

PATENT SPECIFICATION

(11) 1 491 018

1 491 018

- (21) Application No: 55294/74 (22) Filed 20. Dec. 1974
 (31) Convention Application No. 49/001 521
 (32) Filed 25 Dec. 1973
 (31) Convention Application No. 49/020/752
 (32) Filed 20 Feb. 1974
 (31) Convention Application No. 49/042 574
 (32) Filed 15 April 1974
 (31) Convention Application No. 49/082 623
 (32) Filed 17 July 1974
 (31) Convention Application No. 49/131 381
 (32) Filed 13 Nov. 1974 in
 (33) Japan (JA)
 (44) Complete Specification published 9 Nov. 1977
 (51) INT CL² C07D 501/20; A61K 31/545
 (52) Index at acceptance

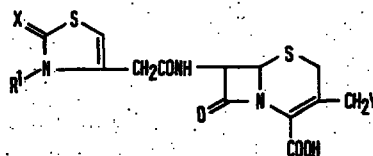


C2C 1314 1371 1382 1384 1412 142X 1432 1440 1450 1464
 1530 1562 1590 1600 1601 214 215 21X 220 22Y 246
 247 250 251 252 255 256 25Y 28X 292 29Y 305 30Y
 311 313 314 31Y 320 321 322 323 328 32Y 334 339 33Y
 340 342 34Y 351 352 355 360 361 366 367 368 36Y 371
 372 373 37Y 380 387 394 396 39Y 40Y 490 519 60Y 612
 614 625 628 638 650 652 658 65X 670 694 750 754 75X
 761 762 768 76Y 78X 790 79Y KE QZ RP SL TX

(54) CEPHALOSPORIN DERIVATIVES

(71) We, TAKEDA YAKUHIN KOGYO KABUSHIKI KAISHA (also known as TAKEDA CHEMICAL INDUSTRIES LTD.), a Corporation organized 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 novel 7-acyl groups and preparations thereof. More particularly, this invention provides 7 - [2-(2 - exo - substituted - 4 - thiazolin - 4 - yl)acetamido]cephalosporin derivatives of the formula:



[I]

or a tautomeric form thereof; wherein R¹ is a hydrogen atom or an alkyl group; X is an oxygen or sulphur atom or a group of formula =NR² wherein R² is a hydrogen atom or an alkyl group, or R¹ and R² can together form an alkylene group, and Y is an acetoxy group or a group of formula SR³ wherein R³ is a nitrogen-containing heterocyclic group, or a pharmaceutically acceptable salt thereof; and also relates to processes for producing the same.

These compounds are found to have a broad antimicrobial spectrum and, in particular, are effective against gram-negative bacteria including *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Proteus morganii*, as well as gram positive ones. Thus, these compounds may be used for antimicrobial agents in therapeutical purposes.

Heretofore, studies on synthetic cephalosporin derivatives have been directed to the conversion of 7-aminocephalosporanic acid to various acyl derivatives at the 7-position or to derivatives at the 3-acetoxy group in order to synthesize compounds

having either a broad antibacterial spectrum or a specific antibacterial spectrum. However, these well-known cephalosporin derivatives are not yet satisfactory in antimicrobial activities against a wide variety of microorganisms. Hence, a compound has been sought after which has a broad or antimicrobial spectrum and is effective even at a lower concentration.

It has now been found that novel cephalosporin derivatives represented by the above formula [I] have broader antimicrobial spectra as compared with those of known cephalosporins. For example, the cephalosporin derivatives [I] are desirable cephalosporin antibiotics, having a strong and broad antimicrobial spectrum especially against such gram-negative bacteria as *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris* and *Proteus morganii*, showing greater inhibitory activity in comparison with known cephalosporins.

Referring, now, to the above formula [I], R³ stands for a nitrogen-containing heterocyclic group containing not less than one nitrogen which may be in the oxide form, and may contain, in addition to the nitrogen or nitrogens, such others as oxygen or/and sulphur. The nitrogen-containing heterocyclic group desirably has one to four hetero atoms in its heterocyclic ring and the ring may be 5 or 6 membered one. As such nitrogen-containing heterocyclic group, there may be mentioned, amongst others, pyridyl, N-oxido-pyridyl, pyrimidyl, pyridazinyl, N-oxido-pyridazinyl, pyrazolyl, diazolyl, thiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1H-tetrazolyl, 2H-tetrazolyl and others. Each of these nitrogen-containing heterocyclic groups may be further substituted and, as the substituents, there may be mentioned the following groups, the term "lower" being used hereinafter to indicate C₁ and C₂ alkyl groups or derivatives:—monovalent groups, for example, lower alkyl (or substituted alkyl) such as methyl, ethyl, or trifluoromethyl, lower alkoxy such as methoxy, or ethoxy, halogen such as chlorine, or bromine, amino, mercapto, hydroxyl, carbamoyl, or carboxy group, or a substituted lower alkyl group, a substituted mercapto group, or a mono- or di-substituted amino group. The substituents in the substituted lower alkyl group may be hydroxyl, mercaptoamino, morpholino, carboxyl, sulfo, carbamoyl, alkoxycarbonyl, mono-, di- or tri-lower alkylamino, mono- or di-lower alkylcarbamoyl, alkoxy, alkylthio, alkylsulfonyl, acyloxy, or morpholinocarbonyl group, wherein the acyloxy group is exemplified by acetoxy, propionyloxy, valeryloxy, caproyloxy, benzoyloxy, or phenyl-acetoxy, and the alkoxy group by methoxy, ethoxy, propoxy, butoxy, isobutoxy, hexyloxy, octyloxy, decyloxy, or dodecyloxy. The substituent of the substituted mercapto group may be a lower alkyl group or a substituted lower alkyl group above mentioned. The substituents of the mono- or di-substituted amino group may be a lower alkyl group, an alkoxycarbonyl, an acyl, carbamoyl, a lower alkylcarbamoyl, or a substituted lower alkyl group mentioned above.

Specifically, use may be made of, for example, a substituted lower alkyl group such as carboxymethyl, carbamoylmethyl, an N-lower alkylcarbamoylmethyl (e.g. N,N-dimethylcarbamoylmethyl), a hydroxy-lower alkyl (e.g. hydroxymethyl, or 2-hydroxyethyl), an acyloxy-lower alkyl (e.g. acetoxymethyl, or 2-acetoxyethyl), an alkoxycarbonylmethyl (e.g. methoxycarbonylmethyl, hexyloxycarbonylmethyl, or octyloxycarbonylmethyl), methylthiomethyl, methylsulfonylmethyl, an N-lower alkyl-amino-lower alkyl (e.g. N,N-dimethylaminomethyl, N,N-dimethylaminoethyl, or N,N,N-trimethylammoniummethyl), or morpholinomethyl, mono- or di-substituted amino groups such as a lower alkylamino (e.g. methylamino), a sulfo-lower alkyl-amino (e.g. 2-sulfo-ethylamino), a hydroxy-lower alkylamino (e.g. hydroxyethyl-amino), a lower alkylamino-lower alkylamino (e.g. 2-dimethylamino-ethylamino, or 2-trimethylammoniummethylamino), an acylamino (e.g. acetyl-amino, 2-dimethylamino-acetyl-amino, or 2-trimethylammonium-acetyl-amino), or a lower alkoxycarbonylamino (e.g. methoxycarbonylamino), a substituted mercapto group such as methylthio, 2-hydroxyethylthio, a 2-acyloxyethylthio (e.g. 2-acetoxyethylthio, 2-phenylacetoxyethylthio, or 2-caproyloxyethylthio), carboxymethylthio, an alkoxycarbonylmethylthio (e.g. methoxycarbonylmethylthio, or hexyloxycarbonylmethylthio), carbamoylmethylthio, an N-lower alkylcarbamoylmethylthio (e.g. N,N-dimethylcarbamoylmethylthio), acetyl-methylthio, an N-lower alkylamino-lower alkylthio (e.g. 2-N,N-dimethylamino-ethylthio, or 2-N,N,N-trimethylammonium-ethylthio), morpholinocarbonylmethylthio, or 2-sulfoethylthio.

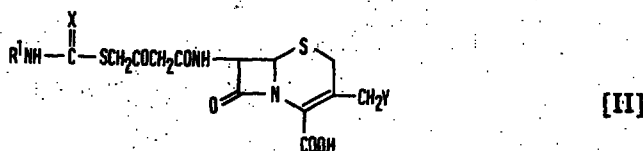
The 7 - [2 - (2 - exo - substituted - 4 - thiazolin - 4 - yl) - acetamido]cephalosporin derivatives [I] of this invention may be used with its 4-carboxyl group being free or after being made into a pharmaceutically acceptable salt with a nontoxic

cation such as sodium, or potassium; a basic amino acid such as arginine, ornithine, lysine, or histidine; or a polyhydroxyalkylamine such as N-methylglucamine, diethanolamine, triethanolamine, or tris-hydroxymethylaminomethane. The compound [I] may also be used after it has been converted to a biologically active ester derivative by esterification of its 4-carboxyl group, said ester derivative being conducive to, for instance, an increased level of the compound in the blood of a patient or/and a longer duration of activity. As the ester residues of use for this purpose, there may be mentioned, for example, alkoxymethyl and α -alkoxyethyl and other α -alkoxy- α -substituted methyl groups, e.g. methoxymethyl, ethoxymethyl, isopropoxymethyl, α -methoxyethyl, or α -ethoxyethyl; alkylthiomethyl groups, e.g. methylthiomethyl, ethylthiomethyl, or isopropylthiomethyl; and acyloxymethyl and α -acyloxy- α -substituted methyl groups, e.g. pivaloyloxymethyl, or α -acetoxybutyl.

The cephalosporin derivatives [I] of the present invention may be prepared by a variety of means. The following are examples of them.

Process 1.

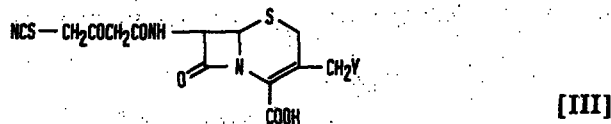
A process for producing cephalosporin derivatives of the formula [I], in which a compound of the formula:



wherein each of the symbols has the same meaning as above, or a salt or an ester thereof, is subjected to ring closure reaction with elimination of water.

Process 2.

