level of 0.5 to 80 mg per kilogram body weight, preferably 1 to 20 mg on the same basis, in 3 to 4 instalments daily.

The compounds (I) may be administered orally or parenterally in varied dosage forms such as injections, capsules, powders, granules and tablets which may be manufactured by established or known procedures. Where the compound (I) is used as an injection, the carrier may, for example, be distilled water or physiological saline. In the case when the compound (I) is used as a capsule, powder, granule or tablet, the compound (I) may be employed, for example, in admixture with pharmacologically acceptable, *per se* known excipients (e.g. starch, lactose, sucrose, calcium carbonate or calcium phosphate), binders (starch, gum arabic, carboxymethyl-cellulose, hydroxypropylcellulose or crystalline cellulose), lubricants (e.g. magnesium stearate or talc), and disintegrating agents (e.g. carboxymethyl calcium or talc).

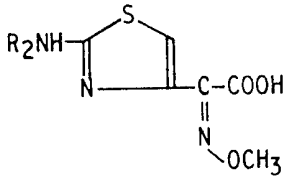
The compounds (I) of this invention may be produced by techniques which are known *per se*.

(1) Thus, the cephalosporin derivative of the formula (I) may be produced by acylating the 7-amino group of a 7-aminocephalosporin compound of the formula (II):



(II)

wherein R_3 is as previously defined with a 2-(2-aminothiazol-4-yl)-2-(*syn*)-methoxyiminoacetic acid of the formula (III):



(III)

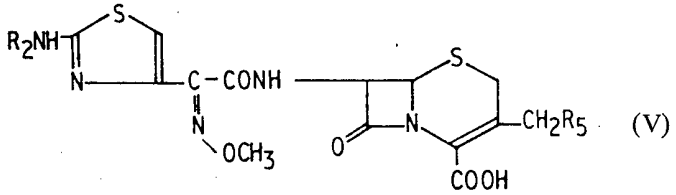
wherein R_2NH is as previously defined, if necessary followed by removing the protective group for the amino group (Process I).

In this process, the compound (III) is employed, either as a free compound or in the form of a reactive derivative, as an acylating agent for the acylation of the amino group in the 7-position on the compound (II). Thus, the free acid (III), an alkali or alkaline earth metal salt of the free acid (III) (e.g. the sodium, potassium or calcium salt), an organic amine salt of the free acid (III) (e.g. the trimethylamine salt or pyridine salt), or a reactive derivative thereof (such as an acid halide (e.g. acid chloride or acid bromide), acid anhydride, mixed acid anhydride, active amide, active ester or the like) is subjected to the aforementioned acylation reaction. As examples of the active ester, there may be mentioned the p-nitrophenyl ester 2,4-dinitrophenyl ester, pentachlorophenyl ester, N-hydroxysuccinimide ester and N-hydroxyphthalimide ester. As examples of the mixed acid anhydride there may be mentioned the mixed acid anhydride with a carbonic acid monoester (e.g. the carbonic acid monomethyl ester or carbonic acid monoisobutyl ester) and a mixed acid anhydride with a lower alkanoic acid which may be substituted by halogen (e.g. pivalic acid or trichloroacetic acid). Where the carboxylic acid (III) is employed as the free acid or in the form of a salt, there is employed a suitable condensing agent. As examples of the condensing agent there may be mentioned N,N'-di-substituted carbodiimides, e.g. N,N'-dicyclohexylcarbodiimide; azolides, e.g. N,N'-carbonylimidazole and N,N'-thionyldiimidazole; dehydrating agents, e.g. N-ethoxycarbonyl-2-ethoxy- 1,2-dihydroquinoline, phosphorus oxychloride and alkoxyacetylene; 2-halogenopyridinium salts (e.g. 2-chloropyridiniummethyl iodide or 2-fluoropyridiniummethyl iodide) and the like. Where such a condensing agent is employed, it is supposed that the reaction proceeds *via* the reactive derivative of the carboxylic acid (III).

The reaction is generally conducted in a suitable inert solvent. As examples of such inert solvent may mention halogenated hydrocarbons, e.g. chloroform or methylene dichloride; ehters, e.g. tetrahydrofuran or dioxane; dimethylformamide; dimethylacetamide; acetone; water and mixtures of such solvents. The proportion of the acylating agent is normally within the range of from 1 to 5, preferably 1 to 2 molar equivalents based on the compound (II). This reaction is generally carried out at a temperature within the range of from -50°C to 40°C inclusive. The reaction time is selected from the range of 1 to 10 hours, preferably 1 to 3 hours. Following the acylation reaction, the protective group for the amino function may be removed, if necessary. The removal of the protective group for the amino function may be generally accomplished by procedures which are known *per se* [e.g. by the procedure described in Japanese Patent Application As Laid Open No. 52083/1975 and in Pure and Applied Chemistry, 7, 335(1963)] or a procedure analogous thereto. It should be understood that, where R_2 in the formula (I) is monohalogenoacetyl (e.g. monochloroacetyl) and R_3 is a carbamoyloxy group whose amino group has been protected, such as N-monohalogenoacetylcarbamoyloxy (e.g. N-monochloroacetylcarbamoyloxy), these two monohalogenoacetyl groups (e.g. monochloroacetyl) may be simultaneously removed. In this sense, the protective group for amino represented by R_2 is preferably a monohalogenoacetyl group. The reaction for removing the monohalogenoacetyl group from the amino group is performed by reacting a compound of the formula (I) whose amino group or groups have been protected by monohalogenoacetyl with thiourea and a basic substance. Normally, this reaction is conducted in a solvent at a temperature near room temperature and, in many instances, goes to completion in a time varying from 1 to 10 hours. The solvent may be any solvent that will not interfere with the present reaction. Thus, there may be mentioned ethers, e.g. diethyl ether, tetrahydrofuran or dioxane; lower alcohols, e.g. methanol or ethanol; halogenated hydrocarbons, e.g. chloroform or methylene dichloride; esters, e.g. ethyl acetate or butyl acetate; ketones, e.g. acetone or methyl ethyl ketone; water; and various mixtures of such solvents.

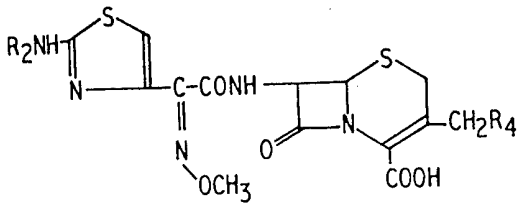
This reaction for the removal of the N-halogenoacetyl group from the N-monohalogenoacetylcarbamoyloxymethyl group in the 3-position of the compound (I) does not proceed to any substantial extent when thioures alone is permitted to act upon the compound (I). However, if the compound (I) is reacted with thiourea and a basic substance, the desired reaction for removing the monohalogenoacetyl group takes place selectively and smoothly to give the 3-carbamoyloxymethyl compound (I). As the basic substance used for the purposes of this reaction, there may be mentioned an alkali metal or alkaline earth metal salt of a lower aliphatic carboxylic acid or an inorganic or organic base having a pKa value of not less than 9.5, preferably within the range of pKa 9.8 to 12.0. As examples of the salt of the lower aliphatic carboxylic acid there may be mentioned the salts of lower aliphatic carboxylic acids of 1 to 6 carbon atoms, such as sodium acetate, potassium acetate, calcium acetate, barium acetate, sodium formate, sodium propionate or potassium hexanoate. As examples of the inorganic base there may be mentioned the alkali metal salts of carbonic acids such as sodium carbonate or potassium carbonate. The organic base may for example be one of the mono-, di- or tri-lower alkyl substituted amines whose lower alkyl group has 1 to 4 carbon atoms, e.g. trimethylamine, triethylamine, ethylamine, methylamine, diethylamine, dimethylamine, tributylamine, dibutylamine or butylamine; and 5- to 6- membered cyclic amines substituted in the N-position by lower alkyl groups of 1 or 2 carbon atoms such as N-methylpyrrolidine, N-ethylpyrrolidine, N-methylpiperazine or N-ethylpiperazine. While, as aforesaid, thiourea is employed in this reaction, the reaction may also be successfully conducted with N- or N,N-substituted thiourea, such as methylthiourea, N,N-diethylthiourea or N,N-hexamethylenethiourea.

(2) The 7-[2-(2-aminothiazol-4-yl)-2-(*syn*)-methoxyiminoacetamido]cephalosporin derivative of the formula (V):



(V)

wherein R_2NH is as previously defined; and R_5 is a residue of a nucleophilic compound, is produced by reacting a compound of the formula (IV):

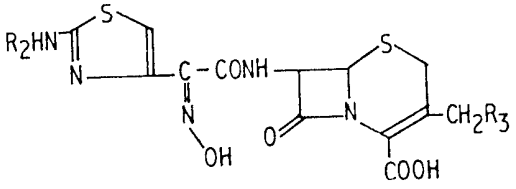


(IV)

wherein R_2NH is as previously defined; and R_4 is acyloxy, carbamoyloxy or halogen, with a nucleophilic compound, if necessary, followed by the removal of the protective group for the amino group (Process 2).

As the acyloxy group represented by R_4 in the formula (IV), there may, for instance, be mentioned acyloxy derived from lower aliphatic carboxylic acid having 2 to 4 carbon atoms, which may optionally be substituted by oxo, carboxy or ethoxycarbamoyl, e.g. acetyloxy, propionyloxy, 3-oxobutyryloxy, 3-carboxypropionyloxy, 3-ethoxycarbamoylpropionyloxy or 4-carboxybutyryloxy; and acyloxy derived from aromatic carboxylic acid, which may optionally be substituted by hydroxy, carboxy, carboethoxycarbamoyl or carboethoxysulfamoyl, e.g. mandelyloxy, 2-carboxybenzoyloxy, 2-(carboethoxycarbamoyl)-benzoyloxy and 2-(carboethoxysulfamoyl)-benzoyloxy. The halogen represented by R_4 may for example be chlorine, bromine or iodine. By the residue of a nucleophilic compound represented by R_5 in the formula (V) is meant the residue of a nucleophilic compound corresponding to the residue of a nucleophilic compound represented by R_3, excluding the acyloxy represented by R_4 or carbamoyloxy. For the purposes of this reaction however, it is generally advantageous to employ a compound (IV) having an acyloxy group derived from a lower aliphatic carboxylic acid, such as acetyloxy or 3-oxobutyryloxy. The nucleophilic compound employed in this reaction is a compound corresponding to the residue of the nucleophilic compound designated by the symbol R_5 in the formula (V). Particularly preferred are the heterocyclic thiol compounds i.e. mercapto compounds which may be substituted. Among the nucleophilic compounds corresponding to the residue represented by R_5, mercapto compounds may be employed in their free form, although it is advantageous to use them in the form of alkali metal salts, e.g. sodium or potassium salts. This reaction is preferably conducted in a solvent. For example, use is made of water, deuterium oxide or an organic solivent that is readily miscible with water and does not react with the reactants, e.g. dimethylformamide, dimethylacetamide, dioxane, acetone, alcohol, acetonitrile, dimethylsulfoxide and tetrahydrofuran. While the reaction temperature and the time vary with such factors as the particular starting material and solvent employed, they are generally in the neighbourhood of 0°C to 100°C, preferably 30° to 70°C, and in the range of 2 to 48 hours, preferably 3 to 15 hours, respectively. The reaction is preferably carried out in the neighbourhood of neutrality and is feasible within the range of from pH 2 to pH 8, preferably pH5 to 8. The progress of this reaction may sometimes be rendered smooth by the addition of a quaternary ammonium salt having surface activity, such as trimethylbenzylammonium bromide or triethylbenzylammonium bromide or triethylbenzylammonium hydroxide. Moreover, more satisfactory results are obtained when the reaction is conducted in an inert gaseous atmosphere such as nitrogen in order to prevent atmospheric oxidation of the mercapto compound.

(3) The cephalosporin derivative of the formula (I) may also be produced by subjecting a 7-[2-(2-aminothiazol -4-yl)-2-(*syn*) -hydroxyimino-acetamido]cephalosporin derivative (VI):



(VI)

wherein R_3 and R_2NH are as previously defined, to O-methylation. The O-methylation is conducted by reacting the compound (VI) with a methylating agent (Process 3).

This O-methylation reaction is normally conducted in a solvent under ice-cooling or in the neighbourhood of room temperature (0°C to 40°C, preferably 5°C to 30°C) and, in many cases, goes to completion within from approximately 5 minutes to 5 hours, preferably 5 minutes to 2 hours. The solvent may be any solvent that will not interfere with the reaction, such as ethers, e.g. tetrahydrofuran or dioxane; lower alcohols, e.g. methanol or ethanol; halogenated hydrocarbons, e.g. chloroform or methylene chloride; esters, e.g. ethyl acetate or butyl acetate; amides, e.g. N,N-dimethylformamide or N,N-dimethylacetamide; water;

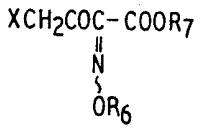
and mixtures of such solvents. The methylating agent may be a methylating agent which is generally employed in organic chemistry, such as methyl halide (e.g. methyl iodide or methyl bromide), dimethyl sulfate, or diazomethane.

The reaction may proceed smoothly in the presence of a suitable base except in the case of diazomethane. As such base, use is normally made of an inorganic base such as alkali metal salts or carbonic acid (e.g. sodium carbonate or potassium carbonate) or alkali metal hydroxides (e.g. sodium hydroxide or potassium hydroxide). Where the stability of the compound (VI) is a consideration, however, sodium carbonate, potassium carbonate or the like is preferably employed. The reaction may also be conducted in a buffer at from pH 7.5 to 8.5.

The cephalosporin compounds (I) which are produced by the several production processes described hereinbefore may each be purified by procedures known *per se*, such as column chromatography, extraction, precipitation, recrystallization and so on. If necessary, each of those compounds may be treated by *per se* known procedures to obtain the desired salts or esters.

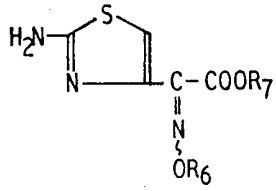
One of the starting materials for this invention i.e. the 2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetic acid derivative (III), may be produced, for example by the several alternative processes described hereinafter in detail.

(I) In the first place, a 4-halogeno-3-oxo-2-oxyiminobutyric acid derivative of formula (VII):



wherein X is halogen, e.g. chlorine or bromine;
R_6 is hydrogen or methyl; R_7 is a lower alkyl group of 1 to 3 carbon atoms, e.g. methyl, ethyl or propyl

is reacted with thiourea to yield a 2-(2-aminothiazol-4-yl)-2-oxyiminoacetic acid derivative of the formula (VIII):

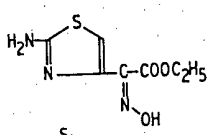
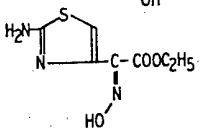
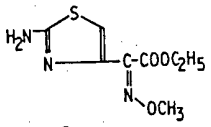
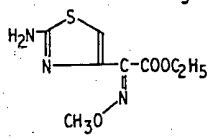
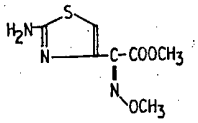
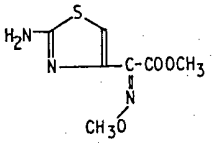
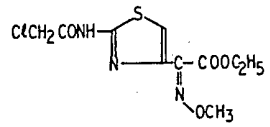
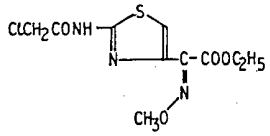
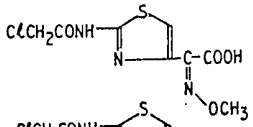
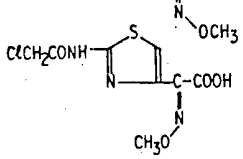
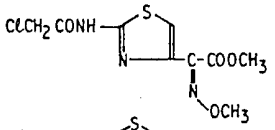
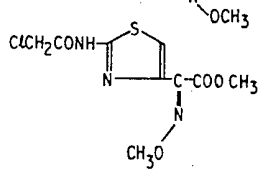


wherein R_6 and R_7 are as previously defined. In both the cases where R_6 is hydrogen and methyl, respectively, the compound (VIII) is normally obtained as a mixture of *syn*- and *anti*-isomers thereof. The reaction is normally conducted by reacting a compound of the formula (VII) with thiourea in an organic solvent such as ethanol, methanol or tetrahydrofuran at room temperature or at elevated temperature (0° to 100°C, preferably 10° to 50°C). The reaction time is selected from the range of 1 to 30 hours, preferably 1 to 5 hours. To isolate the desired *syn*-isomer from the resulting mixture of *syn*- and *anti*-forms of the compound (VIII), one of the following procedures may be successfully followed. These procedures include the procedure of fractional crystallization which takes advantage of the differential crystallizabilities or solubilities of the isomers of the compound (VIII) as such, a salt of the compound (VIII) with hydrogen halide (HBr or HCℓ salt) or a derivative of the compound (VIII) with a protective group on its 2-amino group, the protective group (e.g. monochloroacetyl or dichloroacetyl) having been introduced by a procedure known *per se*; isolation by chromatography and a procedure such that, when the compound (VIII) or the compound (VIII) with a protective group on its 2-amino group is hydrolysed, at its ester position by a *per se* known process to a carboxylic acid derivative of the formula (III), the *syn*-isomer alone is selectively isolated by utilising the difference in the rate of hydrolysis between the *syn*- and *anti*-isomers.

In the last-mentioned procedure, because of the higher rate of hydrolysis for the *anti*-isomer than for the *syn*-isomer, the *anti*-isomer may be selectively hydrolysed and removed. The reaction for hydrolysing the ester linkage of the compound (VIII) with or without a substituent on its 2-amino group is normally conducted in the presence of from 1 to several molar equivalents of an alkali metal hydroxide, e.g. potassium hydroxide or sodium hydroxide at a temperature ranging from 0°C to room temperature, and in water or a mixture of

water with an organic solvent miscible with water, e.g. methanol, ethanol, acetone, tetrahydrofuran, dioxane, N,N-dimethylformamide or N,N-dimethylacetamide. Where R_6 in the compound (VIII) is hydrogen, the *syn*-isomer isolated may be converted to the *syn*-isomer of the compound (VIII) in which R_6 is methyl, by subjecting the former compound (VIII) to methylation. This methylation reaction is normally carried out in a solvent under ice-cooling or at temperatures near room temperature and, in many instances, goes to completion in from a few minutes to several hours. The solvent for this purpose may be any type of solvent only if it does not interfere with the reaction. Thus, for example, tetrahydrofuran, dioxane, methanol, ethanol, chloroform, methylene dichloride, ethyl acetate, butyl acetate, N,N-dimethylformamide, N,N-dimethlacetamide and water, as well as mixtures of such solvents, may be mentioned. As the methylation agent there may be mentioned methyl halides, e.g. methyl iodide and methyl bromide; dimethyl sulfate; and diazomethane; to name but a few. In all cases except that in which diazomethane is employed, the compound (VIII) in which R_6 is hydrogen is reacted with the methylating agent in the presence of a base such as an alkali metal carbonate (e.g. sodium carbonate or potassium carbonate) or an alkali metal hydroxide (e.g. sodium hydroxide or potassium hydroxide). Some of the physical constants of the *syn*-isomers of the compounds (III) and (VIII) thus obtained are shown below (in Table 1) in comparison with the physical constants of the corresponding *anti*-isomers.