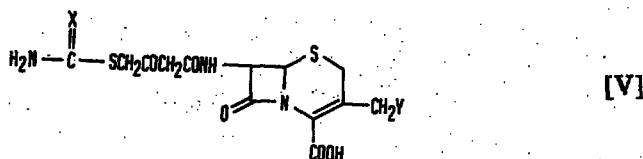
A process for producing cephalosporin derivatives of the formula [I], in which a compound of the formula:



wherein Y has the same meaning as above, or a salt or an ester thereof is allowed to react with a compound of the formula:



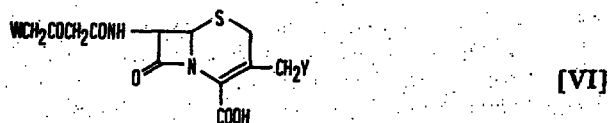
wherein X has the same meaning as above, to obtain a compound of the formula:



wherein each of the symbols has the same meaning as above, and thus obtained compound -V] is subjected to ring closure reaction with elimination of water.

Process 3.

A process for producing cephalosporin derivatives of the formula [I], in which a compound of the formula:



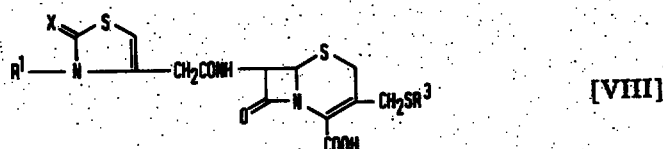
wherein W is a halogen and other symbol has the same meaning given hereinbefore, or a salt or an ester thereof, is allowed to react with a compound of the formula:



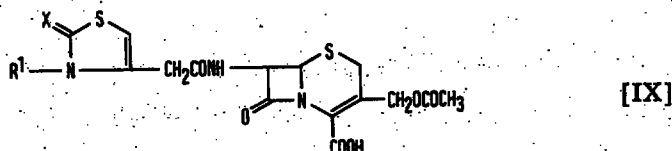
wherein each of the symbols has the meaning given hereinbefore, or a salt thereof, to obtain a compound of the formula [II] and the thus obtained compound [II] is subjected to ring closure reaction with elimination of water.

Process 4.

A process for producing cephalosporin derivatives of the formula:



wherein each of the symbols has the same meaning as above, in which a compound of the formula:



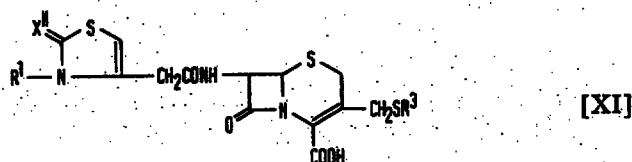
wherein each of the symbols has the same meaning given hereinbefore, or a salt thereof, is allowed to react with a compound of the formula:



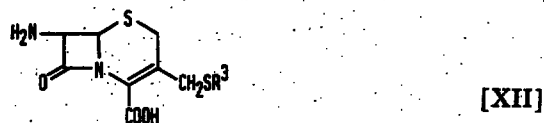
wherein R^3 is the same meaning as above.

Process 5.

A process for producing cephalosporin derivatives of the formula:



wherein X'' represents oxygen, sulfur or an imino group which may be protected, and each of other symbols has the same meaning as above, in which a compound of the formula:



wherein R^3 has the same meaning as above, or a salt or an ester thereof, is allowed to react with a compound of the formula:



wherein X' represents oxygen, sulfur or a protected imino group and R^1 has the same meaning as above, or reactive derivative thereof, and, if desired, the protective group of the imino group is further removed from the product.

A detailed explanation of these processes 1 to 5 follows.

Process 1.

The ring closure reaction of the compounds [II] to the objective compounds [I] takes place readily in a solvent. As the solvent just mentioned, there may be employed, usually, water, alcohols (e.g. methanol, or ethanol), acetone, acetonitrile, chloroform, dioxane, ethylene chloride, tetrahydrofuran, ethyl acetate, dimethylformamide and

dimethylsulfoxide, as well as suitable mixtures of such solvents. The reaction is accelerated by the presence of a Lewis acid or a base which works as a dehydrating catalyst. As said acid, there may be employed any of phosphate buffers of acid pH, hydrochloric acid, phosphoric acid and sulfuric acid, as well as their acidic alkali metal salts, and other inorganic acids and organic acids such as acetic acid and lactic acid. As the base, there may usually be employed any of such inorganic or organic bases as basic phosphate buffers, alkali metal hydroxides (e.g. sodium hydroxide, or potassium hydroxide), alkali metal hydrogen carbonates (e.g. sodium hydrogen carbonate, or potassium hydrogen carbonate, ammonia, N,N-dicyclohexylamine, triethylamine, pyridine, ammonia and N,N-dimethylaniline. The starting compound [II] is subjected to the reaction as the free acid or as an alkali metal salt, e.g. the salt of sodium, or potassium, or as an easily cleavable ester such as the trimethylsilyl ester, methoxymethyl ester, 2-methylsulfonylethyl ester, p-nitrobenzyl ester, 2,2,2-trichloroethyl ester, or trityl ester. The reaction usually proceeds satisfactorily enough at the temperatures from -70°C to room temperature, although it may be conducted under heating or cooling, if necessary. The reaction is carried out under stationary conditions for a few to tens of hours, whereby the ring closure product [I] is formed. When a buffer solution is selected as the solvent, the conversion to [I] may take place to a satisfactory extent merely by dissolving [II] in the buffer and allowing the solution to stand, for the buffer contains the above-mentioned acid or base as one of its components.

Whether an acid is (or acid conditions are) required or a base is (or basic conditions are) required for this reaction can be easily ascertained, for example by mixing [II] with said acid or base in a solvent in a small scale and examining the resultant by thin-layer chromatogram, for the starting compound [II] and desired product [I] can be easily differentiated by thin-layer chromatography. In this way, the selective necessity of an acid or a base and other required reaction conditions can be selected with accuracy.

It should also be understood that some of compounds [II] are so ready to cyclize that they may cyclize under the above-described reaction conditions employed in the production of themselves. In such cases, it is unnecessary to isolate [II] but [I] is formed under the very conditions of manufacture of the starting material. That is to say, the compounds [II] are so likely to cyclize into [I] that even during the preparative reactions of themselves, e.g. the first step of Process 2 and 3, they gradually are transformed into [I]. Therefore, it is practical to conduct the present reaction in combination with the first step of Process 2 and 3.

The 7 - [2 - (2 - exo - substituted - 4 - thiazolin - 4 - yl)acetamido] - cephalosporin derivative [I] thus resulted can be isolated and purified by procedures which are known *per se*, such as solvent extraction, pH adjustment, phasic transfer, distillation, crystallization, recrystallization, chromatography, or de-esterification.

Process 2.

The 7 - (4 - thiocyno - 3 - oxobutyrylamido) - cephalosporin derivative [III] is reacted with water, hydrogen sulfide or an amine of the formula H_2X (X is as hereinbefore defined) [IV]. The molecular state in which [III] is present, the types of solvent, acid and base, the procedure for selecting the conditions of reaction, the reaction conditions and the procedure for isolating the product may be similar to those described above in connection with the conversion of [II] to [I]. Practically, the compounds [V] generated are, without isolation, *in situ*, transformed into [I] spontaneously or, if desired, by the treatment described in the above Process 1.

Process 3.

The halogen W in formula [VI] may usually be chlorine or bromine. As preferred examples of said thiol compound [VII], there may be mentioned thiourea, alkylated or acylated thiourea, N,N'-ethylenethiourea, ammonium dithiocarbamate, and ammonium thiocarbamate. Referring to the reaction of [VI] with [VII], the former compound [VI] is usually subjected to the reaction in its free form and the latter [VII] is used ordinarily in its free form or in the form of a salt at the thiol function thereof with an alkali metal, e.g. lithium, sodium or potassium, or ammonium. The reaction is ordinarily carried out by admixing equimolar proportions of the two materials together with 1 to 2 molecular equivalents of a base in the presence of a solvent. As solvents suited for this reaction, there may be mentioned water, methanol, ethanol, acetone, dioxane, acetonitrile, chloroform, ethylene chloride, tetrahydrofuran, ethyl acetate, dimethylformamide, dimethylacetamide and other common organic solvents which will not interfere with the reaction. Of these solvents, hydrophilic

solvents may be used in admixture with water. As the base, there may be mentioned, among others, alkali hydroxides such as sodium hydroxides, or potassium hydroxide; alkali metal carbonates such as sodium carbonate, or potassium carbonate; alkali metal hydrogen carbonates such as sodium hydrogen carbonate; and organic tertiary amines such as trimethylamine, triethylamine, or pyridine. Since the base is intended for the neutralization of the carboxyl group of the cephalosporin and the hydrogen halide that will be liberated in the course of the reaction, it is desirably used in a proportion of about 2 equivalents when the substituted thiol [VII] is employed in its free form or a proportion of about one equivalent when the same [VII] is employed in the form of an alkali metal salt, for instance. There is no particular limitation upon the reaction temperature, although the reaction ordinarily is desirably conducted under cooling, e.g. -30°C to the room temperature. The reaction generally proceeds fast, going to conclusion within 10 minutes, although at times it takes more than about half an hour to carry through the reaction.

The hydrogen halides or their salts liberated during the reaction of compounds [VI] with [VII] may be served as efficient dehydrating catalyst for the ring closure of the resulted compounds [II] and, therefore, the second step of the present Process 3 proceeds generally without any additional treatments. Alternatively, the intermediates [II] may be isolated and purified by *per se* known process and subjected to the ring closure reaction of the Process 1.

Process 4.

The 7 - [2 - (2 - exo - substituted - 4 - thiazolin - 4 - yl)acetamido] - 3-acetoxymethyl - cephalosporin derivative [IX], which is among the compounds obtained according to the above-described Processes 1 to 3, can be further reacted with a nitrogen-containing heterocyclic thiol of formula R^3SH [X] to obtain a 7 - [2 - (2 - exo - substituted - 4 - thiazolin - 4 - yl)acetamido] - cephalosporin derivative [VIII]. The [IX] to be used may be an isolated compound or the reaction mixture of the above-mentioned Processes 1 to 3. The compounds [IX] may be used as a free form or the salt of the base used in the procedure described above, examples of which are salts with alkali metals such as sodium, or potassium, or organic amines such as trimethylamine, or triethylamine. The nitrogen-containing heterocyclic thiol [X] to be employed is subjected to the reaction in its free form or as a salt at its thiol function with an alkali metal such as lithium, sodium, or potassium.

This reaction is usually effected by heating at 40 to 80°C in the neighborhood of neutrality. The reaction is carried out in a solvent, preferred examples of which are water and aqueous solvents such as mixtures of water with highly polar solvents which will not interfere with the reaction, e.g. acetone, tetrahydrofuran, dimethylformamide, methanol, ethanol, or dimethylsulfoxide.