Table 1

	Structure	NMR spectrum (ppm)	Melting Point (°C)
syn-isomer		In d_6-DMSO 6.80s (5-H) 11.6s (OH)	185.5
anti-isomer		In d_6-DMSO 7.50s (5-H) 12.5s (OH)	145.3
syn-isomer		In $CDCl_3$ 6.74s (5-H) 4.02s (OCH_3)	163 to 164
anti-isomer		In $CDCl_3$ 7.43s (5-H) 4.07s (OCH_3)	114 to 115
syn isomer		In $CDCl_3$ 6.74s (5-H) 4.02s (OCH_3)	164.9
anti-isomer		In $CDCl_3$ 7.48s (5-H), 4.06s (OCH_3)	–
syn-isomer		In $CDCl_3$ 7.15s (5-H) 4.00s (OCH_3)	111 to 112
anti-isomer		In $CDCl_3$ 7.94s (5-H) 4.10s (OCH_3)	81 to 82
syn-isomer		In d_6-DMSO 7.57s (5-H) 3.95s (OCH_3)	170 to 171
anti-isomer		In d_6-DMSO 8.00s (5-H) 4.00s (OCH_3)	182 to 183
syn-isomer		In $CDCl_3$ 7.24s (5-H), 4.02s (OCH_3)	130.8
anti-isomer		In $CDCl_3$ 8.02s (5-H) 4.12s (OCH_3)	–

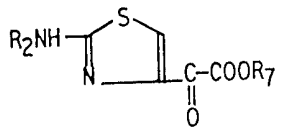
Remarks *s*: singlet

The methoxyimino (hydroxyimino) group in the "*syn*" isomer is cis to the carboxyl function, and in the "*anti*" isomer is trans to the carboxyl function.

(II) The procedure for the selective production of the compound (III) (*syn*-isomer) will hereinafter be described. Whereas the aforementioned reaction of the compound (VII) with thioures yields a mixture of *syn*- and *anti*-isomers of the compound (VIII), in many instances, the *anti*-isomer of the compound (VIII) predominates. Our study of the conditions of this cyclization reaction have shed some light on the conditions needed to lead to the selective formation of the desired *syn*-isomer. Thus, if the reaction of the compound (VII) with thiourea to produce the compound (VIII) is conducted under the conditions described hereinbefore, the *syn*- and *anti*-isomers are normally produced in a ratio which is in the range of from 2:98 to 50:50.

We have found, however, that, if this cyclization reaction is carried out in water or in a mixture of water and a water-miscible solvent such as methanol, ethanol, acetone, tetrahydrofuran, dioxane, N,N-dimethylformamide, N,N-dimethylacetamide or N-methylpiperidone and in the presence of the basic substance, the *syn*-isomer of the compound (VIII) is selectively produced (normally in a ratio of from 85:15 to 100:0). As the basic substance useful for the purposes of this reaction, there may be mentioned alkali metal or alkaline earth metal salts of lower aliphatic carboxylic acids, and inorganic or organic bases having pKa values of not less than 9.5, preferably within the range of 9.8 to 12.0. As examples of the lower aliphatic carboxylic acid salts there may be mentioned salts of lower aliphatic carboxylic acids of 1 to 6 carbon atoms such as sodium acetate, potassium acetate, calcium acetate, barium acetate, sodium formate, sodium propionate or potassium hexanoate; while the inorganic bases mentioned above include alkali metal salts of carbonic acid such as sodium carbonate or potassium carbonate. As the organic bases there may be mentioned tri-lower, alkyl-substituted amines whose lower alkyl group has 1 to 4 carbon atoms such as trimethylamine, triethylamine or tributylamine, and 5- to 6- membered cyclic amines substituted in the N-position by lower alkyl of 1 to 2 carbon atoms such as N-methylpyrrolidine, N-ethylpyrrolidine, N-methylpiperazine or N-ethylpiperazine. Where the N,N-dimethylformamide, N,N-dimethylacetamide or N-methylpyrrolidone is employed as the solvent, it is not always necessary to add the aforesaid basic substance. The reaction temperature and time are generally selected from the range of 0° to 50°C (preferably 0° to 30°C) and the range of 1 to 30 hours (preferably 1 to 5 hours), respectively.

(III) The compound (VIII) (*syn*-isomer) may also be selectively produced by the following procedure. Thus, in a further search for a method of selective production of the *syn*-isomer, we have discovered that, by reacting a 2-aminothiazol-4-ylglyoxyl acid derivative of the formula (IX) with O-methylhydroxylamine, the *syn*-isomer of the methoxyimino compound may be selectively obtained, i.e.:

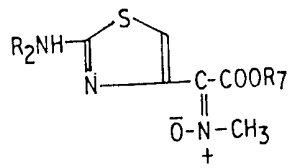


(IX)

wherein R_2 and R_7 are as previously defined.

Normally, this reaction may be conducted smoothly in a suitable solvent at a pH of about 4.0 to 9.0. The solvent mentioned may be any type of solvent unless it interferes with the reaction. Thus, for example, ethers such as diethyl ether, tetrahydrofuran or dioxane; lower alcohols such as methanol or ethanol; halogenated hydrocarbons such as chloroform or methylene dichloride; esters such as ethyl acetate or butyl acetate; water and mixtures of such solvents may be mentioned. While this reaction proceeds in the neighbourhood of room temperature, it may be accelerated by heating. The reaction temperature and time are generally selected from the range of 0° to 100°C (preferably 0° to 50°C) and the range of 1 to 10 hours (preferably 1 to 5 hours), respectively.

The starting compound (IX) for this reaction may be produced by the reaction described hereinafter, thus, the hydrolysis of a nitron compound of the formula (X):



(X)

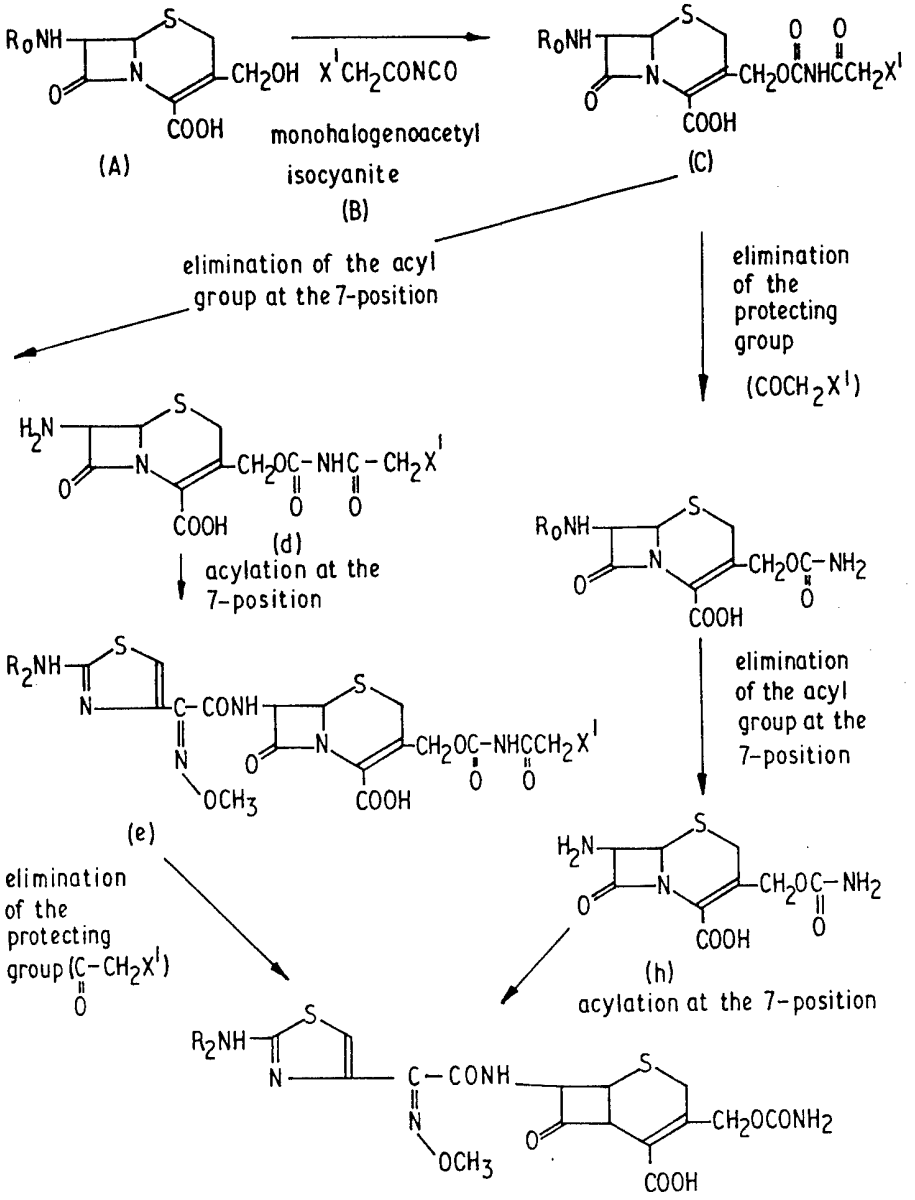
wherein R_2 and R_7 are as previously defined yields the compound (IX). This hydrolysis reaction takes place smoothly in the presence of a mineral acid, and is normally conducted in a solvent. As examples of the mineral acid, we may mention hydrogen chloride, sulfuric acid and phosphoric acid. The solvent may be of any desired type that will not interfere with the reaction. Thus, there may be mentioned ethers, e.g. tetrahydrofuran or dioxane; alcohols, e.g. methanol or ethanol; ketones e.g. acetone or methyl ethyl ketone; water, and mixtures of such solvents. Normally this reaction may be conducted under ice-cooling or at room temperature. The starting compound (X) may be obtained by subjecting to methylation a compound of the formula (VIII) wherein R_6 is hydrogen and whose amino group in 2-position has been protected.

The conditions of this methylation reaction are essentially the same as the conditions under which the aforesaid compound (VIII) wherein R_6 is hydrogen is methylated [cf. the aforesaid method (I)].

Under the described conditions of methylation, the methylation of the *syn*-isomer of the compound (VIII) wherein R_6 is hydrogen does not give any substantial amount of this nitron compound (X) but the methylation of the *anti*-isomer of the compound (VIII) wherein R_6 is hydrogen yields the nitron compound (X) as a dominant product.

The compound of the formula (VII) may be produced, for example by the methods described in Journal of Medicinal Chemistry, *16*, 978(1973), Helvetica Chimica Acta, *49*, 26(1966), Journal of the American Chemical Society, *60*, 1328(1938) and West German Patent Application As Laid Open (Offenlegungsschrift) No. 2556736, or by procedures similar to such methods. The compound of the formula (II) used in this invention may be produced, for example, by a suitable method chosen from the methods described in U.S. Patents Nos. 3875151 and 3697515, West German Patent Application As Laid Open No. 2461478, West German Patent Application As Laid Open No. 2607064 (Dutch Patent Application No. 7601902), West German Patent Application As Laid Open No. 2619243, Japanese Patent Application As Laid Open Nos. 52083/1975, West German Patent Applications As Laid Open Nos. 2460331 and 2460332, or by processes analogous to these methods.

Among others, the compound (I) wherein R_3 is a carbamoyloxy or monohaloacetylcarbamoyloxy group may also be produced, for example, by the method described below:



Wherein R_o is hydrogen or an acyl group, X' is halogen such as chlorine, bromine or iodine and R_2NH is as previously defined.

The reaction of the 3-desacetylcephalosporanic acid derivative of the formula (A) with a monohalogenogenoacetyl isocyanate (B) is normally conducted smoothly by contacting the two reactants in a suitable solvent, either under ice-cooling or at a temperature near room temperature. The solvent employed for this purpose may be any solvent which will not interfere with this reaction. Thus, for example, ethers such as diethyl ether, tetrahydrofuran or dioxane; ketones such as acetone or methyl ethyl ketone; halogenated hydrocarbons such as chloroform, methylene dichloride or tri-chloroethane; esters such as ethyl acetate or butyl acetate; and mixtures of such solvents may be mentioned. The amount of the monohalogenoacetyl isocyanate (B) is from 1 to several moles per mole of the starting compound (A). The monohalogenoacetyl isocyanate (B) may be produced, for example, by the method described in Journal of Organic Chemistry, 27, 3742(1962) or a method analogous thereto.

The reaction for removing the 7-acyl group from the compound of formula (C) [or (g)] may be any of the reactions generally used for the deacylation of penicillins and cephalosporins. Thus, for example, the procedures described in, for example, West German Patent Applications As Laid Open Nos. 2460331 and 2460332, Japanese Patent Publications Nos. 13862/1966, 40899/1970 and No. 34387/1972 and U.S. Patent No. 3632578 may be

successfully employed. By way of illustration, the compound (C) [or (g)] is treated with an imino halide-forming agent to yield the corresponding imino halide in the first place, and the latter compound is then treated with an alcohol to yield the corresponding imino ether. This imide ether is hydrolysed to the corresponding 7-amino derivative (d) [or (h)].

As the imino halide-forming agent, there may be employed one of the halides derived from carbon, phosphorus or/and sulfur and the acid halides derived from their oxy-acids (e.g. phosphorus oxychloride, phosphorus pentachloride, phosphorus trichloride, thionyl chloride, phosgene, oxalyl chloride, protocatechuoyl-phosphorus trichloride or *p*-toluenesulfonyl chloride), for instance. This imino-halide-forming reaction is normally conducted with advantage in a solvent. The solvents for this purpose include not only the common inert solvents (such as methylene dichloride or chloroform) but tertiary amines (e.g. triethylamine, pyridine or dimethylaniline) and other solvents as well as mixtures of such solvents. The imino ether-forming reaction is accomplished by contacting the imino halide reaction mixture with an alcohol. The alcohols that may be normally employed include lower alkanols containing 1 to 4 carbon atoms such as methanol, ethanol and *n*-butanol. The aforementioned hydrolysis is accomplished by contacting the reaction mixture containing the product imino ether with water. In order to preclude side-reactions, the aforementioned reactions are preferably carried out under cooling.

The reaction for removing the monohaloacetyl group from the compound (c) [or (e)] is substantially the same reaction as that for removing the same group from the compound (I), which is described above.

In the above formulae (A) and (B), the acyl groups represented by R_0 may be any of the following exemplary groups: acyl groups derived from straight-chain aliphatic carboxylic acids containing up to 10 carbon atoms and acyl groups derived from cycloaliphatic carboxylic acids of up to 6 carbon atoms, e.g. formyl, acetyl, propionoyl, hexanoyl, butanoyl, heptanoyl, octanoyl or cyclopentanoyl; acyl groups derived from phenyl- or phenoxy-substituted lower (up to 4 carbon atoms) aliphatic carboxylic acids, e.g. phenylacetyl, phenoxyacetyl, α-phenoxypropionyl, α-phenoxybutyryl or *p*-nitrophenylacetyl; acetyl or mercaptoacetyl groups substituted by a 5- or 6-memebered heterocyclic group including one N, S or O hetero atom or a 5- or 6-membered heterocyclic group including the hetero atom and an additional 1 to 3 hetero atoms consisting of N, S or O, which latter heterocyclic group, in turn, may optionally be substituted by amino or hydroxyl, or by the corresponding heterocyclic oxy group, e.g. 2-thienylacetyl, tetrazolylacetyl, tetrazolythioacetyl, α∂ (2-pyridyloxy)-acetyl, α-(3-pyridyloxy)-acetyl, α-(4-pyridyloxy)-acetyl, 2-(2-hydroxy thiazol-4-yl)-acetyl, 2-(2-aminothiazol-4-yl)-acetyl, 4-pyridylthioacetyl, 1-pyrazolylacetyl, 2-furylacetyl or 6-(2'-oxo-3'- methylpyridazinyl)-thioacetyl; acyl groups derived from mono-substituted aliphatic carboxylic acids, e.g. cyanoacetyl, acetoacetyl, ω-halogenoacetoacetyl, 4-methylthio-3-oxobutyryl or 4-carbamoylmethylthio- 3-oxo-butyryl; α-substituted phenylacetyl groups, e.g. mandelyl, α-carboxyphenylacetyl, α-aminophenylacetyl, α-sulfophenylacetyl, α-sulfo-(*p*-aminophenyl)-acetyl or α∂ (β-methylsulfonylethoxycarbonyl) -aminophenylacetyl; glycyl groups substituted in the α-position by a 5- or 6-membered ring including one O or S atom as the hetero atom or a 5- or 6-membered ring including the hetero-atom and one N atom as an additional hetero atom, which latter ring is substituted by amino or hydroxyl, e.g. phenylglycyl, 1-cyclohexenylglycyl, cyclohexadienylglycyl, thienylglycyl, *p*-hydroxyphenylglycyl, furylglycyl, 2-aminothiazol-4-ylglycyl or 2-hydroxythiazol-4-ylglycyl; acyl groups derived from di-substituted aliphatic carboxylic acid such as 5-amino-5-carboxyvaleryl; and heterocyclic acyl groups, e.g. 5-methyl-3-phenyl- 4-isooxazolylcarbonyl or 3-(2,6-dichlorophenyl) -5-methyl-4-isooxazolylcarbonyl.

The compound (A) may be produced generally ① by acylating 7-aminocephalosporanic acid (7-ACA) with an acylating agent corresponding to the acyl group represented by R_0 by a *per se* known method for the acylation of an amino group at the 7-position of the cephalosporin compound mentioned hereinbefore, and removing the 3-acetyl group enzymatically from the same cephalosporin having a 3-acetoxymethyl group [Biochemical Journal *81*, 591(1961)] or ② by the fermentative production of 7-(D-5-aminoadipinamido)-3-hydroxymethyl-3-cephem- 4-carboxylic acid (cephalosporadesic acid, desacetylcephalosporin C, DCPC) [Nature 246, 154(1973); Japanese Patent Laid Open No. 491/1974)], for instance.

The optionally substituted heterocyclic thiol compound R_5SH, wherein R_5 is as defined hereinbefore, which is employed as a nucleophilic compound in accordance with this invention, may be synthesized, for example, by the methods described in Journal fur praktische Chemie, NF *133*(1932), Heterocyclic Compounds, 8, edited by Robert C Elderfield (John Wiley & Sons) and Advances in Heterocyclic, Chemistry, edited by A. R. Katritaky, A. J. Boulton (Academic Press) or by processes analogous thereto.

The compound (IV) may be produced, for example, by the method described in Belgian

Patent No. 719710 or a process analogous thereto. As an alternative, it may be produced by the application of the aforementioned Process (1) to the compound (III) and the compound (II) wherein $-CH_2R_3$ is $-CH_2R_4$, which is obtainable by one of the methods mentioned hereinbefore as the methods for the production of the compound (II) or processes analogous thereto. The compound (VI) may be produced, for example, by a procedure analogous to the method described in West German Patent Application As Laid Open No. 2556736, or by reacting the compound (II) with the *syn*-isomer of the compound (VIII), wherein R_6 is hydrogen.

The present invention is illustrated in further detail below with reference to specific examples, but it is to be understood that the examples are solely for the purpose of illustration and not to be construed as limitations of the invention. In this specification, "g", "mg", "kg", "mℓ", "cm", "ppm", "Hz", "MHz", "mol", "mmol", "mcg", "Calcd.", "DMSO", "nm", and "decomp." are abbreviations of "gram", "milligram", "kilogram", "milliliter", "centimeter", "part per million", "Herz", "mega Herz", "*Mole*", "milli-*Mole*", "microgram", "Calculated", "dimethylsulfoxide", "Nanometer", and "decomposed", respectively. Resins named "Amberlite" (trade mark) are products manufactured by the Rohm & Haas Company in the U.S.A. All the temperatures are uncorrected and the percentages are all on a weight basis except where specifically defined otherwise. The NMR spectra given therein were measured using a Varian Model HA 100 (100 MHz) or T60 (60 MHz) spectrometer with tetramethylsilane as the internal or external reference and all δ values are in ppm. The symbol *s* stands for a singlet, *d* a doublet, *t* a triplet, *q* a quartet, *m* a multiplet, and J a coupling constant.

Reference Example 1

10 g of ethyl 3-oxo-2-hydroximinobutyrate are dissolved in a solution of 13.3 g of sodium carbonate in 120 mℓ of water and this is followed by the addition of 30 mℓ of methanol. The mixture is cooled with ice and, under stirring, 15.8 g of dimethyl sulphate are added dropwise over a period of 3 minutes. After the dropwise addition has been completed, the ice-bath is removed and the mixture is stirred at room temperature for 40 minutes. The reaction mixture (pH 8 or higher) is extracted twice with ethyl acetate and the extracts are pooled, washed with water and dried. The solvent is then evaporated off under reduced pressure and the residue is subjected to distillation under reduced pressure. By the above procedure 9 g of ethyl 3-oxo-2-methoxyiminobutyrate are obtained as a pale-yellow oil boiling at 56-61°C/0.3-0.4 mmHg.

Elemental analysis, for $C_7H_{11}NO_4$:

Calculated:	C, 48.54;	H, 6.40;	N, 8.08
Found:	C, 48.41;	H, 6.51;	N, 7.96

NMR spectrum (60 MHz, in $CDC\ell_3$):

2.40 ppm(3H, singlet, CH_3CO), 4.10 ppm(3H, singlet, $=NOCH_3$)

Reference Example 2

(1) 27.3 g of Ethyl 3-oxo-2-methoxyiminobutyrate are dissolved in 120 mℓ of chloroform, and the resulting solution is warmed to 40°C. Then, a solution of 25.3 g of bromine in 30 mℓ of chloroform is added dropwise over a period of 30 minutes. The mixture is stirred and allowed to react at room temperature for 1 hour. The resulting reaction mixture is washed with a 5 % aqueous solution of sodium bicarbonate and with water in that order, and the organic layer is dried. The solvent is then distilled off under reduced pressure to yield 36.2 g of ethyl 4-bromo-3-oxo- 2-methoxyiminobutyrate as an oily product.

NRM spectrum (60 MHz, in $CDC\ell_3$):

4.16 ppm(3H, singlet, OCH_3), 4.36 ppm(2H, singlet, $BrCH_2CO$)

(2) In 20 mℓ of ethanol are dissolved 5 g of the above product, followed by the addition of 1.8 g of thiourea. The mixture is heated under reflux for 3 hours. After cooling, the precipitate is collected by filtration and dissolved in 20 mℓ of water, to which sodium bicarbonate is added. The oil that has separated is extracted with ethyl acetate. The ethyl acetate layer is washed and dried. Thereafter, the ethyl acetate is evaporated off to yield white crystals. Recrystallization from ethanol yields 2.6 g (57.2 %) of ethyl 2-(2-aminothiazol- 4-yl)-2-(*anti*)- methoxyiminoacetate as white crystals, melting point: 114-115°C.

Elemental analysis, for $C_8H_{11}N_3O_3S$:

Calculated:	C,41.91;	H, 4.84;	N, 18.33
Found:	C, 41.71;	H, 4.75;	N, 18.07

NMR spectrum (60 MHz, in $CDC\ell_3$):

4.07 ppm(3H, s., OCH_3), 5.80 ppm(2H, br. s., NH_2), 7.43 ppm (1H, s., thiazole 5H)

(3) The filtrate obtained upon collection of the first crop of precipitate is concentrated under reduced pressure and sodium bicarbonate is added to the residue. The mixture is

extracted with ethyl acetate and the oil obtained from the ethyl acetate layer is purified by column chromatography on silica gel. By the above procedure there are obtained 59 mg (1.3 %) of ethyl 2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetate as white crystals, melting point: 163-164°C.

Elemental analysis, for $C_8H_{11}N_3O_3S$:

Calculated:	C, 41.91;	H, 4.84;	N, 18.33
Found:	C,41.57;	H, 4.76;	N, 18.07

NMR spectrum (60 MHz, in $CDC\ell_3$):
4.02 ppm(3H, s., OCH_3), 5.80 ppm(2H, br. s., NH_2), 6.74 ppm(1H, s., thiazole 5H)

Reference Example 3

121 g of Ethyl 4-chloro-3-oxo-2-hydroxyiminoacetate together with 47.6 g of thiourea are added to 600 mℓ of ethanol and the resulting mixture is stirred at room temperature for 3 hours. The ethanol is then evaporated off under reduced pressure and 350 mℓ of water are added. The water layer is washed with diethyl ether, neutralized with sodium bicarbonate (to pH 7.5) and extracted with ethyl acetate-tetrahydrofuran (1:1). The organic layer is washed with water and dried. The solvent is then distilled off to yield 45 g of crystalline product.

A 1 g portion of the latter product is collected and purified by column chromatography on silica gel (eluting solvent: ethyl acetate-*n*-hexane). The first fraction gives 650 mg of the *anti*-isomer of ethyl 2-(2-aminothiazol-4-yl) -2-hydroxyiminoacetate and 150 mg of the *syn*-isomer are obtained from the second fraction

Anti-isomer: white crystals, melting pint: 145.3°C

Syn-isomer: pale yellowish white crystals, melting point: 185.5°C.

Elemental analysis, for $C_7H_9N_3O_3S$:

Calculated:	C, 39.06;	H, 4.21;	N 19.52
Found(*Anti*-):	C,38.81;	H, 4.20;	N, 19.62
(*Syn*-):	C, 39.28;	H, 4.10;	N, 19.63

NMR spectrum (60 MHz, in d_6-DMSO):
Anti-isomer: 7.10 ppm(2H, br. s., NH_2), 7.50 ppm(1H, s., thiazole 5-H), 12.5 ppm(1H, s., OH).
Syn-isomer: 6.80 ppm(1H, s., thiazole 5-H), 7.12 ppm(2H, br. s., NH_2), 11.6 ppm(1H, s., OH)

Reference Example 4

10.6 g of Sodium carbonate are dissolved in 150 mℓ of water, followed by the addition of a solution of 10.7 g of ethyl 2-(2-aminothiazol-4-yl) -2-(*syn*)-hydroxyiminoacetate in a mixture of 150 mℓ of tetrahydrofuran and 50 mℓ of methanol. Under ice-cooling, 12.6 g of dimethyl sulphate are added dropwise over a period of 5 minutes. After the dropwise addition has been completed, the ice-bath is removed and the mixture is stirred at room temperature. During stirring, white crystals start separating out. After 3 hours, most of the organic solvent is distilled off under reduced pressure and the residue is cooled with ice. The resulting precipitate is collected by filtration, washed with water and dried. 5 g of Ethyl 2-(2-aminothiazol-4-yl)-2- (*syn*)-methoxyiminoacetate are obtained by the above procedure as white crystals. This product is identified by the NMR spectrum and other properties with ethyl 2-(2-aminothiazol-4- yl)-2-(*syn*) -methoxyiminoacetate.

Reference Example 5

2.15 g of Ethyl 2-(2-aminothiazol-4-yl)-2-(*syn*) -methoxyiminoacetate (melting point: 163-164°C) are dissolved in 10 mℓ of N,N-dimethylacetamide and, under ice-cooling, 1.27 g of chloroacetyl chloride are added dropwise. The resulting reaction mixture is stirred under ice-cooling for 30 minutes and then at room temperature for 30 minutes. The mixture is then diluted with 50 mℓ of water and extracted twice with 100 mℓ portions of ethyl acetate. The extracts are pooled together, and are then washed with a 5% aqueous solution of sodium bicarbonate and a saturated aqueous solution of sodium chloride in that order, and finally dried. The solvent is evaporated off to yield 2.04 g of ethyl 2-(2-chloroacetamidothiazol-4-yl) -2-(*syn*)-methoxyiminoacetate as a crystalline product, melting point: 111-112°C.

Elemental analysis, for $C_{10}H_{12}N_3O_4SC\ell$:

Calculated:	C, 39.29;	H, 3.96;	N, 13.74
Found:	C, 39.15;	H, 3.91;	N, 13.69

NMR spectrum (60 MHz, in CDC_3):
4.00 ppm(3H, s., $=NOCH_3$), 4.24 ppm(2H, s, CCH_2CO), 7.15 ppm(1H, s., thiazole 5-H)

Reference Example 6

9.62 g of Ethyl 2-(2-chloroacetamidothiazol-4-yl) -2-(*syn*)-methoxyiminoacetate are added to a solution of 9 g of potassium hydroxide in a mixture of 85 mℓ of water and 452 mℓ of ethanol, and the resulting mixture is stirred at room temperature for 2 hours. The ethanol is

distilled off under reduced pressure and, following the addition of 85 mℓ of ethyl acetate. The water layer is adjusted to pH 2 with 10% hydrochloric acid and extracted twice with 200 mℓ portions of ethyl acetate. The extracts are combined, washed with a saturated aqueous solution of sodium chloride and dried. The solvent is then distilled off to yield 7.63 g of 2-(2-chloroacetamidothiazol-4-yl) -2-(*syn*)-methoxyiminoacetic acid as crystals melting at 170-171°C.

Elemental analysis, for $C_8H_8N_3O_4SC\ell$:

Calculated:	C, 34.60;	H, 2.90;	N, 15.13
Found:	C, 34.97;	H, 3.03;	N, 14.74

NMR spectrum (60 mHz, in d_6-DMSO): 3.95 ppm(3H, singlet, $=NOCH_3$), 4.40 ppm(2H, singlet $C\ell CH_2CO$), 7.57 ppm (1H, singlet, thiazole 5-H)

Reference Example 7

2.38 g of a 7:8 mixture of *syn*- and *anti*-isomers of ethyl 2-(2-aminothiazol-4-yl) -2-methoxyiminoacetate are chloroacetylated with chloroacetyl chloride as in Reference Example 5, and 30 mℓ of ether are added to the resulting mixture of the *syn*- and *anti*- forms of ethyl 2-(2-chloroacetamidothiazol-4-yl) -2-methoxyiminoacetate. The crystals that have spearated out are collected by filtration [Product (A)]. In NMR spectrum and other properties, this product is identified with the sample of ethyl 2-(2-chloroacetamidothiazol-4-yl) -2-(*syn*)-methoxyiminoacetate obtained in Reference Example 5. Yield: 600 mg.

The oil obtained upon concentration of the filtrate (2.42 g., a mixture of *syn*- and *anti*-isomers) is added under ice-cooling to a solution of 879 mg of potassium hydroxide in a mixture of 5 mℓ water and 80 mℓ ethanol and the entire mixture is stirred at that temperature for 15 minutes. The ethanol is distilled off under reduced pressure and the residue is diluted with 50 mℓ of water extracted twice with 100 mℓ portions of ethyl acetate. The ethyl acetate layer is washed with water and dried. The ethyl acetate is then distilled off to yield 577 mg of ethyl 2-(2-chloroacetamidothiazol-4-yl) -2-(*syn*)-methoxyiminoacetate [Product (B)]. In NMR spectrum and other properties, this product is identified with the *syn*-isomer according to Reference Example 5. The products (A) and (B) give a total yield of 1076 g or a recovery rate of 96.8%.

Reference Example 8

67.8 g of Ethyl 4-chloro-3-oxo-2-hydroxyiminoacetate are dissolved in 600 mℓ of 50 % aqueous tetrahydrofuran. This is followed by the addition of 155 g of sodium acetate trihydrate and 53.2 g of thiourea. The resulting mixture is stirred at room temperature for 4 hours. The reaction mixture is adjusted to pH 7.0 with sodium bicarbonate and, following the addition of sodium chloride, it is extracted twice with 300 mℓ of tetrahydrofuran. The extracts are combined, washed (with water) and dried. The tetrahydrofuran is then distilled off to yield 27.5 g of ethyl 2-(2-aminothiazol- 4-yl)-2-hydroxyiminoacetate as crystals. Based on NMR and other data, this product is found to be a 82:18 mixture of *syn*- and *anti*-isomers.

A similar reaction is carried out without using sodium acetate. Based on the same criteria, the resulting product is found to be a 25:75 mixture of *syn*- and *anti*-isomers.

Reference Example 9

The reaction of Reference Example 8 is repeated except that 50 % aqueous ethanol is used instead of 50 % aqueous tetrahydrofuran. In this case also, where sodium acetate is employed, an 83:17 mixture of *syn*- and *anti*-isomers of ethyl 2-(2-aminothiazol-4-yl) -2-hydroxyiminoacetate is obtained. In contrast, where sodium acetate is not employed, the above reaction yields a 50:50 mixture of *syn*- and *anti*-isomers. The proportions of *syn* and *anti*-isomers are determined by NMR spectra and other methods.

Reference Example 10

The reaction of Reference Example 9 is repeated except that N,N-dimethylacetamide is used instead of 50 % aqueous tetrahydrofuran-sodium acetate. This procedure yields an 85:15 mixture of *syn*- and *anti*-isomers of ethyl 2-(2-aminothiazol-4- yl)-2-hydroxyiminoacetate.

Reference Example 11

200 mg of Ethyl 2-aminothiazol-4-yl-glyoxylate are dissolved in 10 mℓ of 50 % aqueous ethanol and this is followed by the addition of 166 mg of O-methylhydroxylamine hydrochloride and thereafter 168 mg of sodium bicarbonate. The mixture is stirred in a closed vessel at 70°C for 5 hours. The reaction mixture is concentrated under reduced pressure and the residue is diluted with 10 mℓ of water and extracted with ethyl acetate. The ethyl acetate layer is washed with water and dried. The ethyl acetate is then distilled off to yield ethyl 2-(2-aminothiazol-4- yl)-2-methoxyiminoacetate as crystals. Based on NMR and other data, this product is found to be an 83:17 mixture of *syn*- and *anti*-isomers.

Reference Example 12

2.44 g of the Methylnitron of ethyl 2-(2-aminothiazol-4-yl) -2-(*anti*)-hydroxyiminoacetate,

which is N-(2-aminothiazol-4-yl-ethoxycarbonyl) methylenemethylamine N-oxide, melting point: 184-185°C are suspended to 70 mℓ of ethanol containing 10 % of HCℓ. The mixture is stirred at room temperature for 16 hours. The reaction mixture is concentrated under reduced pressure and following the addition of 10 mℓ of water, the residue is adjusted to pH 7.5 with a 5 % aqueous solution of sodium bicarbonate and extracted with ethyl acetate. The ethyl acetate layer is washed with water and dried. The ethyl acetate is then distilled off and the residue is recrystallized from ethanol. 1.54 g of Ethyl 2-aminothiazol- 4-ylglyoxylate are obtained by the above procedure as yellow crystals melting at 143.3°C.

Elemental analysis, for $C_7H_8N_2O_3S$:

Calculated;	C, 41.98;	H, 4.02;	N, 13.99
Found:	C, 41.83;	H, 4.14;	N, 13.98

Reference Example 13

1 g Of the same N-(2-aminothiazol-4-yl-ethoxycarbonyl) -methylenemethylamine N-oxide as is used in Reference Example 12 is dissolved in 50 mℓ of 1N-hydrochloric acid, and the resulting solution is stirred at room temperature for 5 hours. The reaction mixture is neutralized with sodium carbonate and extracted with ethyl acetate. Thereafter, the procedure of Reference Example 12 is repeated to yield 0.5 g of ethyl 2-aminothiazol-4-ylglyoxylate. This product is identified by its NMR and other data with the product obtained in Reference Example 12.

Reference Example 14

1.2 g Of the methylnitron of 2-(2-aminothiazol-4-yl) -2-(*syn*)-hydroxyiminoacetate, i.e. N-(2-aminothiazol-4-yl-ethoxycarbonyl)-methylenemethylamine N-oxide, melting point: 111.6°C are suspended in 20 mℓ of ethanol containing 10 % of HCℓ, and the resulting suspension is stirred at room temperature for 16 hours. Thereafter, the procedure of Reference Example 12 is repeated to yield 0.7 g of ethyl 2-aminothiazol- 4-ylglyoxylate as yellow crystals. Its NMR and other properties show that this product is identical with the product according to Reference Example 12.

Reference Example 15

1g of Ethyl 2-(2-aminothiazol-4-yl)-2-(*anti*) -hydroxyiminoacetate (melting point: 145.3°C) are added to a mixture of 10 mℓ tetrahydrofuran and 5 mℓ ethyl acetate. This is followed by the addition of an excess of diazomethane-ether solution. The mixture is allowed to stand at room temperature for 2 days. The residual diazomethane is decomposed with acetic acid, and the reaction mixture is then concentrated under reduced pressure and the residue is recrystallized from ethyl acetate. 0.8 g Of the methylnitron compound i.e. N-(2-aminothiazol-4- yl-ethoxycarbonyl) -methylenemethylamine N-oxide is obtained by the above procedure as yellow crystals melting at 184-185°C.

Elemental analysis, for $C_8H_{11}N_3O_3S$:

Calculated:	C, 41.91;	H, 4.84;	N, 18.33
Found:	C,41.86;	H, 4.75;	N, 18.35

NMR spectrum (60 MHz, in $CDC\ell_3$): 3.82(3H, singlet, $\rightarrow N-CH_3$), 5.27 ppm(2H, br. singlet, NH_2), 8.49 ppm (1H, singlet, thiazole 5-H)

Reference Example 16

215 mg Of ethyl 2-(2-aminothiazol-4-yl)-2-(*anti*)-hydroxyiminoacetate (melting point: 145.3°C) are added to a solution of 23 mg sodium in 8 mℓ methanol and 280 mg of methyl iodide are then added at room temperature. The mixture is stirred for 45 minutes, and is then concentrated under reduced pressure. The residue is diluted with water (pH 7 or higher) and extracted with ethyl acetate. The ethyl acetate layer is washed with water, dried and concentrated. The residue is recrystallized from tetrahydrofuran-ethyl acetate. 160 mg Of the methylnitron compound are obtained by the above procedure as yellow crystals. This product completely identical with the product obtained in Reference Example 15.