When [IX] is used in its free form, it is sometimes desirable to incorporate in the reaction system a base such as sodium hydrogen carbonate, potassium hydrogen carbonate, sodium carbonate, or potassium carbonate, so as to adjust the pH to neutral. If necessary, a buffer solution may also be employed. The reaction time and other conditions of reaction should be determined with reference to such factors as the types of starting materials and solvent, and temperature. The cephalosporin derivatives [VIII] thus resulted can be isolated and purified by conventional procedures similar to those hereinbefore described.

Process 5.

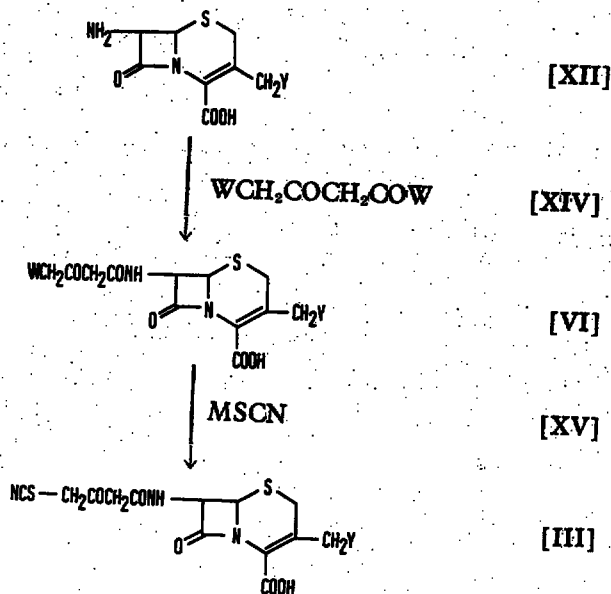
In conducting this reaction, the 4-carboxyl group of 7-amino compound [XII] may be in any form that can be easily converted into a free carboxyl group by treatment with an alkali, acid or enzyme or by reduction, or in the form of an ester which is active *in vivo*. Thus, the corresponding salts with alkali metals, alkaline earth metals, or organic amines, e.g. sodium, potassium, magnesium, calcium, aluminum, or triethylamine, and the corresponding β -methylsulfonylethyl, trimethylsilyl, dimethylsilyl, benzhydryl, β,β -trichloroethyl, phenacyl, p-methoxybenzyl, p-nitrobenzyl, or methoxymethyl esters may be mentioned. The carboxylic acid compound [XIII] can be used in the acylation reaction as the free acid or as the corresponding salt with sodium, potassium, calcium, trimethylamine, or pyridine or, further, as reactive derivatives such as acid halide, acid anhydride, mixed acid anhydride, cyclic carboxyanhydride, active amide, or ester, among which the acid chloride, alkyl carbonate anhydride, aliphatic carboxylic acid anhydride, and acid azolide are more commonly employed. As the active ester, there may be used, for example, P-nitrophenyl ester, 2,4-dinitrophenyl ester, pentachlorophenyl ester, N-hydroxysuccinimidyl ester, or N-hydroxyphthalimidyl ester. As the mixed acid anhydride, there may be used, for

example, anhydride with carbonate monoesters (e.g. monomethyl carbonate, or mono-iso-butyl carbonate), or halogen substituted or non-substituted C_1 to C_8 alkanolic acids (e.g. pivalic acid, or trichloroacetic acid). When the symbol X represents imino group, it is desirable that the imino group is protected prior to the acylation with an easily removable protective group such as proton, t-butoxycarbonyl or trichloroethoxy carbonyl group. The acylation reaction can be conducted advantageously in a solvent. As said solvent, use may be made of the common solvents and their mixtures unless such solvents do not interfere with the present reaction. There may be mentioned, therefore, such solvents as water, acetone, tetrahydrofuran, dioxane, acetonitrile, chloroform, dichloromethane, dichloroethylene, pyridine, dimethylaniline, and dimethyl sulfoxide. While the reaction temperature is virtually optional, the reaction usually is carried out under cooling or at room temperature. When the carboxylic acid compound [XIII] is employed in the form of free acid or salt, a suitable condensing agent is used together. The condensing agent includes, among others, di-substituted carbodiimides (e.g. N,N'-dicyclohexylcarbodiimide), azolide compounds (e.g. N,N'-carbonylimidazole, or N,N'-thionylimidazole), and such dehydrating agents as N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, phosphorus oxychloride, and alkoxyacetylene. It appears that when such a condensing agent is employed, the reaction proceeds via a reactive intermediate at the carboxyl group. When the reaction proceeds with the liberation of acid, a base is preferably added to the reaction system to neutralize the acid. As the bases suitable for this purpose, there may be commonly used aliphatic, aromatic or heterocyclic nitrogen-containing bases or alkali metal carbonates and bicarbonates such as triethylamine, N,N-dimethylaniline, N-ethylmorpholine, pyridine, collidine, 2,6-lutidine, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, and potassium hydrogen carbonate. When a dehydrating reagent is employed, it is, of course, preferable to exclude water from the solvent. It is sometimes desirable to carry out the method in an inert gas such as nitrogen gas to the exclusion of moisture.

The compound [XI] resulted is, if necessary, subjected to a procedure for removal of the protective group, and then to an usual work-up for isolation and purification similar to that hereinbefore mentioned. When the imino group of the starting compound [XII] is protected with a proton delivered from an acid, a free imino compound [XIII] is obtained only by shifting the pH to alkaline side in the purification procedure. When the imino group is protected with an acyl group, a conventional de-acylation procedure for the group is employed, e.g. acid treatment for formyl, amyloxy carbonyl, or t-butoxycarbonyl group, reduction for 2,2,2-trichloroethoxy carbonyl, benzylcarbonyl, or p-nitrobenzyloxy carbonyl group, and an alkali treatment for 2-methylsulfonyl-ethoxycarbonyl group.

Preparation of the starting materials for use in Process 1 to 5

The 3-nitrogen-containing heterocyclic thiomethyl compounds [III], may be prepared by the reaction formulated below;



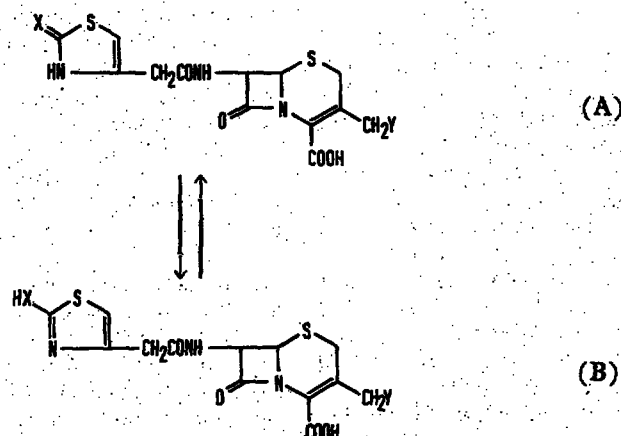
wherein M represents an alkali metal and each other symbols is the same meaning as above.

The nitrogen-containing heterocyclic thiol compounds [X] include novel compounds which are not described themselves in the literature and such novel compounds are prepared by *per se* known heterocyclic synthesis described in e.g. Chapter 5 of Heterocyclic Chemistry (A. R. Katritzky and J. M. Logowski, published by John Wiley & Sons . . . , 1960) or by a *per se* known modification reactions on easily or commercially available nitrogen-containing heterocyclic thiols.

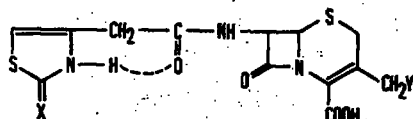
The amino compounds [XII] and their preparation are described and claimed in our copending British Patent Application No. 9056/77 (Serial No. 1491020), and the halogen-containing derivatives thereof (VI) and their preparation are described and claimed in our copending British Patent Application No. 1777/77 (Serial No. 1491019).

Structure and Nomenclature

When R^1 is hydrogen, the compounds [I] may take the two tautomeric forms as formulated below:



wherein each of the symbols used has the same meaning given hereinbefore. The actual physical data of such compounds indicate that, when X is oxygen or sulfur, the compounds [I] exist exclusively in thiazoline form (A); whereas, when X is imino group, they exist in an equilibrium state between the two forms, even if the equilibrium lies toward the tautomer (A) by the contribution of the intramolecular association depicted below.



However, the nomenclature of the compounds [I] in the present invention is enforced, when R^1 is hydrogen or an alkyl and X is oxygen or sulfur, by the thiazoline form (A) and, when R^1 is hydrogen and X is imino group, by the thiazole form (B) in conformity with the nomenclature of similar compounds adopted by Chemical Abstracts. The tautomeric isomers, however, are all included within the scope of this invention.

The 7 - [2 - (2 - exo - substituted - 4 - thiazolin - 4 - yl)acetamido] - cephalosporin derivatives [I] thus obtained have a broad and potent antimicrobial spectrum, showing activity against gram-negative and gram-positive bacteria, and especially against such gram-negative bacteria as *Escherichia coli*, *Klebsiella Pneumoniae*, *Protus vulgaris* and *Proteus morganii*, these compounds [I] are more potent than the hitherto-known cephalosporins. Thus, these compounds yield excellent therapeutic effects in the treatment of infections with these bacteria in human beings and animals.

Like the known cephalosporins, the contemplated compounds [I] of this invention can each be administered orally or parenterally in the form of powders or in such exemplary forms as solutions or suspensions in admixture with a physiologically acceptable vehicle or excipient in accordance with the established pharmaceutical procedure.