Reference Example 17

The filtrate after collection of the precipitated ethyl 2-(2-aminothiazol-4-yl)-2- (*syn*)-methoxyiminoacetate from the concentrated reaction mixture in the procedure of Reference Example 4 is extracted with tetrahydrofuranethyl acetate (1:1). The extract is washed with water, dried and concentrated. 20 mℓ of tetrahydrofuran are added to the residual brown-coloured oil, and the mixture is allowed to stand in a refrigerator overnight. The resulting crystals are collected by filtration and recrystallized from ethyl acetate. 1.3 g Of the methylnitron of ethyl 2-(2-aminothiazol-4-yl)-2-(*syn*) -hydroxyiminoacetate, i.e. N-(2-aminothiazol- 4-yl-ethoxycarbonyl) -methylenemethylamine N-oxide are obtained by the above procedure as yellow crystals melting at 111.6°C.

Elemental analysis, for $C_8H_{11}N_3OS$:

Calculated:	C, 41.91;	H, 4,84;	N, 18.33
Found:	C,41.89;	H. 4.91;	N, 18.44

NMR spectrum (60 MHz, in $CDC\ell_3$): 4.14 ppm(3H, singlet, N-CH), 5.34 ppm(2H, br. singlet, NH_2), 6.62 ppm (1H, singlet, thiazole 5-H)

Reference Example 18

1.5 g Of ethyl 4-brom-3-oxo-2-methoxyiminobutyrate are dissolved in 10 mℓ of tetrahydrofuran and, after 7 mℓ of water are added, 2.4 g of sodium acetate trihydrate and 0.9 g of thiourea are further added. The mixture is stirred at room temperature for 17 hours, after which it is concentrated under reduced pressure. The concentrate is adjusted with dilute hydrochloride acid to a pH of substantially 1.5 and is washed with ethyl acetate. The water layer is neutralized with sodium bicarbonate and extracted with ethyl acetate. The ethyl acetate layer is washed with water, dried and concentrated under reduced pressure to yield 0.8 g of yellowish crystals. This product is the ethyl 2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetate. This product is identified by NMR and other data with a *syn*-isomer obtained in Reference Example 2.

Reference Example 19

2g Of ethyl 4-brom-3-oxo-2-methoxyiminobutyrate are dissolved in 10 mℓ of dimethylformamide. This is followed by the addition of 1.2 g of thiourea. The mixture is reacted at room temperature for 5 hours. 20 mℓ of a saturated aqueous solution of sodium chloride are added to the reaction mixture and the pH of the mixture is then adjusted with dilute hydrochloric acid to a pH of substantially 1.5. Thereafter, the procedure of Reference Example 18 is followed to yield 1.1 g of pale-yellow crystals. This product is identified by NMR and other data to be an 87:13 mixture of the *syn*- and *anti*-isomers of ethyl 2-(2-aminothiazol-4-yl) -2-methoxyiminoacetate. Washing the product with a small quantity of diethylether gives the *syn*-isomer substantially free of the *anti*-isomer.

Reference Example 20

(1) 20 g Of 7-(5-carboxy-5-benzamidovalerylamido) -desacetylcephalosporanic acid are dissolved in 80 mℓ of anhydrous acetone and this is followed by the addition of 7 g of chloroacetyl isocyanate. The resulting mixture is stirred at 20°C for 40 minutes, and 200 mℓ of ether are then added. The precipitate is collected by filtration and washed with 50 mℓ of ether. 19.6 g Of 7-(5-carboxy-5-benzamidovalerylamido)-3-(N-chloroacetyl)carbamoyloxymethyl-3-cephem-4-carboxylic acid are obtained as a white powder by the above procedure.
white powder by the above procedure.
NMR spectrum (60 MHz, in d_6-DMSO): 3.54 ppm(2H, quartet; 2-CH_2), 4.50 ppm(2H, singlet, -NHCOCH_2C), 4.98 ppm (2H, quartet,

$$-CH_2\overset{O}{\overset{\|}{O}}C\text{-NH}),$$

5.04 ppm(1H, doublet, 6-H), 5.77 ppm(1H, doublet, 7-H)

(2) 6 g Of 7-(5-carboxy-5-benzamidovalerylamido)-3-(N-chloroactyl)carbamoyloxymethyl-3-cephem-4-carboxylic acid are suspended in 80 mℓ of methylenechloride containing 7.6 mℓ of N,N-dimethylaniline. The mixture is cooled to -50°C, at which temperature 2.25 mℓ of phosphorus trichloride are added. The mixture is then stirred at -30°C for 1.5 hours to yield a clear solution. 4.17 g Of phosphorus pentachloride are added to this solution and the resulting mixture is stirred at -25°C for 2.5 hours. The mixture is cooled to -40°C and 37 mℓ of cold methanol are added quickly. The mixture is then stirred at -5°C for 25 minutes and, following the addition of 22 mℓ of water, is adjusted to pH 3.5 with dilute aqueous ammonia. The reaction mixture is allowed to stand at 5°C for 1 hour and the precipitate is collected by filtration. 1.76 g Of 7-amino-3-(N-chloroacetyl) carbamoyloxy-methyl-3- cephem-4-carboxylic acid are obtained as colourless crystals by the above procedure.
Elemental analysis, for $C_{11}H_{12}C\ell N_3O_6S$:

Calculated:	C, 37.78;	H, 3.46;	N, 12.01
Found:	C, 38.02;	H, 3.86;	N, 11.81

NMR spectrum (60 MHz, in CF_3COOH): 3.78 ppm(2H, br. singlet, 2-CH_2), 4.35 ppm(2H, singlet, -NHCO$CH_2C\ell$), 5.42 ppm(2H, br. singlet, 6-H, 7-H), 5.46 ppm(2H, quartet, -CH_2OCONH)

Reference Example 21

While a mixture of sodium azide, ethanol and water is stirred under reflux, an ethanolic solution of N,N-dimethylaminoethyl isothiocyanate is added dropwise. The mixture is further refluxed for 45 minutes, after which time the ethanol is distilled off under reduced pressure. The residual solution is made acidic with 1N-hydrochloric acid and extracted with ethyl acetate. The extract is dried and concentrated to dryness and the crystalline residue is stirred with *n*-hexane, recovered by filtration and recrystallized from toluene. 1-(2-N,N-dimethylaminoethyl) -1H-tetrazol-5-thiol is obtained by the above procedure.

melting point: 217-219°C (recrystallized from aqueous ethanol)
NMR (60 MHz, in $D_2O + NaHCO_3$): δ 3.03(s, $N(CH_3)_2$), 3.58 (t, CH_2), 4.70(t, CH_2)

Reference Example 22

(1) While a mixture of glycine-N,N-dimethylamide, triethylamine and methylene chloride is stirred, carbon disulphide and methyliodide are added in that order. The mixture is stirred at room temperature for 1 hour, and is then shaken vigorously with a 5 % aqueous solution of phosphoric acid. The organic layer is recovered, washed with water, dried and concentrated to dryness under reduced pressure. The crystalline residue is stirred with *n*-hexane, recovered by filtration and dried. Methyl 2-(N,N-dimethylcarbamoylmethyl)-dithiocarbamate is obtained by the above procedure.
IR (KBr, cm^{-1}): 1626, 1543
NMR(60MHz, in d_6-DMSO) δ: 2.62(s, CH_3S), 3.02(s, $N(CH_3)_2$), 4.42(d, J=4Hz, CH_2), 8.30(br. s., NH)
(2) A mixture of methyl 2-(N,N-dimethylcarbamoylmethyl) -dithiocarbamate, sodium azide and ethanol is stirred under heating at 80°C for 6.5 hours. The reaction mixture is adjusted to pH 2.5 with 10 % hydrochloric acid and is then, concentrated to dryness under reduced pressure. The residue is extracted with 100 mℓ of methanol and the methanol extract is treated with activated carbon and dried. The residual power is recrystallized from water. 1-N,N-dimethylcarbamoyl-methyl- 1-H-tetrazol-5-thiol is obtained by the above procedure.
melting point: 195-198°C (decomp.)
NMR (60 MHz, in d_6-DMSO) δ: 2.87 & 3.07 (each s, $N(CH_3)_2$), 5.21 (s, CH_2CO)
(3) Using a solution of sodium hydroxide, 1-N-N-dimethylcarbamoylmethyl-1H-tetrazole-5-thiol is hydrolyzed to yield 1-carboxymethyl-1H-tetrazole-5-thiol.
melting point: 156-160°C (decomp.)
IR (KBr, cm^{-1}): 1713
NMR (60 MHz, in d_6-DMSO) : 5.03 (s, CH_2CO), 12.09 (br. s, NH & -COOH)

Reference Example 23

38g of sodium nitrite and 53g of methyl acetoacetate are added to 200 ml of water and, under ice-cooling and stirring, 200 ml of 4N-sulphuric acid are added dropwise over a period of about an hour. During this dropwise addition, the temperature of the reaction mixture is maintained at 5-8°C. The mixture is further stirred within that temperature range for 2.5 hours, after which it is extracted twice with 300ml portions of ethyl acetate. The extracts are pooled and washed twice with a saturated aqueous solution of sodium chloride. Then, a solution of 96.7g sodium carbonate in 1 l of water is divided into 3 equal portions, with which 3-oxo-2-hydroxyiminobutyrate is extracted from the above ethyl acetate layer (3 times). 200ml of methanol are added to the water layer (1 l) and, after cooling with ice, 150g of dimethyl sulphate are added dropwise with stirring over a period of 10 minutes. After the dropwise addition has been completed, the mixture is stirred at room temperature for 1.5 hours and extracted twice with 300 ml portions of ethyl acetate. The extracts are pooled, washed with water and dried. The ethyl acetate is then distilled off and the residue is cooled with ice, whereupon it solidifies. The solid residue is collected by filtration and washed with a small amount of water. 52.3g of methyl 3-oxo-2-methoxy iminobutyrate are obtained by the above procedure as white crystals melting at 64.4°C.
Elemental analysis, for $C_6H_9NO_4$:

Calculated:	C, 45.28;	H 5.70;	N, 8.80
Found:	C, 44.93;	H 5.61;	N, 8.71

NMR spectrum (60 MHz, in $CDCl_3$): 2.40 ppm (3H, singlet, $-\overset{\overset{O}{\|}}{C}-CH_3$),
3.86 ppm (3H, singlet, $COOH_3$), 4.10 ppm (3H, singlet, $=NOCH_3$)

Reference Example 24

40g of methyl 3-oxo-2-methoxyiminobutyrate are dissolved in 150 ml of chloroform and the resulting solution is heated to 40°C. A solution of 40g bromine in 50 ml chloroform is then added dropwise over a period of one hour. The resulting reaction is allowed to continue under stirring at room temperature for one hour. The reaction mixture is washed with a 5% aqueous solution of sodium bicarbonate and water in that order, and the organic layer is dried. The solvent is then distilled off to yield 52.1g of methyl 4-bromo-3-oxo-2- methoxy-iminobutyrate as an oil.
NMR spectrum (60 MHz, in $CDCl_3$) : 3.82 ppm (3H, singlet, $COOCH_3$), 4.09 ppm(3H, singlet, $=N-OCH_3$), 4.27ppm (2H, singlet, $BrCH_2CO$)
52g of methyl 4-bromo-3-oxo-2-methoxyiminobutyrate are dissolved in 350 ml of tetrahydrofuran. This is followed by the addition of 250 ml of water and, further, by the addition of 89.1g of sodium acetate trihydrate and 33.2g of thiourea. The mixture is stirred at room

temperature for 18 hours. 200 ml of a 5% aqueous solution of sodium bicarbonate are added to the reaction mixture, and this is followed by extraction with ethyl acetate. The organic layer is washed with water, dried and concentrated under reduced pressure to remove the solvent. 200 ml of ether are added to the concentrate and the resulting precipitate is collected by filtration. 24.8 of methyl 2-(2-aminothiazol- 4-yl)-2-(*syn*)- methoxyiminoacetate are obtained by the above procedure as crystals melting at 164.9°C.

Elemental analysis, for $C_7H_9N_3O_3S$:

Calculated:	C, 39.06;	H, 4.21;	N, 19.52
Found:	C, 38.78;	H, 4.15;	N, 19.33

NRM spectrum (60 MHz, in $CDC\ell_3$) : 3.84 ppm(3H, singlet, $COOCH_3$), 4.02 ppm(3H, singlet, $=NOCH_3$), 5.74 ppm (2H, br. singlet, NH_2), 6.74 ppm(1H, singlet, thiazole 5-H)

Reference Example 25

21.5 g of Methyl 2-(2-aminothiazol-4-yl)-2- (*syn*)-methoxyiminoacetate are dissolved in 90 ml of N,N-dimethylacetamide and, under ice-cooling, 13.6 g of chloroacetyl chloride are added dropwise. The resulting mixture is stirred under ice-cooling for 30 minutes and, then, at room temperature for 30 minutes. Following the addition of 500 ml of water, the reaction mixture is extracted twice with ethyl acetate. The extracts are pooled, washed with a 5 % aqueous solution of sodium bicarbonate and water in that order, and dried. The solvent is then distilled off to yield 25 g of methyl 2-(2-chloroacetamidothiazol-4-yl) -2-(*syn*)-methoxyiminoacetate as crystals melting at 130.8°C.

Elemental analysis, for $C_9H_{11}N_3O_4SCl$:

Calculated:	C, 37.03;	H, 3.45;	N, 14.40
Found:	C, 37.30;	H, 3.40;	N, 14.35

NMR spectrum (60 MHz, in $CDCl_3$) : 3.90 ppm(3H, singlet, $COOCH_3$), 4.02 ppm(3H, singlet $=NOCH_3$), 4.26 ppm (2H, singlet, $ClCH_2CO$), 7.24 ppm(1H, singlet, thiazole 5-H).

Reference Example 26

20 g of methyl 2-(2-chloroacetamidothiazol-4-yl) -2-(*syn*)-methoxyiminoacetate are added to a solution of 19.2 g of potassium hydroxide in a mixture of 170 ml water and 900 ml ethanol and the resulting solution is stirred at room temperature for 2 hours. The ethanol is distilled off under reduced pressure and, following the addition of 170 ml of water, the residue is washed with 200 ml of ethyl acetate. The water layer is adjusted to pH 2 with 10 % hydrochloric acid and extracted twice with 300 ml portions of ethyl acetate.

The extracts are pooled, washed with a saturated aqueous solution of sodium chloride and dried. The solvent is distilled off to yield 16.8 g of 2-(2-chloroacetamidothiazol-4-yl) -2-(*syn*)-methoxyiminoacetic acid as crystals. In its NMR spectrum and other properties, this product is found to be identical with the product obtained in Reference Example 6.

Reference Example 27

(1) Six grams of 7-(5-carboxy-5-benzamidovalerylamido) -3-(N-chloroacetyl)-carbamoyloxymethyl- 3-cephem -4-carboxylic acid are suspended in 80 ml of methylene dichloride containing 7.6 ml of N,N-dimethylaniline, and, under cooling at -50°, 2.25 ml of phosphorus trichloride are added. The resulting mixture is stirred at -30°C for 1.5 hours until a clear solution is obtained. 4.17 g of phosphorus pentachloride are added to this solution and the resulting mixture is stirred at -25°C for 2.5 hours. It is then cooled to -40°C and 37 ml of cold methanol are added quickly. The mixture is stirred at -5°C for 25 minutes, after which it is diluted with 22 ml of water and adjusted to pH 3.5 with dilute aqueous ammonia. The reaction mixture is allowed to stand at 5°C for 1 hour and the resulting precipitate is collected by filtration. 1.76 g of 7-amino-3-(N-chloroacetyl) -carbamoyloxymethyl-3-cephem- 4-carboxylic acid are obtained by the above procedure as a colourless crystalline product.

Elemental analysis, for $C_{11}H_{12}ClN_3O_6S$:

Calculated:	C, 37.78;	H, 3.46;	N, 12.01
Found:	C, 38.02;	H, 3.86;	N, 11.81

NMR spectrum (60 MHz, in CF_3COOH):

3.78 ppm(2H, broad singlet, 2-CH_2), 4.35 ppm(2H, singlet, -NHCOCH_2Cl), 5.42 ppm(2H, broad singlet,

(2) 1.05 g of the 7-amino-3-(N-chloroacetyl) carbamoyloxymethyl- 3-cephem-4-carboxylic acid obtained in the above (1) are dissolved in N,N-dimethylacetamide and, under ice-cooling, 998 mg of 2-chloroacetamidothiazol-4- yl-α-(*anti*)- methoxyiminoacetyl chloride hydrochloride are added. The mixture is stirred under ice-cooling for 15 minutes and, then, at room temperature for 2 hours. Thereafter, following the addition of 50 ml of water, the reaction mixture is extracted twice with 100 ml portions of ethyl acetate. The organic layers

are pooled, washed with a saturated aqueous solution of sodium chloride and dried over magnesium sulphate. The ethyl acetate is then distilled off. 2.2 g of 7-[(2-chloroacetamidothiazol-4-yl) -α(*anti*)-methoxyimino] -acetamido-3-(N-chloroacetyl) carbamoyl-oxymethyl-3- cephem-4-carboxylic acid are obtained by the above procedure as a white powder.

Note: Production of 2-chloroacetamidothiazol-4-yl-α- (*anti*)-methoxyiminoacetyl chloride

(i) 10 g of ethyl α-(*anti*)-methoxyimino-α-(2-aminothiazol-4-yl)-acetate are dissolved in 100 ml of dimethylacetamide and, under cooling with ice, 5.91 g of chloroacetyl chloride are added dropwise. The mixture is stirred at room temperature for 1 hour, at the end of which time it is poured into ice-water. The mixture is extracted with ethyl acetate and the organic layer is washed, dried and distilled to remove the solvent. By the procedure there are obtained 12.66 g of ethyl α-(*anti*)-methoxyimino- α-[2-(chloroacetamido) thiazol-4-yl]acetate as crystals,
melting point: 81.82°C.
Elemental analysis, for $C_{10}H_{12}N_3O_4SCl$:

Calculated:	C, 39.29;	H, 3.96
Found:	C, 38.74;	H, 3.58

The nuclear magnetic resonance spectrum(60 MHz, in $CDCl_3$) of this product gives singlets, one at 4.10 ppm being assignable to methoxy protons, at 4.24 ppm assignable to chloroacetyl protons and at 7.94 ppm assignable to thiazole 5-hydrogen.

(ii) 12.66 g of ethyl α-(*anti*)-methoxyimino-α-[2-(chloroacetamido)thiazol-4-yl] acetate are added to a solution of 11.74 g of potassium hydroxide in a mixture of 25 ml water and 500 ml ethanol. The mixture is stirred at room temperature for 20 minutes, ethanol is distilled off under reduced pressure and the residue is diluted with water. The mixture is acidified to 1N-hydrochloric acid and the resulting precipitate is collected by filtration. 10.54 g of α-(*anti*)-methoxyimino- α-[2-(chloroacetamido)- thiazol-4-yl]acetic acid, melting point: 182-183°C are obtained by the above procedure.
Elemental analysis, for $C_8H_8N_3O_4SCl$:

Calculated:	C, 34.60;	H, 2.90;	N, 15.13
Found:	C, 34.53;	H, 3.00;	N, 14.80

The nuclear magnetic resonance spectrum (60 MHz, in d_6-DMSO) of the above product shows singlets, assignable to methoxyprotons at 400 ppm, chloroacetyl protons at 4.38 ppm and thiazole 5-hydrogen, at 8.00 ppm, respectively.

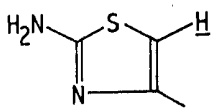
(iii) 555.4 mg of α-(*anti*)-methoxyimino-α-[2- (chloroacetamido)thiazol- 4-yl]acetic acid are suspended in 5 ml of methylene chloride and, under ice-cooling, 416.3 mg of phosphorus pentachloride are added. The mixture is reacted under stirring for 30 minutes. *n*-Hexane is added to the reaction mixture and the resulting precipitate is collected by filtration. 620 mg of α-(*anti*)-methoximino- α-[2-(chloroacetamido)thiazol- 4-yl]-acetyl chloride hydrochloride are obtained by the above procedure.
Elemental analysis, for $C_8H_7N_3O_3SCl_2 \cdot HCl$:

	C, 28.89;	H, 2.42;	N, 12.63
	C, 28.35;	H, 2.81;	N, 12.00

(3) 2.2g of the 7-[2-chloroacetamidothiazol-4-yl)-α- (*anti*)-methoxyimino]acetamido-3-(N-chloroacetyl) -carbamoyloxymethyl-3-cephem-4-carboxylic acid obtained in the above (2) are dissolved in 50 ml of tetrahydrofuran. This is followed by the addition of 913 mg of finely powdered thiourea and 1.63 g of sodium acetate trihydrate. The mixture is stirred at room temperature for 17 hours. The precipitate is collected by filtration, washed with diethyl ether and dissolved in 10 ml of water. The solution is brought to pH 7 with sodium bicarbonate and passed through a column of Amberlite XAD-2 (trade mark). 360 mg of sodium 7-[(2-aminothiazol- 4-yl)-α-(*anti*)- methoxyimino] acetamido-3-carbamoyloxymethyl- 3-cephem-4-carboxylate are obtained as a white powder by the above procedure.
Elemental analysis, for $C_{15}H_{15}N_6O_7S_2Na \cdot 2.5H_2O$:

Calculated:	C, 34.42;	H, 3.85;	N, 16.05
Found:	C, 34.43;	H, 3.70;	N, 15.68

NMR spectrum (60 MHz, in D_2O):
3.55 ppm(2H, quartet, 2-CH_2), 4.11 ppm(3H, singlet, $=NOCH_3$), 4.81 ppm(2H, quartet, -CH_2OCONH_2), 5.21 ppm(1H, doublet, 6-H), 5.82 ppm(1H, doublet, 7-H), 7.55 ppm(1H, singlet,



The antibacterial activity [MIC (γ/ml)] of the sodium 7-[(2-aminothiazol- 4-yl)-α-(*anti*)-methoxyimino]- acetamido-3-carbamoyloxymethyl-3- cephem-4-carboxylate according to this example is shown below.

Microorganism		MIC (γ/ml)
Escherichia coli 0—111		0.78
Klebsiella pneumoniae DT		1.56
Klebsiella pneumoniae GN 3835		6.25
Serratia marcescens IFO 12648		12.5
Serratia	TN0024	6.25
Proteus vulgaris	IFO 3988	0.39
Proteus mirabilis	GN 4359	0.78
Proteus organii	IFO 3168	0.78
Proteus rettgeri 8	TNO 336	< 0.2
Proteus rettgeri	GN 4733	0.78
Enterobacter cloacae	IFO 12937	25
Citrobacter freundii	GN 99	1.56
Citrobacter freundii	GN 1706	3.13

Reference Example 28

(1) In 20 ml of N,N-dimethylacetamide there are dissolved 1.05 g of 7-amino-3- (N-chloroacetyl) carbamoyloxymethyl-3-cephem-4-carboxylic acid and, under ice-cooling, 869 mg of 2-chloroacetamidothiazol- 4-ylacetyl chloride hydrochloride are added. The mixture is stirred under ice-cooling for 15 minutes and, then, at room temperature for 2 hours. After this reaction, the mixture is diluted with 50 mℓ of water and extracted twice with 100 mℓ portions of ethyl acetate. The organic layers are pooled, washed with a saturated aqueous solution of sodium chloride and dried over magnesium sulphate. The ethyl acetate is then distilled off to yield a white powder of 7-(2-chloroacetamidothiazol- 4-yl)acetamido-3-(N-chloroacetyl) carbamoyloxymethyl-3-cephem- 4-carboxylic acid.
Yield: 1.6 g.

Note: Production of 2-chloroacetamidothiaxol-4-ylacetyl chloride

In 15 mℓ of dimethylacetamide there are dissolved 4 g of ethyl 2-aminothiazol-4-ylacetate and, under ice-cooling, 3.62 g of chloroacetyl chloride are added drop-wise. The mixture is stirred under ice-cooling for 30 minutes and, then, at room temperature for another 30 minutes. Following the addition of 50 mℓ of water, the mixture is extracted twice with 100 mℓ portions of ethyl acetatetetrahydrofuran. The extract is washed with 100 mℓ of a 5% aqueous solution of sodium bicarbonate and, then, with 100 mℓ of a saturated aqueous solution of sodium chloride, followed by drying. The solvent is then distilled off. By the above procedure there are obtained 2.95 g of ethyl 2-chloroacetamidothiazol-4-ylacetate as an oily product. The entire amount of this oil is suspended in 100 mℓ of methanol and, under ice-cooling, 12 mℓ of water containing 761 mg of sodium hydroxide are added. The mixture is stirred at room temperature for 30 minutes, at the end of which time a major portion of the methanol is distilled off under reduced pressure. To the residue are added 10 mℓ of water. The water layer is washed with 50 mℓ of ethyl acetate and, after the addition of 20 mℓ of ethyl acetate, it is adjusted to pH 2 with 10% hydrochloric acid. The mixture is shaken well and the organic layer is collected, washed with a saturated aqueous solution of sodium chloride and dried. The solvent is then distilled off. By the above procedure there are obtained 1.51 g of 2-chloro-acetamidothiazol-4-ylacetic acid as colourless crystals,
melting point: 202-203°C.
Elemental analysis, for $C_7H_7C\ell N_2O_3S$:

Calcd.	C, 35.83;	H, 3.01;	N, 11.94
Found	C, 36.01;	H, 2.96;	N, 11.61

938 mg of the above product are suspended to 20 mℓ of methylene dichloride and, under

ice-cooling, 1g of phosphorous pentachloride is added. The mixture is stirred at room temperature for 30 minutes. Following the addition of 50 mℓ of petroleum ether, the precipitate is collected by filtration and washed with 10 mℓ of petroleum ether. 1.06 g of 2-chloroacetamidothiazol- 4-ylacetyl chloride hydrochloride are obtained as colourless crystals by the above procedure.

Elemental analysis, for $C_7H_6Cℓ_2N_2O_2S.HCℓ$:

Calculated:	C, 29.04;	H, 2.44;	N, 9.67
Found:	C, 28.96;	H, 2.24;	N, 9.61

IR spectrum (KBr) : 1780 cm^{-1} (-COCℓ)

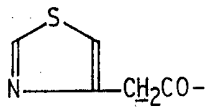
(2) 1.6g of the 7-(2-chloroacetamidothiazol-4-yl) acetamido-3-(N-chloroacetyl) carbamoyloxymethyl-3-cephem-4-carboxylic acid obtained in the above (1) are dissolved in 40 mℓ of tetrahydrofuran.

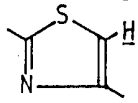
860 mg of thiourea are added to this solution, followed by addition of sodium acetate trihydrate. The mixture is stirred at room temperature overnight. The precipitate is collected by filtration, washed with diethyl ether and dissolved in 10 mℓ of water. The solution is brought to pH 7 with sodium bicarbonate and purified by column chromatography on Amberlite XAD-2 (trade mark). 152 mg of sodium 7-(2-aminothiazol-4-yl) acetamido-3-carbamoyloxy- methyl-3-cephem-4-carboxylate are obtained as a white powder by the above procedure.

Elemental analysis, for $C_{14}H_{14}N_5O_6S_2Na.2H_2O$

Calculated:	C, 35.67;	H, 3.85;	N, 14.85
Found:	C, 35.97;	H, 3.88;	N, 14.64

NMR spectrum (60 MHz, in D_2O):

3.52 ppm (2H, quartet, 2-CH_2), 3.61 ppm (2H, singlet, )

4.78 ppm(2H, quartet, -CH_2OCONH-), 5.14 ppm(1H, doublet, 6-H), 5.68 ppm (1H, doublet, 7-H), 6.52 ppm(1H, singlet, )

Example 1

(1) 290 mg of 7-amino-3-(N-chloroacetyl)carbamoyloxymethyl-3-cephem-4-carboxylic acid were dissolved in 6 ml of N,N-dimethylacetamide and, 276 mg of 2-(2-chloroacetamidothiazol-4-yl) -2-(*syn*)-methoxyiminoacetyl chloride hydrochloride are added under ice-cooling. The mixture is stirred under ice-cooling for 15 minutes and at room temperature for 2 hours. Thereafter, the reaction mixture is diluted with 30 ml of water and extracted twice with 50 ml portions of ethyl acetate. The extracts are pooled, washed with 50 ml of a saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulphate. The ethyl acetate is distilled off to yield 402 mg of 7-[2-(2-chloroacetamidothiazol-4-yl) -2-(*syn*)-methoxyimino]- acetamido-3-(N-chloroacetyl) carbamoyloxymethyl-3-cephem- 4-carboxylic acid as viscous oil.

NMR spectrum (60 MHz, in $CDCl_3$): 3.50 ppm (2H, quartet, 2-CH_2), 3.99 ppm(3H, singlet, $NOCH_3$), 4.04, 4.30 ppm (2Hx2, singlet x 2, $ClCH_2CO$ x 2), 5.10 ppm(1H, doublet, 6-H), 5.73 ppm(1H, doublet, 7-H), 7.32 ppm(1H, singlet, thiazole, 5-H)

(2) The entire amount of the above product is dissolved in 9 ml of tetrahydrofuran, followed by the addition of 168 mg of thiourea and 300 mg of sodium acetate trihydrate. The mixture is stirred at room temperature for 4 hours. The precipitate is collected by filtration, washed with ether and dissolved in 5 ml of water. The solution is adjusted to a pH of approximately 7 with sodium bicarbonate and purified by colume chromatography on Amberlite XAD-2 (trade mark). 58 mg of sodium 7-[2-(2-aminothiazol-4-yl)- 2-(*syn*)-methoxyiminoacetamido] -3-carbamoyloxymethyl-3- cephem-4-carboxylate are obtained as a white powder by the above procedure.

Elemental analysis, for $C_{15}H_{15}N_6O_7S_2Na\cdot 3H_2O$

Calculated:	C, 33.84;	H, 3.98;	N, 15.78
Found:	C, 33.94;	H, 3.82;	N, 15.42

NMR spectrum (60 MHz, in D_2O): 3.47 ppm(2H, quartet, 2-CH_2), 3.92 ppm(3H, singlet, $=NOCH_3$), 4.68 ppm (2H, quartet, -CHOCONH$_2$), 5.27 ppm(1H, doublet, 6-H), 5.72 ppm (1H, doublet, 7-H), 6.95 ppm (1H, singlet, thiazole 5-H)

Method for the production of 2-(2-chloroacetamidothiazol-4-yl)-2- (*syn*)-methoxyiminoacetyl chloride.

278 mg of the 2-(2-chloroacetamidothiazol-4-yl) -2-(*syn*)-methoxyiminoacetic acid obtained in Reference Example 6 are suspended in 5 ml of methylene chloride and, under ice-cooling, 208 mg of phosphorus pentachloride are added. The mixture is stirred at room temperature for 30 minutes, after which it is washed with petroleum ether. 276 mg of 2-(2-chloroacetamidothiazol-4-yl) -2-(*syn*)-methoxyiminoacetyl chloride are obtained as a powder by the above procedure.

Elemental analysis, for $C_8H_7N_3O_3SCl_2 \cdot HCl$:

Calculated:	C, 28.89;	H, 2.42;	N, 12.63
Found:	C, 28.47;	H, 2.73;	N, 12.12

Example 2

500 mg of 2-(2-chloroacetamidothiazol-4-yl) -2-(*syn*)-methoxyiminoacetic acid are dissolved in 22 ml of dry tetrahydrofuran and, under stirring, 182 mg of triethylamine are added. This mixture is cooled to -10°C and 245 mg of isobutyl chloroformate are added dropwise. The mixture is stirred at that temperature for 2 hours. 182 mg of triethylamine together with a solution (ice-cooled) of 590 mg of 7-amino-3-(1-methyl- 1H-tetrazol-5-yl) thiomethyl-3-cephem- 4-carboxylic acid in 18 ml of a 50% aqueous tetrahydrofuran are added to the resulting solution of mixed acid anhydride. The resulting mixture is stirred under ice-cooling for 1 hour and at room temperature for 2 hours. Thereafter, most of the tetrahydrofuran is distilled off under reduced pressure and the residue is diluted with 100 ml of water and with 40 ml of ethyl acetate. Then, under stirring, the aqueous layer is adjusted to a pH of substantially 2 with 1N-HCl. The layers are separated and the water layer is extracted with 60 ml of ethyl acetate. The ethyl acetate layers are pooled, washed with 50 ml of a saturated aqueous solution of sodium chloride and dried. The ethyl acetate is distilled off to yield 700 mg of 7-[2-(2-chloroacetamidothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido]-3- (1-methyl-1H-tetrazol-4-yl) thiomethyl-3-cephem- 4-carboxylic acid as a viscous oil.

(2) The entire amount of the above product is dissolved in 15 ml of tetrahydrofuran, and this is followed by the addition of 226 mg of thiourea and 406 mg of sodium acetate trihydrate. The mixture is stirred at room temperature for 4 hours. After the reaction, the precipitate is collected by filtration, washed with ether and dissolved in 10 ml of water. The solution is adjusted to a pH of substantially 7.0 with sodium bicarbonate and purified by column chromatography on Amberlite XAD-2 (trade marks). By the above procedure there are obtained 125 mg of sodium 7-[2-(2-aminothiazol- 4-yl)-2-(*syn*) -methoxyiminoacetamido]- 3-(1-methyl-1H-tetrazol-4-yl) thiomethyl-3-cephem-4-carboxylate as a white powder.

Elemental analysis, for $C_{16}H_{16}N_9O_5S_3Na \cdot 2H_2O$

Calculated:	C, 33,74;	H, 3.54;	N, 22.13
Found:	C, 34.18;	H, 3.57;	N, 21.79

NMR spectrum (60 MHz, in D_2O): 3.59 ppm(2H, quartet, 2-CH_2), 3.93 ppm(3H, singlet, =$NOCH_3$), 3.98 ppm(3H, singlet, N-CH_3), 4.08 ppm(2H, quartet, 3-CH_2), 5.12 ppm(1H, doublet, 6-H), 5.72 ppm(1H, doublet, 7-H), 6.93 ppm(1H, singlet, thiazole 5-H)

Example 3

(1) 762 mg of 7-aminocephalosporanic acid are dissolved in 15 ml of N,N-dimethylacetamide and, under ice-cooling, 931 mg of 2-(2-chloroacetamidothiazol-4-yl) -2-methoxyiminoacetyl chloride hydrochloride (prepared from the *syn*-isomer) are added. The mixture is stirred under ice-cooling for 15 minutes and at room temperature for 2 hours. The resulting reaction mixture is diluted with 10 ml of water and extracted with 100 ml portions of ethyl acetate. The extracts are pooled, washed with 100 ml of a saturated aqueous solution of sodium chloride and dried. The ethyl acetate is distilled off to yield 1.4 g of 7-[2-(2-chloroacetamidothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido]- cephalosporanic acid as an oil.

(2) The entire amount of the above product, is dissolved in 30ml of tetrahydrofuran, and this is followed by the addition of 500 mg of thiourea and, then, of 895 mg of sodium acetate trihydrate. The mixture is stirred at room temperature for 4 hours. The resulting precipitate is collected by filtration, washed with ether and dissolved in 6 ml of water. The solution is adjusted to a pH of substantially 7.0 with sodium bicarbonate and purified by means of column chromatography on Amberlite XAD-2 (trade marks). 78 mg of sodium 7-[2-(2-aminothiazol- 4-yl)-2-(*syn*)- methoxyiminoacetamido]cephalosporanate are obtained as a white powder by the above procedure.

Elemental analysis, for $C_{16}H_{16}N_5O_7S_2Na \cdot 2.5H_2O$

Calculated:	C, 36.78;	H, 4.05;	N, 13.40
Found:	C, 36.93;	H, 3.80:	N, 12.68

NMR spectrum (60 MHz, in D_2O): 2.07 ppm(3H, singlet, $COCH_3$), 3.52 ppm (2H, quartet, 2-CH_2), 3.98 ppm (3H, singlet, $=NOCH_3$), 4.75 ppm (2H, quartet, 3-CH_2), 5.21 ppm (1H, doublet, 6-H), 5.81 (1H, doublet, 7-H), 7.01 ppm (1H, singlet, thiazole 5-H)

Example 4

1g of the sodium 7-[2-2-aminothiazol-4-yl)-2-(*syn*) -methoxyiminoacetamido]-cephalosporanate obtained in Example 3, 270 mg of 2-methyl-1,3,4-oxadiazole-5-thiol potassium salt and 7mg of triethylbenzylammonium bromide are added to 10 ml of water. The resulting mixture is stirred in gaseous nitrogen at 60°C for 6 hours. After cooling, the reaction mixture is purified by means of column chromatography on Amberlite XAD-2 (trade mark). 110 mg of sodium 7-[2-(2-aminothiazol-4- yl)-2-(*syn*)-methoxyiminoacetamido]-3- (2-methyl-1,3,4-oxadiazol-4-yl) thiomethyl-3-cephem-4-carboxylate are obtained as a white powder by the above procedure.