Specifically, in the treatment of various human diseases caused by the above-mentioned bacteria, suppurative diseases, respiratory-organ infections, bile-duct infections, infections of the intestines, urinary-tract infections and obsteric and gynecologic infections, the contemplated compounds of this invention, such as sodium 7 - [2 - (2-aminothiazol - 4 - yl)acetamido] - 3 - (1,3,4 - thiadiazol - 2 - yl)thiomethyl - 3 - cephem - 4 - carboxylate, sodium 7 - [2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - (1-methyltetrazol - 5 - yl)thiomethyl - 3 - cephem - 4 - carboxylate, sodium 7 - [2 - (2 - oxo - 4 - thiazolin - 4 - yl)acetamido] - 3 - (1 - methyltetrazol - 5 - yl) - thiomethyl - 3 - cephem - 4 - carboxylate, sodium 7 - [2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - (5 - methyl - 1,3,4 - thiadiazol - 2 - yl) - thiomethyl - 3 - cephem - 4 - carboxylate, sodium 7 - [2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - [2 - (2-hydroxyethylthio) - 1,3,4 - thiadiazol - 5 - yl]thiomethyl - 3 - cephem - 4 - carboxylate, sodium 7 - [2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - [2 - (N,N - dimethylcarbamoylmethyl) - 1,3,4 - thiadiazol - 5 - yl]thiomethyl - 3 - cephem - 4 - carboxylate, sodium 7 - [2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - [2 - (2-acetoxyethylthio) - 1,3,4 - thiadiazol - 5 - yl]thiomethyl - 3 - cephem - 4 - carboxylate, disodium 7 - [2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - (2 - carboxymethyl - 1,3,4 - thiadiazol - 5 - yl)thiomethyl - 3 - cephem - 4 - carboxylate, sodium 7 - [2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - (2 - carbamoylmethyl - 1,3,4 - thiadiazol - 5 - yl)thiomethyl - 3 - cephem - 4 - carboxylate, and sodium 7 - [2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - (2 - carbamoylmethylthio - 1,3,4 - thiadiazol - 5 - yl)thiomethyl - 3 - cephem - 4 - carboxylate, are each desirably administered parenterally (*non-orally*) at a daily dose level of 5 to 20 mg./kg. body weight in 3 to 4 divided doses per day.

The present invention is illustrated in further detail below with reference to 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, and that many variations may be resorted to without departing from the spirit and scope of the invention. In this specification, "g.", "mg.", "kg.", "ml.", "cm.", "ppm", "Hz", "MHz", "mol", "m mol", "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", "dimethyl sulfoxide", "Nano meter", and "decomposed", respectively. Resins named "Amberlite" (Registered Trade Mark) are products manufactured by Rohm & Hars Co. in U.S.A. All the temperatures are uncorrected and the percentages are all on the weight basis except specifically defined. 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 and 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.

Production of (2-oxo-4-thiazolin-4-yl)-acetic acid

1) Ethyl (2-oxo-4-thiazolin-4-yl)acetate

A mixture of 2.1 g. of thiocarbamic acid —O— methyl ester, 1 g. of ethyl 4-bromoacetoacetate and 1 ml. of dimethylacetamide is allowed to stand at room temperature for 16 hours. To this mixture is added 40 ml. of ethyl acetate. The mixture is washed with water (40 ml. $\times$ 3) and dehydrated. The solvent is distilled off and the residue is further concentrated to dryness to give crystals. The crystalline mass is triturated with ether and filtered under suction. The procedure yields the above-indicated compound.

Yield 1.07 g. (57%)

m.p. 106°—110°C.

IR(cm^{-1} , KBr): 1745, 1655

NMR(60MHz, d_6 -DMSO, δ): 1.23(*t*, 7Hz, CH_3CH_2 —), 3.40(*s*, CH_2CO), 4.17(*q*, 7Hz, CH_3CH_2), 6.05(*s*, thiazole 5—H), 11.05(broad *s*, thiazoline NH)

2) (2-oxo-4-thiazolin-4-yl)acetic acid

In a mixture of 5 ml. of 1 *N* aqueous sodium hydroxide and 5 ml. of tetrahydrofuran is dissolved 0.83 g. of the crystals obtained in the above procedure 1), and the solution is allowed to stand in a refrigerator for 3 days. The tetrahydrofuran is distilled off under reduced pressure and the residue is adjusted to pH 2.5 with concentrated phosphoric acid and extracted with a 1:1 mixture of ethyl acetate and tetrahydrofuran (5 ml. $\times$ 2). The organic layers are pooled, dehydrated and concentrated to

(18)

10

1,491,018

10

dryness under reduced pressure. Ether is added to the residue and the inner wall of the vessel is rubbed, whereupon crystals separate out. These crystals are recovered by filtration. The procedure yields 0.39 g. (55%) of the above-indicated compound.

m.p. 112°C (decomp.)

IR(cm^{-1} , KBr): 1725

NMR(60MHz, d_6 -DMSO, δ): 3.37(s, CH_2CO), 6.08(s, thiazoline 5—H), 11.06-broad s, thiazoline NH)

Reference Example 2.

Production of (2-thioxo-4-thiazolin-4-yl)-acetic acid

1) Ethyl (2-thioxo-4-thiazolin-4-yl)acetate

In 25 ml. of water is dissolved 6.2 g. of ammonium dithiocarbamate and, then, 11.8 g. of ethyl-4-bromoacetoacetate is added to the solution. The heat generated thereby brings the solution temperature to about 50°C. This mixture is stirred at room temperature for a day and, then, at 90° to 100°C for 2 hours. After cooling, the reaction mixture is extracted with ethyl acetate. The ethyl acetate layer is washed with a saturated aqueous solution of sodium chloride and dried. The solvent is then distilled off and the residue is triturated with the addition of ether, whereupon crystals separate out. The crystals are recovered by filtration and washed with ether. The procedure yields 2.5 g. (22%) of the above-indicated compound.

IR(cm^{-1} , KBr): 1732

NMR(60MHz, d_6 -DMSO + CDCl_3 , δ): 1.27(t, $J=7\text{Hz}$, CH_3CH_2), 3.57(s, CH_2CO), 4.19(q, $J=7\text{Hz}$, CH_3CH_2), 6.50(s, thiazoline 5—H), 12.89(broad s, thiazoline NH)

2) (2-thioxo-4-thiazolin-4-yl)acetic acid

In 19.24 ml. of a 1 N aqueous solution of sodium hydroxide are dissolved 1.68 g. of the crystals obtained in procedure 1) and the solution is stirred at room temperature for 4 hours. This reaction mixture is brought to pH 2 with concentrated phosphoric acid and extracted with ethyl acetate (60 ml. $\times$ 4). The extracts are pooled, dehydrated and concentrated under reduced pressure. Ether is added to the residue and the mixture is allowed to stand, whereupon crystals separated. The crystals are recovered by filtration under suction. The described procedure yields 1.42 g. (98%) of the above-indicated compound.

m.p. 155°—157°C

IR(cm^{-1} , KBr): 1697

NMR(60MHz, d_6 -DMSO, δ): 3.52(s, CH_2CO), 6.63(s, thiazoline 5—H), 8.8(broad s, COOH), 13.0 (broad s, thiazoline NH).

Example 1.

Production of 7 - [2 - (2 - oxo - 4 - thiazolin - 4 - yl)acetamido] - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylic acid

In 5 ml. of a phosphate buffer solution of pH 6.4 are dissolved 0.413 g. of 7 - (4 - thiocyno - 3 - oxobutyramido) - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylic acid and 0.084 g. of sodium hydrogen carbonate and the solution is allowed to stand at room temperature for 48 hours. This mixed solution is adjusted to pH 3.0 with a 50% aqueous solution of phosphoric acid, then saturated with sodium chloride and extracted with ethyl acetate (3 $\times$ 10 ml.). The ethyl acetate solution is washed with an aqueous solution of sodium chloride, dehydrated and concentrated. Following the addition of ether, the concentrate is allowed to stand, whereupon crystals emerge. These crystals are recovered by filtration under suction. The described procedure gives the above-indicated compound. Yield 0.18 grams. Melting point: 180°C.

IR(cm^{-1} , KBr): 1775, 1715, 1665

UV λ_{max} (ϵ in 1% aqueous NaHCO_3): 248 nm (1.14×10^4)

NMR (δ in d_6 -DMSO): 2.01(s, CH_3CO), 3.33(s, CH_2CO), 3.43 & 3.66(ABq, $J_{18\text{Hz}}$, 2— CH_2), 4.69 & 5.00 (ABq, $J_{13\text{Hz}}$, 3— CH_2), 5.08(d, $J_{4.5\text{Hz}}$, 6—H), 5.69(dd, $J_{4.5}$ & 8.0Hz , 7—H), 6.00(s, thiazoline 5—H), 8.96(d, $J_{8.0\text{Hz}}$, CONH)

Elemental analysis: Calcd. for $\text{C}_{15}\text{H}_{12}\text{N}_4\text{O}_7\text{S}_2$

C, 43.58; H, 3.66; N, 10.16

Found: C, 43.37; H, 3.48; N, 9.77

Example 2.

Production of 7 - [2 - (2 - oxo - 4 - thiazolin - 4 - yl)acetamido] - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid

In 27 ml. of a phosphate buffer solution of pH 6.4 are dissolved 0.67 g. of 7 - (4 - thiocyano - 3 - oxobutyramido) - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylic acid and 0.116 g. of sodium hydrogen carbonate and the resulting solution is allowed to stand overnight. To this mixed solution is added 0.168 g. of 1-methyl-tetrazole-5-thiol and the mixture is stirred at 56—59°C for 8 hours. After cooling, the reaction mixture is adjusted to pH 3 with a 50% aqueous solution of phosphoric acid and extracted with ethyl acetate (3×20 ml.). The ethyl acetate solution is washed with water, dehydrated, concentrated and allowed to stand. The resulting crystals are recovered by filtration under suction. The described procedure gives the above-indicated compound. This product includes one mole of ethyl acetate as the solvent of crystallization. Yield 0.25 grams. Melting point: 107°C(decomp.).

IR(cm⁻¹, KBr): 1785, 1730, 1660

UVλ_{max}(ε in ethanol): 244 nm(1.22×10⁴)

NMR(δ in d₆-DMSO): 3.34(s, CH₂CO), 3.70(m, 2—CH₂), 3.92(s, tetrazole CH₃), 4.30(m, 3—CH₂), 5.07(d, J5Hz, 6—H), 5.68(dd, J5 & 8Hz, 7—H), 6.01(s, thiazoline 5—H), 8.98(d, J8Hz, CONH)

Elemental analysis: Calcd. for C₁₅H₁₅N₇O₅S₃ · CH₃COOC₂H₅,

C, 40.92; H, 4.16; N, 17.57

Found: C, 40.51; H, 4.00; N, 16.61

Antibacterial spectra
(mcg/ml., agar dilution method)

Strain of microorganism	Product of this example	Cephaloridine	Cephazolin
<i>S. aureus</i> 209P	<0.78	0.05	0.1
<i>S. aureus</i> 1840	<0.78	0.39	1.56
<i>E. coli</i> NIHJ JC-2	<0.78	6.25	1.56
<i>E. coli</i> 0-111	<0.78	3.125	1.56
<i>K. pneumoniae</i> DT	<0.78	3.125	1.56

Example 3.