Elemental analysis, for $C_{17}H_{16}N_7O_6S_3Na.2H_2O$:

Calculated:	C, 35.85;	H, 3.54;	N, 17.21
Found:	C, 35.73;	H, 3.72;	N, 17.01

NMR spectrum (60 MHz, in D_2O): 8.42 ppm (3H, singlet, oxadiazole 2-CH_3), 3.55 ppm (2H, quartet, 2-CH_2), 4.02 ppm (3H, singlet, $=NOCH_3$), 5.13 ppm (1H, doublet, 6-H), 5.73 ppm (1H, doublet, 7-H), 6.97 ppm (1H, singlet, thiazole 5-H)

Example 5

(1) 833 mg of 2-(2-chloroacetamidothiazol-4-yl) -2-(*syn*)-methoxyiminoacetic acid, 380 mg of N-hydroxysuccinimide and 630 mg of dicyclohexylcarbodiimide are added to 10 ml of tetrahydrofuran, and the resulting mixture is stirred at room temperature for 45 minutes. The precipitate is filtered off and the filtrate is cooled to 5°C. It is then added to a mixed solution of 650 mg of 7-aminodesacetoxycephalosporanic acid and 2 ml of bis(trimethylsilyl) -acetamide in methylene chloride, which has been previously cooled. The mixture is stirred at room temperature overnight and the solvent is then distilled off under reduced pressure. 50 ml of water together with 50 ml of ethyl acetate are added to the resulting oil, and the mixture is adjusted to pH of substantially 2.5 with 1N-hydrochloric acid. The two layers are separated, and then extracted with two 50 ml portions of ethyl acetate. The ethyl acetate layers are pooled, washed with water and dried. The ethyl acetate is then distilled off to yield 1.1 g of 7-[2-(2-chloroacetamidothiazol- 4-yl)-2-(*syn*)- methoxyiminoacetamido]∂ desacetoxycephalosporanic acid as an oil.

(2) The entire amount of the above product is dissolved in 25 ml of tetrahydrofuran, followed by the addition of thiourea and, then, of 632 mg of sodium acetate trihydrate. The mixture is stirred at room temperature for 4 hours. The precipitate is collected by filtration, washed with ether and dissolved in 10 ml of water. The solution is adjusted to a pH of substantially 7.0 with sodium bicarbonate, and is purified by means of column chromatography on Amberlite XAD-2 (trade mark). 120 mg of sodium 7-[2-(2-aminothiazol- 4-yl)-2-(*syn*) -methoxyiminoacetamido]desacetoxycephaloporante are obtained as a white powder by the above procedure.

Elemental analysis, for $C_{14}H_{14}N_5O_5S_2Na\cdot1.5H_2O$

Calculated:	C, 37.67;	H, 3.84;	N, 15.68
Found:	C, 37.37;	H, 3.98;	N, 15.38

NMR spectrum (60 MHz, in D_2O) δ : 1.94 ppm (3H, singlet, 3-CH_3), 3.46 ppm(2H, quartet, 2-CH_2), 4.00 ppm(3H, singlet, $=NOCH_3$), 5.17 ppm(1H, doublet, 6-H), 5.76 ppm (1H, doublet, 7-H), 6.99 ppm(1H, singlet, thiazole 5-H)

The minimal inhibitory concentrations (μg/ml) of some of the compounds according to the above Examples are as follows.

Microorganism	Compound of Ex. 1	Compound of Ex. 3	Compound of Ex. 2	Compound of Ex. 5
	Compound			
E. coli NIHJ	0.10	0.20	0.10	0.78
E. coli 0-111	0.024	0.05	0.024	0.39
E. coli T–7	0.39	0.78	0.78	6.25
K.pneumonia DT	< 0.012	0.024	0.024	0.20
K.pneumonia GN 3835	0.05	0.05	0.20	0.20
Ps. aeruginosa Pd 1	50	25	12.5	> 100
Ps. aeruginosa PM 3	3.13	1.56	0.78	25
Ps. aeruginosa P2	25	50	50	> 100
Ps. aeruginosa GN3407	> 100	50	50	> 100
Serr.marcescens IFO 12648	1.56	3.13	0.78	12.5
Serratia TN 0024	0.20	0.78	0.20	1.56
P. vulgaris IFO 3988	≦ 0.02	0.024	0.024	0.20
P. vulgaris GN 4413	1.56	0.78	0.39	1.56
P. mirabilis GN 4359	≦ 0.02	0.05	0.10	0.10
P. morganii IF03168	0.39	0.20	0.05	12.5
P. rettgeri 8(TN0336)	≦ 0.012	≦ 0.012	≦ 0.012	≦ 0.012
P. rettgeri 8 GN 4733	0.05	0.20	0.20	0.10
Ent. cloacae TN1282	6.25	6.25	1.56	50
Cit. freundii GN 99	0.20	0.20	0.10	3.13
Cit. freundii GN1706	0.39	0.39	0.20	6.25
Acinetobacter anitratus TN-1140	6.25	25	25	12.5

(Note) The following abbreviations are used to denote the microorganisms employed.

E: *Escherichia* K: *Klebsiella* Ps: *Pseudomonas*
Serr: *Serratia* P: *Proteus* Ent: *Enterobacter*
Cit: *Citrobacter*

Example 6

(1) 500 mg of 2-(2-chloroacetamidothiazol-4-yl)-2-(*syn*) -methoxyiminoacetic acid are dissolved in 20 mℓ of dry tetrahydrofuran, and, under stirring, 182 mg of triethylamine are added. The mixture is cooled to -10°C, after which 245 mg of isobutyl chloroformate are added dropwise. The mixture is stirred at that temperature for 2 hours. A solution (ice-cooled) of 180 mg of triethylamine and 492 mg 7-amino-3-carbamoyloxymethyl-3-cephem-4-carboxylic acid in a 50% aqueous tetrahydrofuran is added to the resulting mixed acid anhydride solution. The resulting mixture is stirred under ice-cooling for 1 hour and, then, at room temperature for 2 hours. Most of the tetrahydrofuran is distilled off under reduced pressure, and 100 mℓ of water and 40 mℓ of ethyl acetate are added to the residue. The mixture is adjusted to a pH of substantially 2 with 1N-hydrochloric acid. The two layers are separated and the water layer is extracted twice with 50 mℓ portions of ethyl acetate. The ethyl acetate layers are pooled, washed with water, dried and concentrated. 650 mg of 7-[2-(2-chloroacetamidothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido] -3-carbamoyloxymethyl-3- cephem-4-carboxylic acid are obtained as an oil by the above procedure.

(2) The entire amount of the above product is dissolved in 15 mℓ of tetrahydrofuran, followed by the addition of 226 mg of thiourea and 406 mg of sodium acetate trihydrate. The mixture is stirred at room temperature for 4 hours. The precipitate is collected by filtration, dissolved in 10 mℓ of water, adjusted to a pH of substantially 7 with sodium bicarbonate and purified by column chromatography of Amberlite XAD-2 (trade mark). 120 mg of sodium

7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido] -3-carbamoyloxymethyl-3-cephem-4-carboxylate are obtained as a white powder by the above procedure. In NMR spectrum and other properties, this product is found to be identical with the product obtained in Example 1.

Example 7

(1) 1,11 g of 2-(2-chloroacetamidothiazol-4-yl)-2- (*syn*)-methoxyiminoacetic acid are dissolved in 45 mℓ of dry tetrahydrofuran and, under stirring, 815 mg of tri-n-butylamine are added. The mixture is cooled to -10°C and 544 mg of isobutyl chloroformate are added dropwise. The mixture is stirred at -10°C for 2 hours, after which a cold solution of 741 mg of tri-n-butylamine and 1.4 g of 7-amino-3-(N-chloroacetyl) carbamoyloxymethyl-3-cephem-4-carboxylic acid in 40 mℓ of a 50% aqueous tetrahydrofuran is added. The mixture is stirred under ice-cooling for 1 hour and a roond at room temperature for 2 hours. Most of the tetrahydrofuran is distilled off under reduced pressure and the residue is diluted with 25 mℓ of water and washed with 40 mℓ of ethyl acetate. The water layer is recovered and, following the addition of 50 mℓ of ethyl acetate, it is adjusted to a pH of substantially 2.5 with 1N-hydrochloric acid. The mixture is separated into two layers. The water layer is further extracted twice with 50 mℓ portions of ethyl acetate. The extracts are pooled, washed with 100 mℓ of a saturated aqueous solution of sodium chloride, dried and finally concentrated. By the above procedure there is obtained 1 g of 7-[2-(2-chloroacetamidothiazol- 4-yl)-2-(*syn*) -methoxyiminoacetamido] -3-(N-chloroacetyl) carbamoyloxymethyl-3-cephem-4-carboxylic acid as an oil.

(2) The entire amount of the above product is dissolved in 22 ml of tetrahydrofuran, followed by the addition of 499 mg of thiourea and then, of 892 mg of sodium acetate trihydrate. The mixture is stirred at room temperature for 4 hours. The precipitate is collected by filtration, washed with ether and dissolved in 10 mℓ of water. The solution is adjusted to a pH of substantially 7 with sodium bicarbonate and purified by means of column chromatography on Amberlite XAD-2 (trade mark). 153 mg of sodium 7-[2-(2-aminothiazol- 4-yl)-2-(*syn*)- methoxyiminoacetamido]-3- carbamoyloxymethyl-3-cephem-4-carboxylate are obtained as a white powder by the above procedure. Based on NMR and other data, this product is found to be indentical with the compound obtained in Example 1.

Example 8

277 mg of 2-(2-chloroacetamidothiazol-4-yl)-2- (*syn*)-methoxyiminoacetic acid and 270 mg of t-butyl 7-aminodesacetoxycephalosporanate are dissolved in 20 mℓ of tetrahydrofuran followed by the addition of 206 mg of dicyclohexylcarbodiimide. The mixture is reached under stirring at room temperature for 6 hours. The precipitated urea derivative is filtered off and the filtrate is poured in to 50 mℓ of water and extracted with ethyl acetate. The ethyl acetate layer is washed with 0.5N-hydrochloric acid, water and a saturated aqueous solution of sodium chloride in that order, dried and finally concentrated. 320 mg of t-butyl 7-[2-(2-chloroacetamidothiazol- 4-yl)-2-(*syn*)- methoxyiminoacetamido] desacetoxycephalosporanate are obtained as an oil by the above procedure. NMR spectrum (60 Mhz, in $CDR\ell_3$) : 1.53 ppm (9H, singlet, t-C_4H_9), 2.13 ppm(3H, singlet, 3-CH_3), 3.39 ppm (2H, quartet, 2-CH_2), 4,06 ppm(3H, singlet, =$NOCH_3$), 4.29 ppm(2H, singlet, $C\ell CH_2CO$). 5.06 ppm(1H, doublet, 6-H), 5.86 ppm(1H, doublet of doublet, 7-H), 7.20 ppm(1H, singlet, thiazole 5-H), 8.14 ppm(1H, doublet, 7-CONH).

(2) The entire amount of the above product is dissolved in 12 mℓ of tetrahydrofuran, followed by the addition of 100 mg thiourea and 200 mg sodium acetate trihydrate. The mixture is stirred at room temperature for 8 hours. The reaction mixture is diluted with 30 mℓ of water and extracted with ethyl acetate. The ethyl acetate layer is washed with water, dried and concentrated. The resulting oil is purified by chromatography or silica gel. By the above procedure there are obtained 128 mg of t-butyl 7-[2-(2-aminothiazol-4-yl) -(*syn*)-methoxyiminoacetamido] desacetoxycephalosporanate as a powder.

NMR spectrum (60 MHz, in $CDR\ell_3$) ; 1.52 ppm(9H, singlet, t-C_4H_9), 2.10 ppm (3H, singlet, 3-CH_3), 3.40 ppm(2H, quartet, 2-CH_2), 4.00 ppm(3H, singlet, =$NOCH_3$), 5.05 ppm(1H,doublet, 6-H), 5.98 ppm(1H,doublet of doublet, 7-H), 6.66 ppm(1H, singlet, thiazole 5-H), 8.28 ppm(1H, doublet, 7-CONH).

(3) The entire amount of the above product is dissolved in a mixture of 1 mℓ trifluoroacetic acid and 0.1 mℓ anisole and the solution is stirred at room temperature for 1.5 hours, after which time ether is added. The resulting precipitate is collected by filtration and washed with ether. 70 mg of 7-[2-(2-aminothiazol-4-yl)-2- (*syn*)-methoxyiminoacetamido] -desacetoxycephalosporanic acid trifluoroacetate are obtained as a powder by the above procedure.

In NMR spectrum (60 MHz, in D_2O including $NaHCO_3$), this product is identified with the product obtained in Example 5.

Example 9

By the acylation of the 7-amino group of the corresponding cephalosporin compounds in a manner similar to that described in Example 2 (process A), and by using sodium 7-[2-(2-aminothiazol-4-yl)-2- (*syn*)-methoxyiminoacetamido]cephalosporanate and heterocyclic thiol compounds in a manner similar to that described in Example 4 (Process B), the following compounds are produced:

G(a) Sodium 7-[2-(2-aminothiazol-4-yl)-2-(*syn*) methoxyiminoacetamido]-3-(2-methyl-1,3,4-thiadiazol-5-yl) -thiomethyl-3-cephem-4-carboxylate (Process B)

NMR spectrum (60 MHz, in D_2O): 2.57 ppm(3H, singlet, thiazole 2-CH_3), 3.52 ppm(2H, quartet, 2-CH_2), 3.95ppm(3H, singlet, =$NOCH_3$), 5.18 ppm(1H, singlet, 6-H), 5.73 ppm(1H,singlet, 6-H), 5.73 ppm(1H, singlet, 7-H), 6.95 ppm(1H, singlet, thiazole 5-H)

(b) Disodium 7-[2-(2-aminothiazol-4-yl)-2-(*syn*) -methoxyiminoacetamido]-3-(2-carboxymethyl-1,3,4-thiadiazol-5-yl) -thiomethyl-3-cephem-4-carboxylate (Process B)

NMR spectrum (60 MHz, in D_2O): 3.56 ppm (2H, quartet, 2-CH_2), 3.96 ppm(3H, singlet, =$NOCH_3$), 4.18 ppm (2H, singlet, CH_2COONa), 5.20 ppm (1H, doublet, 6-H), 5.74 ppm(1H, doublet, 7-H), 6.97 ppm(1H, singlet, thiazole 5-H)

(c) Sodium 7-[2-(2-aminothiazol-4-yl)2-(*syn*) -methoxyiminoacetamido]-3-(1,2,3-triazol-5-yl) -thiomethyl-3-cephem-4-carboxylate (Process B)

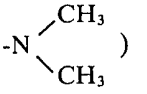
NMR spectrum (60 MHz, in D_2O): 3.57 ppm(2H, quartet, 2-CH_2), 3.94 ppm(3H, singlet, = $NOCH_3$), 5.21 ppm (1H, doublet, 6-H), 5.72 ppm(1H,doublet, 7-H), 6.94 ppm(1H, singlet, thiazole 5-H), 7.95 ppm(1H, singlet, triazole 4-H)

(d) Disodium 7-[2-(2-aminothiazol-4-yl)-2-(*syn*) -methoxyiminoacetamido]-3- (1-carboxymethyl-1,2,3,4-tetrazol-5-yl) -thiomethyl-3-cephem-4-carboxyate (Process B)

NMR spectrum (60 MHz, in D_2O): 3,55 ppm(2H, quartet, 2-CH_2), 3.96 ppm(3H,singlet, = $NOCH_3$), 4.72 ppm(2H, singlet, -N-CH_2COONa), 5.18 ppm(1H, doublet, 6-H), 5.72 ppm(1H, doublet, 7-H), 6.95 ppm(H, singlet, thiazole 5-H)

(e) 7-[2-(2-Aminothiazol-4-yl)-2-(*syn*) -methoxyiminoacetamido]-3-[1-(2-N, N-dimethylaminoethyl) -1,2,3,4-tetrazol-5-yl] -thiomethyl-3-cephem-4-carboxylic acid betaine (Process A,B)

NMR spectrum (60 MHz, in D_2O): 3.01 ppm(6H, singlet,



3.50 ppm(2H, quartet, 2-CH_2), 3.98 ppm (3H, singlet, =$NOCH_3$), 5.18 ppm(1H, doublet, 6-H), 5.74 ppm(1H, doublet, 7-H), 6.96 ppm(1H, singlet, thiazole 5-H)

(f) Sodium 7-[2-(2-aminothiazol-4-yl)-2-(*syn*) -methoxyiminoacetamido]-3-(6- methyl-1-oxopyridazin-3-yl)thiomethyl-3-cephem-4-carboxylate (Process B)

NMR spectrum (60 MHz, in D_2O): 2.60 ppm(3H, singlet, pyridazine 6-CH_3), 3.52 (2H, quartet, 2-CH_2), 3.98 ppm(3H, singlet, =$NOCH_3$), 5.21 ppm(1H, doublet, 6-H), 5.76 ppm(1H, doublet, 7-H), 6.95 ppm(1H, singlet, thiazole 5-H)

The minimum inhibitory concentration ($\mu g/m\ell$) of some of the compounds obtained as mentioned above are as follows.

Microorganism	Compound (a)	Compound (e)
E. coli NIHJ	0.20	0.20
E. coli 0–111	0.10	0.024
E. coli T–7	1.56	1.56
K. pneumoniae DT	0.05	0.10
K. preumoniae GN 3835	0.39	0.20
Serr. marcescens IFO 12648	0.78	1.56
Serratia TN 0024	0.78	0.78
P. vulgaris IFO 3988	0.10	0.20
P. vulgaris GN 4413	1.56	1.56
P. mirabilis GN 4359	0.20	0.39
P. morganii IFO 3168	0.10	0.20
P. rettgeri 8(TNO 336)	≦ 0.012	0.024
P. rettgeri GN 4733	0.39	0.78
Ent. cloacae IFO12937	3.13	6.25
Cit. freundii GN 99	0.20	0.20
Cit. freundii GN 1706	0.78	0.78

Example 10

280 mg of sodium carbonate are dissolved in a mixture of 20 mℓ water and 10 mℓ methanol, followed by the addition of 477 mg of 7-[2-(2-aminothiazol-4-yl)2-2(*syn*) -hydroxyiminoacetamido] -cephalosporanic acid. 300 mg of dimethyl sulphate are added dropwise to this mixed solution under ice-cooling and with stirring. Then, after 25 mimutes, 300 mg of potassium carbonate and 300 mg of dimethyl sulphate are added. After another 25 minutes, the reaction mixture is concentrated under reduced pressure and subjected to column chromatography on Amberlite XAD-2 (trade mark), elution being carried out with water. Sodium 7-[2-(2-aminothiazol- 4-yl)-2-(*syn*) -methoxyiminoacetamido]cephalosporanate is obtained by the above procedure. In NMR spectrum, etc., this product is identified with the compound obtained in Example 3.

Example 11

(1) 2.42 g of triethylamine are added to a suspension of 5.54 g of 2-(2-chloroacetamido-thiazol-4-yl) -2-(*syn*)-methoxyiminoacetic acid in 70 mℓ of methylene chloride to obtain a solution. Under ice-cooling and stirring, 4.16 g of phosphorus pentachloride are added in a single dose to the above solution. After 5 minutes, the ice-bath is removed and the mixture is stirred at room temperature for 20 minutes, after which it is concentrated under reduced pressure. 150 mℓ of hexane are added to the residue followed by decantations (twice). After the addition of 90 mℓ of anhydrous tetrahydrofuran, the precipitated triethylamine hydrochloride is filtered off, whereupon a solution of 2-(2-chloroacetamidothiazol-4-yl) -2-(*syn*)-methoxyiminoacetyl chloride in tetrahydrofuran is obtained.

On the other hand, to a suspension of 4.28 g of 7-aminodesacetoxycephalosporanic acid (7-ADCA) in a mixture of 50 mℓ water and 50 mℓ tetrahydrofuran there are added, under ice-cooling, 4.444 g of triethylamine to prepare a homogeneous solution. Under ice-cooling, the previously prepared acid chloride solution is added dropwise to the above solution over a period of 15 minutes. The resulting mixture is stirred at room temperature for 2 hours, after which a saturated aqueous solution of sodium chloride is added. The mixture is adjusted to a pH of substantially 2 with dilute hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer is washed with a saturated aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated to yield 8 g of a yellowish white powder. The powder is washed with 50 mℓ of methanol and the insolubles are collected by filtration. By the above procedure there are obtained 4.6 g of 7-[2-(2-chloroacetamido-thiazol- 4-yl)-2-(*syn*) -methoxyiminoacetamido] desacetoxy-cephalosporanic acid as a white powder.

NMR spectrum (60 MHz, in d_6-DMSO): 2.04 ppm (3H, singlet 3-CH_3). 3.50 ppm (2H, broad singlet, 2-CH_2), 3.92 ppm (3H, singlet, OCH_3), 4.40 ppm(2H, singlet, $C\ell CH_2CO$), 5.18 ppm(1H, doublet, 6-H), 5.78 ppm(1H, doubletx2, 7-H), 7.50 ppm(1H, singlet, thiazole 5-H).

(2) The above product is reacted and the treated in the same manner as Example 5 -(2) to yield sodium 7-[2-(2-amino-thiazol- 4-yl)-2-(*syn*)-methoxyiminoacetamido]desacetoxy-cephalosporanate as a white powder. In NMR spectra and other properties, this product is identified with the product obtained in Example 5.

Example 12

Sodium 7-[2-(2-aminothiazol-4-yl)-2-(*syn*) -methoxyiminoacetamido] desacetox-ycephalosporanate is suspended in 25 mℓ of dimethylformamide and, under ice-cooling. 3.75 g of iodomethyl pivalate are added, with 3 mℓ of dimethylformamide being further added. After 17 minutes, 100 mℓ of ethyl acetate are added to the reaction mixture and the insolubles are filtered off. The filtrate is washed with water, a 5% aqueous solution of sodium bicarbonate and a saturated aqueous solution of sodium chloride in that order and dried over magnesium sulphate. The ethyl acetate is then distilled off and the resulting oil, (2.4 g) is purified by chromatography on silica gel. By the above procedure there is obtained 1 g of pivaloyloxymethyl 7-[2-(2-aminothiazol- 4-yl)-2-(*syn*) methoxyiminoacetamido] desacetox-ycephalosporanate as a white powder.

Elemental analysis, for $C_{20}H_{25}N_5O_7S_2$

Calcd.	C,46.95;	H, 4.92;	N, 13.69
Found	C, 46.92;	H, 4.88;	N, 13.13

NMR spectrum (60 MHz, in CDC ℓ_3): 1.24 ppm (9H, singlet, $-C(CH_3)_3$), 2.16 ppm, 3.44 ppm(2H, doublet, $2\text{-}CH_2$), 4.10 ppm(3H, singlet, OCH_3), 516 ppm(1H, doublet, 6-H, 5.94 ppm(2H, singlet, $-OCH_2O$), 6.86 ppm(1H, singlet, thiazole, 5-H)

Example 13

0.7 g of the 7-[2-(2-chloroacetamidothiazol-4-yl) -2-(syn)-methoxyiminoacetamido] desacetoxycephalosporanic acid obtained by the procedure of Example 11-(1) is dissolved in an ice-cooled solution of 149 mg of triethylamine in 7 mℓ of dimethylformamide. Following the addition of 715 mg of iodomethyl pivalate, the mixture is stirred for 15 minutes. To this reaction mixture are added 40 mℓ of ethyl acetate and the mixture is washed with water a 5% aqueous solution of sodium bicarbonate and a saturated aqueous solution of sodium chloride in that order followed drying over magnesium sulphate. The ethyl acetate is distilled off to yield 0.8 g of crude pivaloyloxymethyl 7-[2-(2-chloroacetamidothiazol -4-yl)-2-(*syn*) -methoxyiminoacetamido]desacetoxycephalosporanate as a brown oil.

This product is dissolved in 3mℓ of dimethylacetamide, followed by the addition of 206 mg of thiourea. The mixture is stirred at room temperature overnight. To this are added 40 mℓ of ethyl acetate, and the resulting mixture is washed twice with 30 mℓ portions of a saturated aqueous solution of sodium chloride and dried over magnesuim sulphate. The ethyl acetate is distilled off and the resulting brown-coloured oil(0.4 g) is purified by chromatography on silica gel. By the above procedure there is obtained 0.2 g of pivaloyloxymethyl 7-[2-(2-aminothiazol -4-yl)-2-(*syn*)-methoxyiminoacetamido] desacetoxycephalosporanate as a white powder.

In NMR spectrum and other properties, this product is identified with the product obtained in Example 12.

Example 14

To a suspension of 831 mg of 2-(2-chloroacetamido-thiazol -4-yl)-2-(syn) -methoxyiminoacetic acid in 10 mℓ of methylene chloride are added 360 mg of triethylamine and 624 mg of phosphorus pentachloride. The mixture is stirred at room temperature for 20 minutes, after which 100 mℓ of hexane are added. The oil that has separated out is obtained by the decantation of the hexane and dissolved in 15 mℓ of tetrahydrofuran, whereby a solution of 2-(2-chloroacetamidothiazol -4-yl)-2-(*syn*) -methoxyiminoacetyl chloride is obtained.

On the other hand, 984 mg of 7-amino-3-(1-methyl -1H-tetrazol-5-yl)thiomethyl -3-cephem- 4-carboxylic acid and 660 mg of triethylamine are dissolved in 15 mℓ of a 50% aqueous tetrahydrofuran and, under ice-cooling, the previously prepared acid chloride solution is added dropwise to this solution. The mixture is stirred under ice-cooling for 2 hours, after which the reaction mixture is diluted with water, adjusted on a pH of substantially 2 with dilute hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer is washed with a saturated aqueous solution of sodium chloride and dried over magnesium sulphate. The ethyl acetate is distilled off and the residue is treated with ether. The resulting crystals are collected by filtration. By the above procedure there are obtained 1.3 g of7-[2-(2-chloroacetamidothiazol -4-yl)-2-(*syn*) -methoxyiminoacetamido] -3-(1-methyl-1H-tetrazol-5-yl)thiomethyl -3-cephem-4-carboxylic acid.

This product is identical with the intermediate obtained by the first part of the process described in Example 2. 5.8g of the product prepared as above are dissolved in 20 mℓ of dimethylacetamide and, under ice-cooling, 1.53 g of thiourea are added. The mixture is stirred at room temperature for 15 hours. To this reaction mixture are added 200 mℓ of

ice-water and the pH of the mixture is adjusted to pH 3.5 with sodium bicarbonate. The resultant precipitate is collected by filtration and dissolved in a 10% aqueous solution of sodium bicarbonate. The solution is then passed through a column packed with Amberlite XAD-2 (trade mark). By this purification procedure there are obtained 1.58 g of sodium 7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido] -3-(1-methyl-1H-tetrazol-5-yl) -thiomethyl-3-cephem -4-carboxylate as a white powder.

In NMR spectrum and other properties, this product is identified with the product obtained in Example 2.

Example 15

1 g of sodium 7-[2-(2-aminothiazol-4-yl) -2-(syn) -methoxyiminoacetamido] -3-(1-methyl-1H-tetrazol-5yl)thiomethyl -3-cephem-4-carboxylate is dissolved in 10 mℓ of dimethylformamide and, under ice-cooling and stirring, 0.85 g of iodomethyl pivalate is added. The mixture is stirred for 15 minutes. Following the addition of 40 mℓ of ethyl acetate, the reaction mixture is washed with water, a 5% aqueous solution of sodium bicarbonate and a saturated aqueous solution of sodium chloride in that order and, then, dried over magnesium sulphate. The ethyl acetate is distilled off under reduced pressure and the residue is dissolved in a small amount of ethyl acetate and filtered. Ether is added to the filtrate followed by cooling. The resulting precipitate is collected by filtration. By the above procedure there is obtained 0.4 g of pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido] -3-(1-methyl-1H-tetrazol -5-yl)-thiomethyl -3-cephem-4-carboxylate as a white powder.

Elemental analysis, for $C_{22}H_{27}N_9O_7S_3$:

Calculated:	C, 42.27;	H, 4.34
Found:	C, 42.29;	H, 4.40

NMR spectrum (60 MHz, in $CDC\ell_3$): 1.22 ppm(9H, singlet, $-C(CH_3)_3$),3.80 ppm(2H, broad singlet, 2-CH_2), 3.94, 4.06 ppm(3Hx2, singletx2, N-CH_3 & $-OCH_3$), 5.94 ppm(2H, singlet, $-OCH_2O$), 5.12 ppm (1H, doublet, 6-H), 6.06 ppm(1H, doubletx2, 7-H, 4.44 ppm (2H, doublet, 3-CH_2), 6.81 ppm(1H, singlet, thiazole 5-H).

Example 16

2.776 g of 2-(2-chloroacetamidothiazol-4-yl) -2-(*syn*) -methoxyiminoacetic acid and 1.2 g of triethylamine are dissolved in 20 mℓ of methylene chloride, followed by the addition of 2.08 g of phosphorus pentachloride. The mixture is stirred at room temperature for 20 minutes, after which 150 mℓ of hexane are added. The resulting oily precipitate is separated and dissolved in 20 mℓ of tetrahydrofuran to prepare a solution of 2-(2-chloroacetamidothiazol -4-yl)-2-(*syn*) -methoxyiminoacetyl chloride. On the other hand, 3.143 g of 7-amino-3-acetylacetoxymethyl -3-cephem-4-carboxylic acid and 2.20 g of triethylamine are dissolved in 50 mℓ of a 50% aqueous tetrahydrofuran. To this is added dropwise, under ice-cooling and stirring, the previously prepared acid chloride solution. The mixture is stirred under ice-cooling for 2 hours, after which water is added. The mixture is adjusted to pH 2.0 with dilute hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer is washed with a saturated aqueous solution of sodium chloride and dried over magnesium sulphate. The ethyl acetate is then distilled off and ether is added to the residue. The resulting crystalline product is collected by filtration. By the above procedure there are obtained 4.168 g of 7-[2-(2-chloroacetamidothiazol -4-yl)-2-(*syn*) -methoxyiminoacetamido] -3-acetylacetoxymethyl -3-cephem-4-carboxylic acid.

NMR spectrum (60 MHz, in d_6-DMSO): 2.14 ppm (3H, singlet, $-\overset{\overset{O}{\|}}{C}-CH_3$),
3.60 ppm(4H,broad singlet, $-\overset{\overset{O}{\|}}{C}-CH_2-\overset{\overset{O}{\|}}{C}-$ & 2-CH_2),
3.86 ppm(3H, singlet, OCH_3), 4.34 ppm (2H,singlet, $C\ell CH_2CO$), 4.91 ppm (2H, quartet, 3-CH_2), 5.13 ppm(1H, doublet, 6-H), 15.80 ppm(1H, doubletx2, 7-H), 7.40ppm(1H, singlet, thiazole 5-H)

Example 17

In 20 mℓ of dimethylacetamide there are dissolved 4.00 g of the 7-[2-(2-chloroacetamidothiazol -4-yl)-2-(*syn*) -methoxyiminoacetamido]-3-acetylacetoxymethyl -3-cephem-4-carboxylic acid obtained in Example 16, followed by the addition of 1.06 g of thiourea. The mixture is stirred at room temperature for 17 hours, after which 100 mℓ of ether are added. The oily precipitate is separated and dissolved in a 5% aqueous solution of sodium bicarbonate. The solution is lyophilised and the resulting powdery product is added to 50 mℓ of methanol. The insolubles are filtered off and the filtrate is added to 300 mℓ of ether. The precipitate is collected by

filtration. By the above procedure there are obtained 3.150 g of sodium 7-[2-(2-aminothiazol -4-yl)2-2(*syn*) -methoxyiminoacetamido] -3-acetylacetoxymethyl -3-cephem-4-carboxylate.

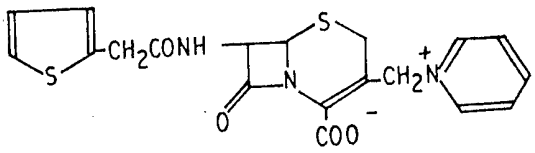
In 10 mℓ of water there are dissolved 933 mg of the above product, 350 mg of 1-(2-N,N-dimethylaminoethyl) -1H-tetrazol -5-thiol and 168 mg of sodium bicarbonate. The mixture is stirred at 55°C for 1 hour and the reaction mixture is directly passed through a column paced with Amberlite XAD-2 for purification. By the above procedure there are obtained 170 mg of sodium 7-[2-(2-aminothiazol -4-yl)-2-(*syn*) -methoxyiminoacetamido] -3-[1-(2-N,N-dimethylaminoethyl) -1H-tetrazol-5-yl]thiomethyl -3-cephem-4-carboxylate as a white powder. In NMR spectrum and other properties, this product is identified with the product obtained in Example 9.

The following table shows the protective effect (ED_{50}*, mg/kg) of the compounds prepared by the above
Examples on infected mice.

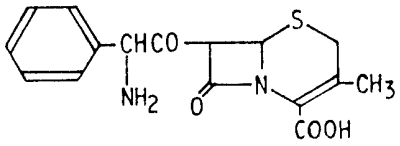
Table

Example No. of Sample	Administration	ED_{50}*	(mg/kg)
1	SC	0.015	(CER : 1.25)
2	SC	0.022	(CER : 1.25)
3	SC	0.018	(CER : 1.25)
5	SC	0.111	(CER : 1.25)
15	Oral	0.11	(CEX : 2.51)
17	Oral	0.27	(CEX : 2.51)

* Test animals : male mice (ICR/SLC)
5 mice per group per single dose
Infection : intraperitoneally with E. *coli* O-111
Observation period: 7 days
( ); control
SC = subcutaneous
CER = cephaloridine



CEX = cephalexin



Example 18

(1) To a suspension of 55.6 g of 2-(2-chloroacetamidothiazol -4-yl)-2-(*syn*) -methoxyiminoacetic acid in 600 ml of methylene chloride there are added 24.3g of triethylamine to obtain a solution. Under ice-cooling and stirring, 41.8g of phosphorous pentachloride are added in two doses to the above solution. After 5 minutes, the ice-bath is removed and the mixture is stirred at room temperature for 20 minutes, after which it is concentrated under reduced pressure. To the residue is added 1ℓ of hexane, followed by decantations (twice). After the addition of 600 ml of anhydrous tetrahydrofuran, the precipitated triethylamine hydrochloride is filtered off, whereupon a solution of 2-(2-chloroacetamidothiazol -4-yl)-2-(*syn*) -methoxyiminoacetyl chloride in tetrahydrofuran is obtained.

On the other hand, to a suspension of 54.7g of 7-amino-3- carbamoyloxymethyl -3-cephem-4- carboxylic acid in a mixture of 400 ml water and 400 ml tetrahydrofuran are

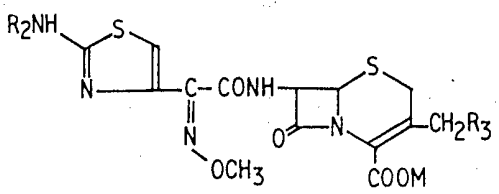
added 61g of triethylamine under ice-cooling to prepare a homogenous solution. Under ice-cooling, the previously prepared acid chloride solution is added dropwise to the latter solution over a period of 30 minutes. The mixture is stirred at room temperature for 2 hours, after which a saturated aqueous soltuion of sodium chloride is added. The mixture is adjusted to a pH of substantially 2 with dilute hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer is washed with a saturated aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated to yield 97.3g of 7-[2-(2-chloroacetamidothiazol -4-yl)-2-(*syn*) -methoxyiminoacetamido] -3-carbamoyloxymethyl -3-cephem-4-carboxylic acid. In NMR spectrum and other properties, this product is identified with the product obtained in part (1) of Example 6.

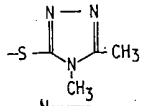
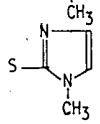
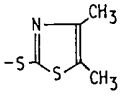
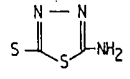
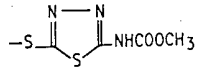
NMR spectrum (60 MHz, in d_6-DMSO): 3.56 ppm (2H, broad singlet, 2-CH_2), 3.93 ppm(3H, singlet, OCH_3, 4.35 ppm (2H, singlet, $CLCH_2CO$), 4.78 ppm 2H, quartet, 3-CH_2), 5.19 ppm (1H, doublet, 6-H), 5.84 ppm (1H, doublet x 2, 7-H), 6.56 ppm (2H, singlet, $OCONH_2$), 7.46 ppm (1H, singlet, thiazole 5-H)

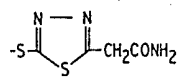
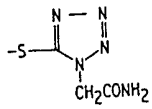
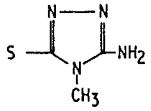
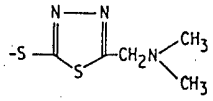
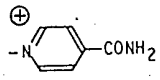
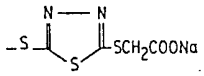
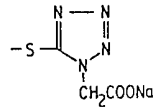
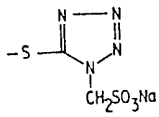
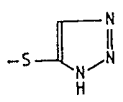
(2) 97.3g of the product prepared as above (1) are dissolved in 500 ml of N,N-dimethylacetamide and, under ice-cooling, 31.2g of thiourea are added to the solution. The mixture is stirred at room temperature for 15 hours. To this reaction mixture are added 2 1 of ether and then the oily product is separated. A suspension of this oily product in 300 ml of water is adjusted to pH 7.0 with sodium bicarbonate. The resulting solution is passed through a column packed with Amberlite XAD-2. By this purification procedure there are obtained 20.2g of sodium 7-[2-(2-aminothiazol -4-yl)-2-(*syn*) -methoxyiminoacetamido] -3-carbamoyloxymethyl -3-cephem-4-carboxylate as a white powder. In NMR spectrum and other properties, this product is identified with the product obtained in Example 1 or 6.