Production of 7 - [2 - (2 - oxo - 4 - thiazolin - 4 - yl)acetamido] - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid

In 5 ml. of a phosphate buffer solution of pH 6.4 are dissolved 0.47 g. of 7 - (4 - thiocyano - 3 - oxobutyramido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid and 0.084 g. of sodium hydrogen carbonate and the solution is allowed to stand at room temperature for 48 hours. This mixed solution is adjusted to pH 2 with a 50% aqueous solution of phosphoric acid and extracted with ethyl acetate (3×20 ml.). The ethyl acetate extracts are pooled, washed with water, dehydrated, concentrated and allowed to stand, whereupon crystals are obtained. These crystals are recovered by filtration. The described procedure gives the above-indicated compound which is in good agreement with the product according to Example 2 in IR and NMR spectra. Yield 0.28 g.

Example 4.

Production of 7 - [2 - (2 - oxo - 4 - thiazolin - 4 - yl)acetamido] - 3 - (1,2,4-thiadiazol - 2 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid

In a mixture of 20 ml. of a phosphate buffer solution of pH 6.4 and 2.5 ml. of tetrahydrofuran are dissolved 0.487 g. of 7 - (4 - thiocyano - 3 - oxobutyramido)-

3 - acetoxymethyl - 3 - cephem - 4 - carboxylic acid and 0.084 g. of sodium hydrogen carbonate, and the resulting solution is allowed to stand overnight. In this mixed solution are dissolved 0.13 g. of 1,3,4-thiadiazole-2-thiol and 0.084 g. of sodium hydrogen carbonate and the solution is stirred under heating at 58°C for 16 hours. After cooling, the solution is rendered acid with a 50% aqueous solution of phosphoric acid, treated with activated carbon and extracted with ethyl acetate (2×20 ml.). The ethyl acetate extract is washed with water, dehydrated, concentrated under reduced pressure and allowed to stand. The resulting crystals are recovered by filtration under suction. The described procedure gives the above-indicated compound. This product includes one mole each of ethyl acetate and water as solvents of crystallization. Yield 0.1 g. Melting point: 122—140°C(decomp.).

IR(cm^{-1} , KBr): 1780, 1650, 1535

NMR(δ in d_6 -DMSO): 3.33(s, CH_2CO), 3.69(m, 2- CH_2), 4.29 & 4.57 (ABQ, J15Hz, 3- CH_2), 5.07(d, J4.5Hz, 6-H), 5.68(dd, J4.5 & 8Hz, 6-H), 5.68(dd, J4.5 & 8Hz, 7-H), 8.98(d, J8Hz, CONH), 9.50(s, thiadiazole 5-H).

Elemental analysis: Calcd. for $\text{C}_{15}\text{H}_{13}\text{N}_5\text{O}_5\text{S}_4 \cdot \text{CH}_3\text{COOC}_2\text{H}_5 \cdot \text{H}_2\text{O}$

C, 39.50; H, 4.01; N, 12.12

Found: C, 39.25; H, 3.15; N, 11.74

Antibacterial spectra (mcg/ml., agar dilution method)

Strain of microorganism	Product of this example	Cephaloridine	Cephazolin
<i>S. aureus</i> 209P	<0.78	0.05	0.01
<i>S. aureus</i> 1840	<0.78	0.39	1.56
<i>E. coli</i> 0-111	1.56	3.125	1.56
<i>K. pneumoniae</i> DT	1.56	3.125	1.56

Example 5.

Production of 7 - [2 - (2 - oxo - 4 - thiazolin - 4 - yl)acetamido] - 3 - (1,3,4 - thiadiazol - 2 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid

In 5 ml. of a phosphate buffer solution of pH 6.4 are dissolved 0.47 g. of 7 - (4 - thiocyanato - 3 - oxobutyramido) - 3 - (1,3,4 - thiadiazol - 2 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid and 0.084 g. of sodium hydrogen carbonate and the solution is allowed to stand at room temperature overnight. This mixed solution is adjusted to pH 3 with a 50% aqueous solution of phosphoric acid and extracted with ethyl acetate (3×20 ml.). The ethyl acetate extract is washed with water, dehydrated, concentrated under reduced pressure and allowed to stand. The resulting crystals are recovered by filtration. The procedure gives the above-indicated compound which is in good agreement with the product according to Example 4 in IR and NMR spectra. Yield 0.23 g.

Example 6.

Production of 7 - [2 - (2 - oxo - 4 - thiazolin - 4 - yl)acetamido] - 3 - (5 - methyl - 1,3,4 - oxadiazol - 2 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid

In a mixture of 20 ml. of a phosphate buffer solution of pH 6.4 and 2.5 ml. of tetrahydrofuran are dissolved 0.487 g. of 7 - (4 - thiocyanato - 3 - oxobutyramido) - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylic acid and 0.084 g. of sodium hydrogen carbonate and the resulting solution is allowed to stand overnight. In this mixed solution are dissolved 0.13 g. of 5 - methyl - 1,3,4 - oxadiazol - 2 - thiol and 0.084 g. of sodium hydrogen carbonate, and the solution is stirred under heating at 58°C for 7 hours. After cooling, the reaction mixture is rendered acid with a 50% aqueous

solution of phosphoric acid and extracted with ethyl acetate (2×20 ml.). The ethyl acetate extract is washed with water, dehydrated and concentrated under reduced pressure. The concentrate is allowed to stand and the resulting crystals are recovered by filtration under suction. The procedure gives the above-indicated compound. This product includes a mole each of ethyl acetate and water as solvents of crystallization. Yield 0.1 g. Melting point: 122—140° (decomp.).

IR (cm⁻¹, KBr): 1784

NMR (δ in d₆-DMSO): 2.44(s, oxadiazole CH₃), 3.32(s, CH₂CO), 3.54 & 3.78(ABq, J18Hz, 2—CH₂), 4.13 & 4.36(ABq, J14Hz, 3—CH₂), 5.06(d, J4.5Hz, 6—H), 5.66(m, 7—H), 6.00(s, thiazoline 5—H), 8.98(d, J9Hz, CONH).

Elemental analysis: Calcd. for C₁₆H₁₅N₅O₆S₃ · CH₃COOC₂H₅ · H₂O

C, 41.72; H, 4.38; N, 12.17

Found: C, 41.40; H, 3.71; N, 12.04

Example 7.

Production of 7 - [2 - (2 - oxo - 4 - thiazolin - 4 - yl)acetamido] - 3 - (5 - methyl - 1,3,4 - oxadiazol - 2 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid

In 5 ml. of a phosphate buffer solution of pH 6.4 are dissolved 0.459 g. of 7 - (4 - thiocyano - 3 - oxobutyramido) - 3 - (5 - methyl - 1,3,4 - oxadiazol - 2 - yl) - thiomethyl - 3 - cephem - 4 - carboxylic acid and 0.084 g. of sodium hydrogen carbonate and the solution is allowed to stand at room temperature overnight. This mixed solution is adjusted to pH 3 with 5% aqueous phosphoric acid solution and extracted with ethyl acetate (3×20 ml.). The ethyl acetate extract is washed with water, dehydrated and concentrated under reduced pressure. The concentrate thus obtained is allowed to stand and the resulting crystals are recovered by filtration. The procedure gives the above-identified product which is in good agreement with the product of Example 6 in IR and NMR spectra. Yield 0.283 g.

Example 8.

Production of 7 - [2 - (2 - oxo - 4 - thiazolin - 4 - yl)acetamido] - 3 - (5 - methyl - 1,3,4 - thiadiazol - 2 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid

In 20 ml. of a phosphate buffer of pH 6.4 are dissolved 0.417 g. of 7 - (4 - thiocyano - 3 - oxobutyramido) - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylic acid and 0.084 g. of sodium hydrogen carbonate and the solution is allowed to stand overnight.

In this mixed solution are dissolved 0.145 g. of 5 - methyl - 1,3,4 - thiadiazole - 2 - thiol and 0.084 g. of sodium hydrogen carbonate, and the solution is stirred under heating at 60°C for 6.5 hours. After cooling, the reaction mixture is rendered acid with 50% aqueous phosphoric acid solution, saturated with sodium chloride and extracted with a 2:1 mixture of ethyl acetate and tetrahydrofuran (3×20 ml.). The extract is washed with a saturated aqueous solution of sodium chloride, dehydrated and concentrated. The concentrate is allowed to stand and the resulting crystals are recovered by filtration. The described procedure gives 0.232 g. (yield 49% of the above-indicated compound).

IR (cm⁻¹, KBr): 1786, 1655, 1535

NMR (δ in d₆-DMSO): 2.63(s, thiadiazole 5—CH₃), 3.30(s, CH₂CO), 3.53 & 3.77(ABq, J18.0Hz, 2—CH₂), 4.18 & 4.49(ABq, J14.0Hz, 3—CH₂), 5.04(d, J5.0Hz, 6—H), 5.65(dd, J5.0 & 8.0Hz, 7—H), 5.98(s, thiazoline 5—H), 8.94(d, J8.0Hz, CONH).

Example 9.

Production of 7 - [2 - (2 - oxo - 4 - thiazolin - 4 - yl)acetamido] - 3 - (5 - methyl - 1,3,4 - thiadiazol - 2 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid

In 5 ml. of a phosphate buffer of pH 6.4 are dissolved 0.485 g. of 7 - (4 - thiocyano - 3 - oxobutyramido) - 3 - (5 - methyl - 1,3,4 - thiadiazol - 2 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid and 0.084 g. of sodium hydrogen carbonate and the solution is allowed to stand at room temperature overnight. This mixed solution is adjusted to pH 3 with a 50% aqueous solution of phosphoric acid and extracted with ethyl acetate (3×20 ml.). The ethyl acetate extract is washed with water, dehydrated and concentrated under reduced pressure. The concentrate is allowed to stand and the resultant crystals are recovered by filtration. The above procedure gives the above-indicated compound which is in good agreement with the product according to Example 8 in IR and NMR spectra.

Example 10.

Production of sodium 7 - [2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylate

In a mixture of 53 ml. of water and 26.4 ml. of tetrahydrofuran are dissolved 0.442 g. of thiourea and 0.889 g. of sodium hydrogen carbonate. Then, 2.3 g. of 7 - (4 - bromo - 3 - oxobutyramido) - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylic acid are gradually added and dissolved. The mixture is stirred at room temperature for 30 minutes, after which time it is concentrated under reduced pressure to remove the tetrahydrofuran and further to a final volume of 20 ml. The residue is chromatographed on a column of polystyrene resin (Amberlite XAD-2) and developed with water. The fractions containing the desired product (with good absorption of ultraviolet light at 254 m μ) are pooled and freeze-dried. The procedure gives the above-indicated compound. Yield 1.305 g. (52.6%).