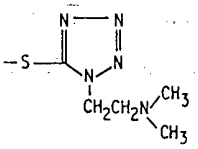
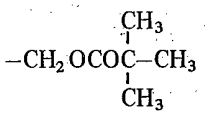
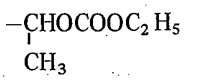
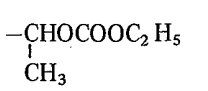
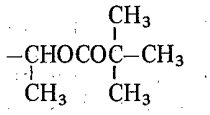
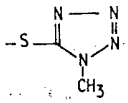
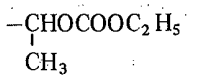
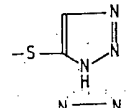
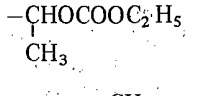
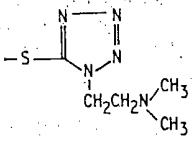
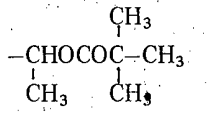
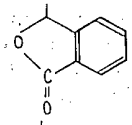
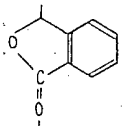
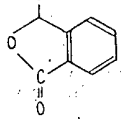
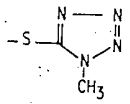
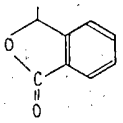
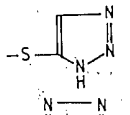
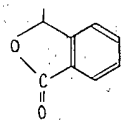
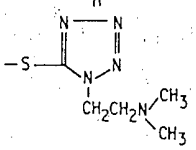
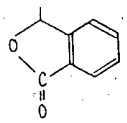
The structures and properties (IR spectrum) of the compounds (No.1 - 33) obtained according to the above processes of this invention are listed in the following table. In this table, by the IR spectrum (cm^{-1}, KBr) is meant the characteristic absorption band due to the β-lactam moiety.

Table



Compound No.	R_2	R_3	M	IR (cm^{-1}, KBr)
1	H		Na	1760
2	H		Na	1763
3	H		Na	1758
4	H		Na	1760
5	H		Na	1763
6	H		Na	1765
7	H		Na	1760

Compound No.	R_2	R_3	M	IR (cm^{-1}, KBr)
8	H		Na	1765
9	H		Na	1768
10	H		Na	1768
11	H	–OH	Na	1760
12	H		Na	1765
13	H		–	1765
14	H		–	1765
15	H		Na	1768
16	H		Na	1765
17	H		Na	1765
18	H	$-OCOCH_3$	$-CH_2OCOC(CH_3)_3$	1760
19	H	$-OCONH_2$	$-CH_2OCOC(CH_3)_2-CH_3$	1763
20	H		$-CH_2OCOC(CH_3)_3$	1765

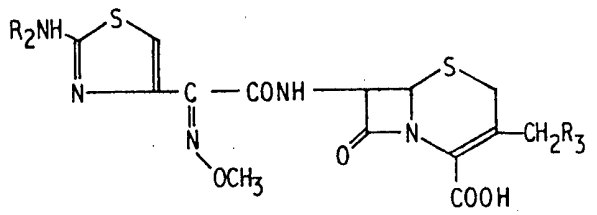
21	H			1768
22	H	H		1760
23	H	$-COCOCH_3$		1763
24	H	$-OCONH_2$		1763
25	H			1765
26	H			1768
27	H			1765
28	H			1760
29	H	$-OCOCH_3$		1763
30	H	$-OCONH_2$		1763
31	H			1765
32	H			1763
33	H			1768

The following are examples of injectable compositions:

250mg of sodium 7-[2-(2-aminothiazol -4-yl)-2-(*syn*) -methoxyiminoacetamido] -3-carbamoyloxymethyl-3- cephem-4-carboxylate, or sodium 7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoactamido] -3-(1-methyl-1H-tetrazol -5-yl)thiomethyl-3-cephem -4-carboxylate, or sodium 7-[2-(2-aminothiazol- 4-yl)-2-(*syn*) -methoxyiminoactamido] cephalosporanate are dissolved in 1 ml of sterilized water before use.

WHAT WE CLAIM IS:

1. A 7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido]cephalosporin derivative of the formula (I):



(I)

wherein R_3 is hydrogen or a residue of a nucleophilic compound; and R_2NH is an amino group which may optionally be protected,
or a pharmaceutically acceptable salt or ester thereof.

2. A compound as claimed in Claim 1, wherein R_2NH is an amino group.

3. A compound as claimed in Claim 1, wherein R_2NH is an amino group protected by a protective group.

4. A compound as claimed in Claim 3, wherein the protecting group is mono-halogenoacetyl.

5. A compound as claimed in any of Claims 2 to 4, wherein R_3 represents the residue of a nucleophilic compound and is hydroxy, mercapto, acyloxy derived from a lower aliphatic carboxylic acid having 2 to 4 carbon atoms which may optionally be substituted, acyloxy derived from an aromatic carboxylic acid which may optionally be substituted, carbamoyloxy, cyano, azido, amino, carbamoylthio, thiocarbamoyloxy, carbamoyloxy whose amino group is protected, phenylglycyloxy, a quaternary ammonium group, or a heterocyclic-thio group whose heterocyclic component is unsubstituted or substituted.

6. A compound as claimed in any of Claims 2 to 4, wherein R_3 is carbamoyloxy, acyloxy derived from a lower aliphatic carboxylic acid having 2 to 4 carbon atoms, or a heterocyclic-thio group whose heterocyclic component is unsubstituted or substituted.

7. A compound as claimed in Claim 6, wherein the heterocyclic component is a 5- or 6-membered ring including 1 to 4 hetero atoms consisiting of oxygen, sulfur or nitrogen atoms, in any combination, any nitrogen atom or atoms present being optionally in oxide form.

8. A compound as claimed in Claim 7 wherein the heterocyclic component is pyridyl, N-oxopyridyl, pyrimidyl, pyridazinyl, N-oxopyridazinyl, pyrazolyl, diazolyl, thiazolyl, thiadiazolyl, oxadiazolyl, triazolyl or tetrazolyl.

9. A compound as claimed in Claim 8, wherein the thiadiazolyl is 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl or 1,2,5-thiadiazolyl; the oxadiazolyl is 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl or 1,2,5-oxadiazolyl, the triazolyl is 1,2,3-triazolyl or 1,2,4-triazolyl; and the tetrazolyl is 1H-tetrazolyl or 2H-tetrazolyl.

10. A compound as claimed in Claim 7, wherein the heterocyclic component is 1,3,4-thiadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1H-tetrazolyl, imidazolyl or thiazolyl.

11. A compound as claimed in any of Claims 2 to 4, wherein R_3 is carbamoyloxy, acetoxy, (1-methyl-1H-tetrazolyl-5-yl) -thio or (2-methyl-1,3,4 -thiadiazol-5-yl)-thio.

12. A compound as claimed in Claim 6, wherein the heterocyclic component is substituted by one or two of any of lower alkyl, lower alkoxy, halogen, trihalogeno-lower alkyl, hydroxy, mercapto, amino, carboxyl, carbamoyl, di-lower alkyl amino-substituted lower alkyl, carboxymethyl, carbamoylmethyl, carboxymethylthio, sulphomethyl and methoxycarbonylamino.

13. A compound as claimed in Claim 6, wherein the heterocyclic component is substituted by one or two of any of lower alkyl, lower alkoxy, halogen, trihalogeno-lower alkyl, hydroxy, mercapto, amino, carboxyl, carbamoyl, di-lower alkyl amino-substituted lower alkyl and carboxymethyl.

14. A compound as claimed in Claim 1, wherein R_3 is a quaternary ammonium group.

15. A compound as claimed in Claim 1, wherein R_3 is 3-oxobutyryloxy group.

16. A compound as claimed in Claim 1, wherein R_3 is an acyloxy group derived from an

aromatic carboxylic acid which may optionally be substituted by a hydroxyl, carboxy, carboethoxycarbamoyl or carboethoxysulfamoyl group.

17. A compound as claimed in Claim 1, wherein R_3 is an unsubstituted or substituted pyridyl, N-oxidopyridyl, pyrimidyl, pyridazinyl, N-oxidopyrizadinlyl, pyrazolyl, imidazolyl, thiazolyl, thiadiazolyl, oxazolyl, oxadiazolyl, triazolyl or tetrazolyl group, the substituent being a lower alkoxyl, halogen, trihalogeno-lower alkyl, hydroxyl, mercapto, carboxyl, carbamoyl, di-lower alkylamino-lower alkyl, carboxymethyl, carbamoylmethyl, carboxymethylthio, sulfomethyl or methoxycarbonylamino group.

18. 7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido] -e-carbamoyloxymethyl-3- cephem-4-carboxylic acid, or its pharmaceutically acceptable salt.

19. 7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido] -3-(1- methyl-1H-tetrazol-5-yl) -thiomethyl-3-cephem-4- carboxylic acid, or its pharmaceutically acceptable salt.

20. 7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido]cephalosporanic acid, or its pharmaceutically acceptable salt.

21. 7-[2-(2-aminothiazol-4-yl)-2-(*syn*) -methoxyiminoacetamido]-3-(2-methyl -1,3,4-oxadiazol-5-yl) -thiomethyl-3-cephem-4- carboxylic acid, or its pharmaceutically acceptable salt.

22. 7-[2-(2-aminothiazol-4-yl)-2- (*syn*)-methoxyiminoacetamido] desacetoxycephalosporanic acid, or its pharmaceutically acceptable salt.

23. 7-[2-(2-aminothiazol-4-yl)-2-(*syn*) -methoxyiminoacetamido] -3-(2-methyl- 1,3,4-thiadiazol -5-yl)-thiomethyl-3-cephem -4-carboxylic acid, or its pharmaceutically acceptable salt.

24. 7-[2-(2-aminothiazol-4-yl)-2- (*syn*)-methoxyiminoacetamido] -3-(2-carboxymethyl-1,3,4 -thiadiazol-5-yl) -thiomethyl-3-cephem -4-carboxylic acid, or its pharmaceutically acceptable salt.

25. 7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido] -3-(1,2,3- triazol-5-yl) -thiomethyl-3-cephem -4-carboxylic acid, or its pharmaceutically acceptable salt.

26. 7-[2-(2-aminothiazol-4-yl)-2- (*syn*)-methoxyiminoacetamido] -3-(1-carboxymethyl-1,2,3,4-tetrazol -5-yl)-thiomethyl -3-cephem-4-carboxylic acid, or its pharmaceutically acceptable salt.

27. 7-[2-(2-aminothiazol-4-yl)-2- (*syn*)-methoxyiminoacetamido] -3-[1- (2-N,N-dimethylaminoethyl) -1,2,3,4-tetrazol-5-yl] -thiomethyl-3-cephem-4-carboxylic acid, or its pharmaceutically acceptable salt.

28. 7-[2-(2-aminothiazol-4-yl)-2- (*syn*)-methoxyiminoacetamido] -3-(6- methyl-1-oxypyridazin-3-yl) -thiomethyl-3-cephem-4- carboxylic acid, or its pharmaceutically acceptable salt.

29. Pivaloyloxymethyl 7-[2-(2-aminothiazoyl-4-yl) -2-(*syn*)-methoxyiminoacetamido] -desacetoxycephalosporanate.

30. Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido] -3-(1-methyl-1H-tetrazol-5-yl) -thiomethyl-3-cephem-4-carboxylate.

31. 7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido] -3-acetyl-acetoxymethyl-3-cephem -4-carboxylic acid, or its pharmaceutically acceptable salt.

32. 7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido] -3-pyridiniummethyl-3-cephem-4-carboxylic acid, or its pharmaceutically acceptable salt.

33. 7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido] -3-(4- carbamoyl-pyridinium) methyl-3-cephem -4-carboxylic acid, or its pharmaceutically acceptable salt.

34. 7-[2-(2-aminothiazol-4-yl)-2-(*syn*)- methoxyiminoacetamido] -3-(1-carbamoylmethyl-1H -tetrazol-5-yl)thiomethyl-3- cephem-4-carboxylic acid, or its pharmaceutically acceptable salt.

35. 7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido] -3-(1- sulfomethyl-1H-tetrazol -5-yl) thiomethyl-3-cephem-4- carboxylic acid, or its pharmaceutically acceptable salt.

36. 7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido] -3-(2-amino-1, 3, 4-thiadiazol-5-yl) thiomethyl-3-cephem-4-carboxylic acid, or its pharmaceutically acceptable salt.

37. 7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido] -3-(2-methoxycarbonylamino-1, 3, 4-thiadiazol-5-yl)thiomethyl -3-cephem-4-carboxylic acid, or its pharmaceutically acceptable salt.

38. 7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido] -3-(2-carbamoylmethyl-1, 3, 4-thiadiazol-5-yl)thiomethyl -3-cephem-4-carboxylic acid, or its pharmaceutically acceptable salt.

39. 7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido] -3-[2- (N,N-dimethylaminomethyl)-1, 3, 4-thiadiazol-5-yl]thiomethyl -3-cephem-4-carboxylic acid or its pharmaceutically acceptable salt.

40. 7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido] -3-(2-carboxymethylthio-1, 3, 4-thiadiazol-5-yl)thiomethyl -3-cephem-4-carboxylic acid, or its pharmaceutically acceptable salt.

41. 7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido] -3-(4, 5-dimethyl-1, 3-thiazol-2-yl)thiomethyl -3-cephem-4-carboxylic acid, or its pharmaceutically acceptable salt.

42. 7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido] -3-(1- methyl-1, 3-diazol-2-yl)thiomethyl -3-cephem-4-carboxylic acid, or its pharmaceutically acceptable salt.

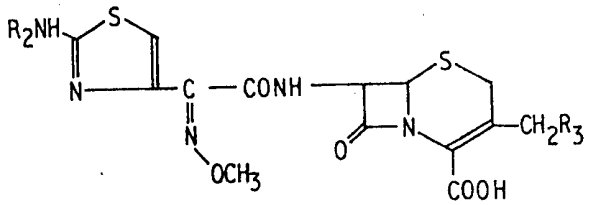
43. 7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyimonoacetamido] -3-(1, 3, 4-triazol-2-yl)thiomethyl -3-cephem-4-carboxylic acid, or its pharmaceutically acceptable salt.

44. 7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido] -3-(1,2- dimethyl-1,3,4 -triazol-5-yl)thiomethyl -3-cephem-4-carboxylic acid, or its pharmaceutically acceptable salt.

45. 7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido] -3-(1- methyl-2-amino-1,3,4-triazol-5-yl)thiomethyl -3-cephem-4-carboxylic acid, or its pharmaceutically acceptable salt.

46. A compound (I) as claimed in Claim 1, or a pharmaceutically acceptable salt or ester thereof, substantially as herein described with reference to any of the specific examples.

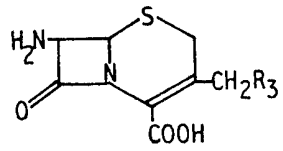
47. A process for producing a 7-[2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido]cephalosporin derivative of the formula (I):



(I)

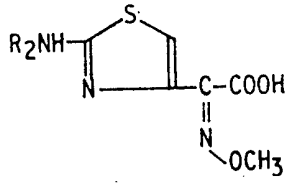
wherein R_3 is hydrogen or a residue of a nucleophilic compound; and R_2NH is an amino group which may optionally be protected,

or a pharmaceutically acceptable salt thereof, which process comprises (1) reacting a 7-aminocephalosporin derivative of the formula (II):



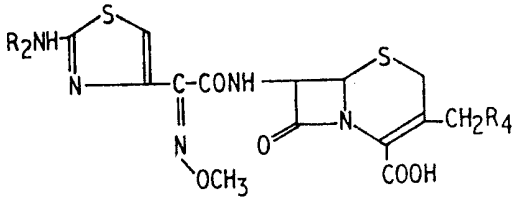
(II)

wherein R_3 has the meaning defined above, with a compound of the formula (III):



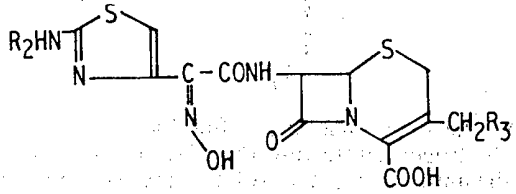
(III)

wherein R_2NH has the meanings defined above, if necessary followed by removing the protective group, or (2) reacting a compound of the formula (IV):



(IV)

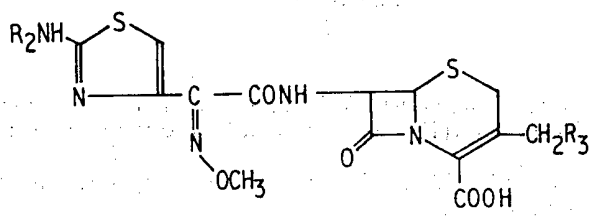
wherein R_2NH has the meanings defined above; and
R_4 is acyloxy, carbamoyloxy or halogen,
with a nucleophilic compound, if necessary followed by removing the protective group, or (3) subjecting a compound of the formula (VI):



(VI)

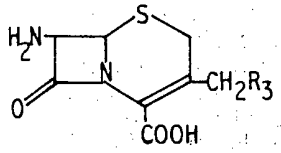
wherein R_3 and R_2NH have the meanings defined above, to a methylation reaction, and, if desired, converting the product obtained by procedure (1), (2) or (3) to a pharmaceutically acceptable salt or ester thereof.

48. A process for producing a 7-]2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetamido]cephalosporin derivative of the formula:



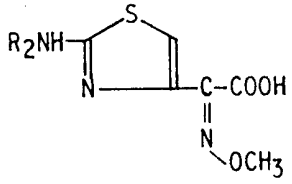
(I)

wherein R_3 is hydrogen or a residue of a nucleophilic compound, R_2NH is an amino group which may optionally be protected,
which comprises reacting a 7-aminocephalosporin derivative of the formula:



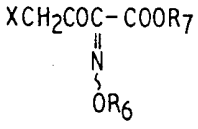
(II)

wherein R_3 has the meanings defined above, with a 2-(2-aminothiazol-4-yl) -2-(*syn*)-methoxyiminoacetic acid of the formula:



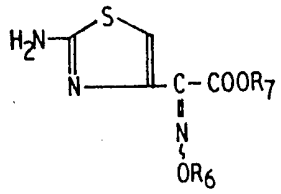
(III)

wherein R_2 has the meanings defined above, which is prepared by (i) reacting a compound of the formula:



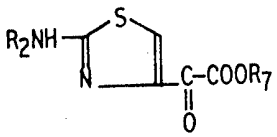
(VII)

wherein X is halogen, R_6 is hydrogen or methyl and R_7 is a lower alkyl of 1 to 3 carbon atoms, with thiourea to obtain a compound of the formula:



(VIII)

wherein R_6 and R_7 have the same meanings defined above,
in the case of R_6 being hydrogen subjecting the obtained compound to a methylation reaction, then protecting the amino group and isolating the *syn* - isomer of the thus obtained compound; or (ii) reacting a compound of the formula (VII) with thiourea in water or a mixture of water and a water-miscible solvent and, if necessary, in the presence of a basic reagent; or (iii) reacting a compound of the formula:



(IX)

wherein R_2 and R_7 are as previously defined, with O-methylhydroxylamine; or a salt or reactive derivative of compound (III), if necessary followed by removing the protective group of the amino group.

49. A process as claimed in Claim 47 or 38, substantially as hereinbefore described with reference to any of the Examples.

50. A compound (I) as defined in Claim 1, or a pharmaceutically acceptable salt or ester thereof, when produced by a process as claimed in any of Claims 47 to 49.

51. A pharmaceutical composition containing a compound (I) or salt or ester thereof as claimed in any of Claims 1 to 46 or in Claim 50, together with a pharmaceutically acceptable excipient or diluent therefor.

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