IR(cm⁻¹, KBr): 1767

UVA max(ϵ in water): 256 nm(1.35×10^4)

NMR(δ in D₂O): 2.15(s, CH₃CO), 3.39 & 3.69(ABq, J18Hz, 2-CH₂), 3.62(s, CH₂CO), 4.75 & 4.94(ABq, J13Hz, 3-CH₂), 5.15(d, J5Hz, 6-H), 5.71(d, J5Hz, 7-H), 6.52(s, thiazole 5-H)

Elemental analysis: Calcd. for C₁₆H₁₅N₄O₆S₂Na . 2H₂O:

C, 38.29; H, 4.07; N, 11.91

Found: C, 38.41; H, 3.90; N, 11.72

Antibacterial spectra
(mcg/ml., agar dilution method)

Strain of microorganism	Product of this example	Cephaloridine	Cephazolin
<i>S. aureus</i> 209P	<0.78	0.05	0.1
<i>S. aureus</i> 1840	1.56	0.39	1.56
<i>E. coli</i> NIHJ JC-2	1.56	6.25	1.56
<i>K. pneumoniae</i> DT	<0.78	3.125	1.56
<i>P. vulgaris</i> Eb-57	<0.78	>100	50

Example 11.

Production of 7 - [2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylic acid

In a mixture of 80 ml. of water and 40 ml. of tetrahydrofuran are dissolved 0.602 g. of thiourea and 0.664 g. of sodium hydrogen carbonate. Then, 3.085 g. of 7 - (4 - chloro - 3 - oxobutyramido) - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylic acid are gradually added and dissolved. The mixture is stirred at room temperature for 1 hour, after which time the tetrahydrofuran is distilled off under reduced pressure. The residue is allowed to stand at room temperature and the resulting crystals are recovered by filtration. The filtrate is further concentrated and allowed to stand, whereupon an additional crop of crystals is obtained. These crystals are recovered and combined with those previously harvested. The described procedure gives 2.703 g. (83%) of the above-indicated compound.

IR(cm⁻¹, KBr): 1776

UVA max(ϵ in water): 256 nm(1.35×10^4)

NMR(δ in d₆-DMSO): 2.01(s, CH₃CO), 3.38(s, CH₂CO), 3.40 & 3.63 (ABq, J18Hz, 2-CH₂), 4.68 & 4.98 (ABq, J13Hz, 3-CH₂), 5.06(d, J5Hz, 6-H), 5.68(dd, J5 & 8Hz, 7-H), 6.23(s, thiazole 5-H), 6.90(broad s, NH₂), 8.82(d, J8Hz, CONH), 9.20(broad s, COOH).

Example 12.

Production of sodium 7 - [2 - (2 - methylaminothiazol - 4 - yl)acetamido] - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylate

In 10 ml. of water and 6 ml. of tetrahydrofuran are dissolved 0.099 g. of N-methylthiourea and 0.168 g. of sodium hydrogen carbonate. Then, 0.435 g. of 7 - (4-bromo - 3 - oxobutylamido) - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylic acid are gradually added and dissolved. The mixture is stirred at room temperature for 30 minutes, after which time the tetrahydrofuran is distilled off under reduced pressure. The residue is chromatographed on a column of polystyrene resin (Amberlite XAD-2) and developed with water. The fractions containing the desired product are pooled and freeze-dried. The procedure gives the above-indicated compound. Yield 0.16 g.

IR(cm^{-1} , KBr): 1763

UV λ max(ϵ in water): 260 nm(1.48×10^4)

NMR(δ in D_2O): 2.15(s, CH_3CO), 2.92(s, CH_3N), 3.38 & 3.62(ABq, J18Hz, 2- CH_2), 3.62(s, CH_2CO), 4.75 & 4.95(ABq, J13Hz, 3- CH_2), 5.15(d, J5Hz, 6-H), 5.71(d, J5Hz, 6-H), 6.48(s, thiazole 5-H)

Elemental analysis: Calcd. for $\text{C}_{16}\text{H}_{17}\text{N}_4\text{O}_6\text{S}_2\text{Na} \cdot 2.5\text{H}_2\text{O}$:

C, 38.94; H, 4.49; N, 11.35;

Found: C, 39.14; H, 4.27; N, 11.03

Example 13.

Production of sodium 7 - [2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - (1,3,4 - thiadiazol - 2 - yl)thiomethyl - 3 - cephem - 4 - carboxylate

In 20 ml. of a phosphate buffer of pH 6.4 are dissolved in 0.47 g. of sodium 7 - [2 - (2 - aminothiazol - 4 - yl) - acetamido] - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylate and 0.14 g. of 1,3,4 - thiadiazole - 2 - thiol and the solution is stirred under heating at 55-60°C for 15 hours. After cooling, 0.084 g. of sodium hydrogen carbonate is added to the reaction mixture. The mixture is then chromatographed on a column of polystyrene resin (Amberlite XAD-2) and developed with water. The fractions containing the desired product are pooled and freeze-dried. The described procedure gives the above-indicated compound. Yield 0.096 g.

IR(cm^{-1} , KBr): 1763

UV λ max(ϵ in water): 262 nm(1.57×10^4)

NMR(δ in D_2O): 3.41 & 3.77(ABq, J18Hz, 2- CH_2), 3.60(s, CH_2CO), 4.09 & 4.54(ABq, J13Hz, 3- CH_2), 5.08(d, J5Hz, 6-H), 5.65(d, J5Hz, 7-H), 6.48(s, thiazole 5-H), 9.42(s, thiadiazole 5-H).

Elemental analysis: Calcd. for $\text{C}_{15}\text{H}_{13}\text{N}_6\text{O}_6\text{S}_4\text{Na} \cdot 3.5\text{H}_2\text{O}$

C, 32.43; H, 3.63; N, 15.13;

Found: C, 32.32; H, 3.05; N, 14.36

Antibacterial spectra
(mcg/ml., agar dilution method)

Strain of microorganism	Product of this example	Cephaloridine	Cephazolin
<i>S. aureus</i> 209P	<0.78	0.05	0.1
<i>S. aureus</i> 1840	<0.78	0.39	1.56
<i>E. coli</i> 0-111	<0.78	3.125	1.56
<i>K. pneumoniae</i> DT	<0.78	3.125	1.56
<i>P. vulgaris</i> Eb-58	<0.78	12.5	6.25

Example 14.

Production of sodium 7 - [2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - (1,3,4-thiadiazol - 2 - yl)thiomethyl - 3 - cephem - 4 - carboxylate

In a mixture of 10 ml. of water and 10 ml. of tetrahydrofuran are dissolved 0.076 g. of thiourea and 0.084 g. of sodium hydrogen carbonate. Then, 0.449 g. of 7 - (4 - chloro - 3 - oxobutyramido) - 3 - (1,3,4 - thiadiazol - 2 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid is added and dissolved. This reaction mixture is allowed to stand at room temperature overnight, after which time it is concentrated under reduced pressure to remove the tetrahydrofuran. To the residue is added 0.16 g. of sodium hydrogen carbonate and the mixture is chromatographed on a column of polystyrene resin (Amberlite XAD-2) using water as the developer solvent. The fractions containing the desired product are pooled and freeze-dried. The procedure gives the above-indicated compound which is in good agreement with the product of Example 13 and IR and NMR spectra. Yield 0.122 g.

Example 15.

Production of sodium 7 - [2 - (2 - acetamidothiazol - 4 - yl)acetamido] - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylate

In a mixture of 10 ml. of water and 10 ml. of tetrahydrofuran are dissolved 0.13 g. of N-acetylthiourea and 0.168 g. of sodium hydrogen carbonate. Then, 0.435 g. of 7 - (4 - bromo - 3 - oxobutyramido) - 3 - acetoxymethyl - cephem - 4 - carboxylic acid is gradually added and dissolved. The mixed solution is stirred at room temperature for 6 hours, after which time it is concentrated under reduced pressure to remove the tetrahydrofuran. The residue is chromatographed on a column of polystyrene resin (Amberlite XAD-2) and developed with water. The fractions containing the desired product are pooled and freeze-dried. The procedure gives the above-indicated compound. Yield 0.193 g.

IR(cm^{-1} , KBr): 1764

UV λ max(ϵ in water): 266 nm(1.60×10^4)

NMR(δ in D_2O): 2.09(s, CH_3CON), 2.22(s, CH_2COO), 3.31 & 3.62(ABq, J18Hz, 2- CH_2), 3.70(s, CH_2CO), 5.09(d, J5Hz, 6-H), 5.66(d, J5Hz, 7-H), 6.93(s, thiazole 5-H)

Elemental analysis: Calcd. for $\text{C}_{17}\text{H}_{17}\text{N}_4\text{O}_7\text{S}_2\text{Na} \cdot 2.5\text{H}_2\text{O}$

C, 39.15; H, 4.25; N, 10.75;

Found: C, 39.19; H, 4.01; N, 10.34

Example 16.

Production of sodium 7 - [2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 3 - cephem - 4 - carboxylate

In a phosphate buffer of pH 6.4 are dissolved 0.47 g. of sodium 7 - [2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylate, 0.138 g. of 1 - methyltetrazole - 5 - thiol and 0.084 g. of sodium hydrogen carbonate and the mixed solution is stirred under heating at 50-55°C for 16 hours. After cooling, this reaction mixture is chromatographed on a column of polystyrene resin (Amberlite XAD-2) and developed with water. The fractions containing the desired product are pooled and freeze-dried. The procedure gives the above-indicated compound. Yield 0.173 g.

IR(cm^{-1} , KBr): 1763

UV λ max(ϵ in water): 260 nm(1.48×10^4)

NMR(δ in D_2O): 3.48 & 3.81(ABq, J17Hz, 2- CH_2), 3.63(s, CH_2CO), 4.06(s, tetrazolyl 1- CH_3), 4.09 & 4.37(d, J14Hz, 3- CH_2), 5.14(d, J5Hz, 6-H), 5.68(d, J5Hz, 7-H), 6.52(s, thiazole 5-H)

Elemental analysis: Calcd. for $\text{C}_{18}\text{H}_{15}\text{N}_8\text{O}_7\text{S}_2 \cdot 2.5\text{H}_2\text{O}$

C, 33.64; H, 3.76; N, 20.92

Found: C, 33.80; H, 3.33; N, 19.86

Antibacterial spectra
(mcg/ml., agar dilution method)

Strain of microorganism	Product of this example	Cephaloridine	Cephazolin
<i>S. aureus</i> 209P	0.39	0.05	0.1
<i>S. aureus</i> 1840	0.78	0.39	1.56
<i>E. coli</i> NIHJ JC-2	0.39	6.25	1.56
<i>E. coli</i> 0-111	0.2	3.125	1.56
<i>K. pneumoniae</i> DT	<0.1	3.125	1.56
<i>P. vulgaris</i> Eb 58	0.39	12.5	6.25
<i>P.morganii</i> Eb 53	3.125	>100	100

Example 17.

Production of sodium 7 - [2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 3 - cephem - 4 - carboxylate

In a mixture of 10 ml. of water and 10 ml. of tetrahydrofuran are dissolved 0.076 g. of thiourea and 0.084 g. of sodium hydrogen carbonate. Then, 0.447 g. of powdery 7 - (4 - chloro - 3 - oxobutyramido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid is added and dissolved. The reaction mixture is allowed to stand at room temperature overnight, after which it is concentrated under reduced pressure to remove the tetrahydrofuran. To the residue is added 0.16 g. of sodium hydrogen carbonate and the resultant mixture is chromatographed on a column of polystyrene resin (Amberlite XAD-2) and developed with water. The fractions containing the desired product are pooled and freeze-dried. The procedure gives the above-indicated compound which is in good agreement with the product of Example 16 in IR and NMR spectra. Yield 0.182 g.

Example 18.

Production of sodium 7 - [2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - (5 - methyl - 1,3,4 - thiadiazol - 2 - yl)thiomethyl - 3 - cephem - 4 - carboxylate

In 20 ml of a phosphate buffer of pH 6.4 are dissolved 0.47 g. of sodium 7 - [2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylate, 0.157 g. of 5 - methyl - 1,3,4 - thiadiazole - 2 - thiol and 0.084 g. of sodium hydrogen carbonate and the mixed solution is stirred under heating at about 55°C for 15 hours. After cooling, the reaction mixture is chromatographed on a column of polystyrene resin (Amberlite XAD-2) and developed with water. The fractions containing the desired product are pooled and freeze-dried. The described procedure gives the above-indicated compound. Yield 0.118 g.

IR (cm⁻¹, KBr): 1763

NMR (δ in D₂O): 2.76(s, thiadiazole 5-CH₃), 3.42 & 3.79 (ABq, J18Hz, 2-CH₂), 3.62(s, CH₂CO), 4.02 & 4.51(ABq, J14Hz, 3-CH₂), 5.11(d, J5Hz, 6-H), 5.68(d, J5Hz, 7-H), 6.50(s, thiazole 5-H)

Elemental analysis: Calcd. for C₁₆H₁₅N₆O₄Na · 2.5H₂O

C, 34.84; H, 3.65; N, 15.23

Found: C, 34.87; H, 3.47; N, 14.82

Example 19.

Production of sodium 7 - [2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - (5 - methyl - 1,3,4 - thiadiazol - 2 - yl)thiomethyl - 3 - cephem - 4 - carboxylate

In a mixture of 10 ml. of water and 10 ml. of tetrahydrofuran are dissolved 0.076 g. of thiourea and 0.084 g. of sodium hydrogen carbonate. Then, 0.463 g. of 7 - (4 - chloro - 3 - oxobutyramido) - 3 - (5 - methyl - 1,3,4 - thiadiazol - 2 - yl)-

thiomethyl - 3 - cephem - 4 - carboxylic acid is added and dissolved. The mixture is allowed to stand at room temperature overnight, after which it is concentrated under reduced pressure to remove the tetrahydrofuran. To the residue is added 0.16 g. of sodium hydrogen carbonate and the mixture is chromatographed on a column of polystyrene resin (Amberlite XAD-2) and developed with water. The fractions containing the desired product are pooled and freeze-dried. The procedure gives the above-indicated compound which is in good agreement with the product of Example 18 in IR and NMR spectra.

Example 20.

Production of sodium 7 - [2 - (N,N' - ethylene - 2 - imino - 4 - thiazolin - 4 - yl) - acetamido] - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylate

In 10 ml. of water are dissolved 0.112 g. of N,N' - ethylene - thiourea and 0.168 g. of sodium hydrogen carbonate and, then, 0.39 g. of 7 - (4 - bromo - 3 - oxobutyramido) - 3 - acetoxymethyl - 3 - cephem - carboxylic acid is gradually added to the above solution. The mixture is allowed to stand at room temperature for 23 hours, after which time it is chromatographed on a column of polystyrene resin (Amberlite XAD-2) and developed with water. The fractions with good absorption of ultra-violet light (at 254 m μ) are collected and freeze-dried. The procedure gives mixed crystals (1:3) of the above-indicated compound and its precyclization precursor compound, i.e. sodium 7 - [4 - (N,N' - ethyleneamidino) - thio - 3 - oxobutyramido] - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylate. Yield 0.084 g.

The following data are the values found for the above-mentioned mixed crystals.

IR(cm⁻¹, KBr): 1768

UV λ max(ϵ in water): 268 nm(1.23 $\times 10^4$)

NMR(δ in D₂O): 6.70(s, thiazoline 5-H)

Elemental analysis: Calcd. for C₁₇H₁₅N₄O₇S₂Na . H₂O

C, 41.13; H, 3.26; N, 11.29

Found: C, 40.98; H, 4.27; N, 11.13

Example 21.

Production of sodium 7 - [2 - (2 - thioxo - 4 - thiazolin - 4 - yl) - acetamido] - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylate

In a mixture of 10 ml. of water and 10 ml. of tetrahydrofuran are dissolved 0.22 g. of ammonium dithiocarbamate and 0.084 g. of sodium hydrogen carbonate. Then, 0.435 g. of 7 - (4 - bromo - 3 - oxobutyramido) - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylic acid is added and dissolved. The mixture is stirred at room temperature for 45 minutes, after which time the tetrahydrofuran is distilled off under reduced pressure. The residue is rendered acid with 50% phosphoric acid and, then, extracted with ethyl acetate. The ethyl acetate extract is further extracted with 1% aqueous sodium hydrogen carbonate (2 $\times$ 15 ml.) and the water layers are pooled and chromatographed on a column of polystyrene resin (Amberlite XAD-2) using water as the developer solvent. The fractions absorbing ultraviolet light are collected and freeze-dried. The procedure gives mixed crystals (1:2) of the above-indicated compound and its precyclization precursor compound, i.e. sodium 7 - (4 - thiocarbamoylthio - 3 - oxobutyramido) - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylate. Yield 0.21 g.

The following data are the values found for the above-mentioned mixed crystals.

IR(cm⁻¹, KBr): 1762

UV λ max(ϵ in water): 246 nm, 273 nm(1.84 $\times 10^4$), 312 nm(4.12 $\times 10^3$)

NMR(δ in D₂O): the signals assignable to sodium 7 - [2 - (2 - thioxo - 4 - thiazolin - 4 - yl)acetamido] - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylate: 2.18(s, CH₃CO), 3.43 & 3.74 (ABq, J18Hz, 2-CH₂), 3.92(s, COCH₂), 4.78 & 4.98 (ABq, J13Hz, 3-CH₂), 5.21(d, J5Hz, 6-H), 5.72(d, J5Hz, 7-H), 6.93(s, thiazoline 5-H); the signals assignable to sodium 7 - (4 - thiocarbamoylthio - 3 - oxobutyramido) - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylate: 2.18(s, CH₃CO), 3.12(s, SCH₂CO), 3.49 & 3.79(ABq, J18Hz, 2-CH₂), 4.78 & 4.98(ABq, J13Hz, 3-CH₂), 5.19(d, J5Hz, 6-H), 5.74(d, J5Hz, 7-H)

Elemental analysis: Calcd. for C₁₅H₁₄N₄O₆S₃Na . 2.5H₂O

C, 36.29; H, 3.86; N, 8.46

Found: C, 36.08; H, 3.67; N, 8.25

Antibacterial spectra
(mcg/ml., agar dilution method)

Strain of microorganism	Product of this example	Cephaloridine	Cephazolin
<i>S. aureus</i> 209P	<0.78	0.05	0.1
<i>S. aureus</i> 1840	1.56	0.39	1.56

Example 22.

Production of sodium 7 - [2 - (2 - methylimino - 3 - methyl - 4 - thiazolin-4 - yl)acetamido] - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylate

In a mixture of 10 ml. of water and 10 ml. of tetrahydrofuran are dissolved 0.115 g. of N,N'-dimethylthiourea and 0.168 g. of sodium hydrogen carbonate. Then, 0.435 g. of 7 - (4 - bromo - 3 - oxobutyramido) - 3 - acetoxymethyl - 3 - cephem-4 - carboxylic acid is gradually added and dissolved. The mixture is allowed to stand at room temperature for 50 minutes, after which time it is concentrated under reduced pressure to remove the tetrahydrofuran. The residue is chromatographed on a column of polysepyrene resin (Amberlite XAD-2) and developed with water. The fractions with good adsorption of ultraviolet radiation (254 mμ) are collected and freeze-dried. The procedure gives mixed crystals (1:2) of the above-indicated compound and its precyclization (uncyclized) precursor compound, i.e. sodium 7 - (4 - N,N' - dimethylamidothio - 3 - oxobutyramido) - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylate. Yield 0.15 g.

The following data are the values found for the above-mentioned mixed crystals.

IR(cm⁻¹, KBr): 1773

NMR(δ in D₂O): the signals assignable to sodium 7 - [2 - (2 - methyl - imino - 3 - methyl - 4 - thiazolin - 4 - yl)acetamido] - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylate; 2.12(s, CH₃CO), 3.08(s, thiazoline 3-CH₃), 3.11(s, CH₃-N=), 3.39 & 3.70(ABq, J18Hz, 2-CH₂), 3.91(s, CH₂CO), 4.73 & 4.92(ABq, J13Hz, 3-CH₂), 5.14(d, J5Hz, 6-H), 5.63(d, J5Hz, 7-H), 6.86(s, thiazoline 5-H); the signals assignable to sodium 7 - (4 - N,N' - dimethylamidinothio - 3 - oxobutyramido) - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylate; 2.12(s, CH₃CO), 3.08(s, CH₃NH), 3.11(s, CH₃-N=), 3.39 & 3.70(ABq, J18Hz, 2-CH₂), 3.51(s, SCH₂CO), 4.73 & 4.92(ABq, J13Hz, 3-CH₂), 5.16(d, J5Hz, 6-H), 5.67(d, J5Hz, 7-H)

Elemental analysis: Calcd. for C₁₇H₁₉N₄O₆S₂Na · 1.5H₂O

C, 41.71; H, 4.53; N, 11.45;

Found: C, 42.08; H, 4.98; N, 11.47

Example 23.

The compounds listed in Tables 1 to 14 are prepared by one or more of the following Methods 1 to 10, as may also be the compounds 7 - [2 - (2 - amino-thiazol - 4 - yl)acetamido] - 3 - [2 - (2 - capryloxyethylthio) - 1,3,4 - thiadiazol-5 - yl]thiomethyl - 3 - cephem - 4 - carboxylic acid and 7 - [2 - (2 - aminothiazol-4 - yl)acetamido] - 3 - (2 - hexyloxycarbonylmethylthio - 1,3,4 - thiadiazol - 5 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid

Method 1.

(1) In 40 ml. of water are dissolved 10.7 g. (30 m mol) of 7 - acetoacetamido-3 - acetoxymethyl - 3 - cephem - 4 - carboxylic acid, 30 m mol of a nitrogen-containing heterocyclic thiol and 5.04 g. (60 m mol) of sodium hydrogen carbonate and the solution is adjusted at pH 7.0 with a 10% aqueous solution of sodium hydroxide, followed by stirring for 4 hours at 60-65°C. After cooling, 2.31 g. (33 m mol) of hydroxylamine hydrochloride is added to the reaction mixture and the mixture is adjusted to pH 3.6 by adding N-hydrochloric acid, followed by

standing at room temperature for overnight. The precipitated crystals of a 7-amino - 3 - (nitrogen - containing heterocyclic)thiomethyl - 3 - cephem - 4-carboxylic acid are collected by filtration, washed with acetone and dried.

(2) A solution of 1.03 g. (13 m mol) of diketene in 5 ml. of methylene chloride is previously chilled to -30°C and a solution of 1.05 g (15 m mol) of chlorine in 10 ml. of carbon tetrachloride or a solution of 2.24 g. (14 m mol) of bromine in 5 ml. of methylene chloride is added dropwise thereto. Meanwhile, 10 m mol of a 7 - amino - 3 - (nitrogen-containing heterocyclic)thiomethyl - 3 - cephem - 4-carboxylic acid and 2.02 g. (20 m mol) of triethylamine are dissolved in 20 ml. of methylene chloride and the solution is chilled to -20°C . To this solution is dropped rapidly the above-prepared reaction mixture. The temperature rises in most cases to the neighbourhood of 0°C caused by the exothermic reaction. After the exothermic reaction is subsided, the temperature is gradually increased to room temperature. After stirring for 15 minutes, the reaction solution is added to a mixture of 150 ml. of ethyl acetate and 100 ml. of a 10% aqueous solution of phosphoric acid under vigorous stirring. The organic layer is separated, washed with water and dried, followed by the evaporation of the solvent. To the residue is added ether and the mixture is allowed to stand. The resultant precipitate of a 7 - (4 - chloro or bromo-3 - oxobutyramido) - 3 - (nitrogen - containing heterocyclic)thiomethyl - 3 - cephem-4 - carboxylic acid is recovered by filtration as powder.

(3) To a mixed solution of 0.304 g. (4 m mol) of thiourea, 2 ml. of tetrahydrofuran and 1 ml. of water, is added dropwise a solution of 2 m mol of 7 - (4 - chloro or bromo) - 3 - oxobutyramido) - 3 - (nitrogen - containing heterocyclic)thiomethyl-3 - cephem - 4 - carboxylic acid (2 m mol) in 3 ml. of tetrahydrofuran and a solution of 0.18 g. (2.2 m mol) of sodium hydrogen carbonate in 2 ml. of water at the same time, followed by stirring for 3 hours. The reaction mixture is subjected to the distillation of the organic solvent and the residue is dissolved in 4 ml. of 0.5 N-aqueous solution of sodium hydroxide. The solution is chromatographed on a column of polystyrene resin (Amberlite XAD-2) and subjected to a development with a gradient elution starting from water to 40% methanol. The fractions containing the desired product are pooled and freeze-dried to give a sodium 7 - [2 - (2-aminothiazol - 4 - yl)acetamido] - 3 - (nitrogen - containing heterocyclic)thiomethyl - 3 - cephem - 4 - carboxylate.

Method 2.

(1) A solution of 60 g. (0.2 mol) of 7 - formamido - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylic acid, 0.2 mol of a nitrogen-containing heterocyclic thiol and 33.6 g. (0.4 mol) of sodium hydrogen carbonate dissolved in 200 ml. of water is adjusted to pH 7.0 by adding a 10% aqueous solution of sodium hydroxide and stirred for 4-5 hours at $60-65^{\circ}\text{C}$, followed by addition of 500 ml. of methanol. The mixture is cooled down with ice and 80 g. of concentrated sulfuric acid is added thereto under stirring and keeping the temperature not exceeding 30°C , followed by standing in ice-room overnight. The reaction mixture is diluted with 1000 ml. of water and the mixed solution is shaken with ethyl acetate (2×400 ml.). The combined aqueous layer is subjected to the filtration under suction to remove undissolved materials and the filtrate is adjusted to pH 3.8 by adding concentrated aqueous ammonia, followed by standing at 0°C for 3 hours. The precipitated crystals are collected by filtration and washed with cold water (100 ml.) and then acetone (300 ml.), followed by drying to give 7 - amino - 3 - (nitrogen-containing heterocyclic)thiomethyl - 3 - cephem - 4 - carboxylic acid.

(2) The material obtained in above (1) is treated in the similar manner as (2) and (3) of Method 1 to obtain a sodium 7 - [2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - (nitrogen - containing heterocyclic)thiomethyl - 3 - cephem - 4 - carboxylate.

Method 3.

A solution of 0.824 g. (2 m mol) of 7 - [2 - (2 - aminothiazol - 4 - yl)-acetamido] - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylic acid, 2.2 m mol of a nitrogen-containing heterocyclic thiol and 0.336 g. (4 m mol) of sodium hydrogen carbonate dissolved in 8 ml. of water (when homogeneous solution is not attained, 4 ml. of tetrahydrofuran is added) is stirred for 6-8 hours under heating at $60-65^{\circ}\text{C}$. After cooling, the reaction mixture is subjected to the distillation of

tetrahydrofuran under suction and the residue is chromatographed on a column of polystyrene resin (Amberlite XAD-2), followed by development with a gradient elution starting from water to 40% methanol. The fractions containing the desired product are pooled and freeze-dried to give a sodium 7 - [2 - (2 - aminothiazol-4 - yl)acetamido] - 3 - (nitrogen-containing heterocyclic)thiomethyl - 3 - cephem-4 - carboxylate.

Method 4.

In 40 ml. of a phosphate buffer of pH 6.4 are dissolved 0.824 g. (2 m mol) of 7 - [2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - acetoxymethyl - 3 - cephem-4 - carboxylic acid, 2.2 m mol of a nitrogen-containing heterocyclic thiol and 0.336 g. (4 m mol) of sodium hydrogen carbonate and the solution is stirred for 7-8 hours under heating at 60-65°C. The reaction solution is concentrated to about 20 ml. under reduced pressure and the concentrate is chromatographed on a column of polystyrene resin (Amberlite XAD-2), followed by development with water, 5% ethanol and 10% ethanol in this order. The fractions containing the desired product are pooled and freeze-dried to give a sodium 7 - [2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - (nitrogen - containing heterocyclic)thiomethyl - 3 - cephem - 4 - carboxylate.

Method 5.

A mixed solution of 0.824 g. (2 m mol) of 7 - [2 - (2 - aminothiazol - 4 - yl)-acetamido] - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylic acid, 0.596 g. (2 m mol) of 2 - (2 - benzoyloxyethylthio) - 1,3,4 - thiadiazole - 5 - thiol, 0.336 g. (4 m mol) of sodium hydrogen carbonate, 5 ml. of tetrahydrofuran and 10 ml. of water is heated at 65°C for 5 hours. The reaction solution is concentrated to dryness and the residue is dissolved in 4 ml. of acetonitrile. The solution is chromatographed on a column of silica-gel and developed with a 5% aqueous solution of acetonitrile and then a 15% aqueous solution of acetonitrile. The fractions containing the desired product are pooled and concentrated to precipitate crystals which are collected by filtration to obtain 0.43 g. of 7 - [2 - (2 - aminothiazol - 4 - yl)-acetamido] - 3 - [2 - (2 - benzoyloxyethylthio) - 1,3,4 - thiadiazol - 5 - yl]thiomethyl - 3 - cephem - 4 - carboxylic acid.

Method 6.

(1) In 100 ml. of acetonitrile are dissolved 0.1 mol of a 7 - (4 - chloro or bromo-3 - oxobutyramido) - 3 - (nitrogen - containing heterocyclic)thiomethyl - 3 - cephem - 4 - carboxylic acid and 14.5 g. (0.15 mol) of potassium thiocyanate and the solution is stirred for 16 hours at room temperature. The reaction solution is subjected to the distillation of the solvent under reduced pressure and to the residue is added 50 ml. of a saturated aqueous solution of sodium chloride. The mixture is adjusted to pH 3 with 50% phosphoric acid and extracted with ether (2 x 100 ml.). The combined extract is washed with a saturated aqueous solution of sodium chloride and dried, followed by concentration to dryness. The residue is triturated with ether and the mixture is allowed to stand. The resultant precipitate of a 7 - (4 - thiocyano - 3 - oxobutyramido) - 3 - (nitrogen - containing heterocyclic)thiomethyl - 3 - cephem - 4 - carboxylic acid is recovered by filtration as a powder.

(2) In 50 ml. of a phosphate buffer solution of pH 6.4 are dissolved 10 m mol of 7 - (4 - thiocyano - 3 - oxobutyrylamido) - 3 - (nitrogen - containing heterocyclic)thiomethyl - 3 - cephem - 4 - carboxylic acid and 0.84 g. (10 m mol) of sodium hydrogen carbonate and the solution is allowed to stand at room temperature for 2 days. The mixed solution is adjusted to pH 3.0 with 50% phosphoric acid and saturated with sodium chloride, followed by the extraction with ethyl acetate (3 x 100 ml.). The combined extract is washed with 10% aqueous solution of sodium chloride and dried. The dried solution is concentrated and to the concentrate is added ether, followed by standing. The precipitated crystals are collected by filtration under suction to obtain a 7 - [2 - (2 - oxo - 4 - thiazolin - 4 - yl)acetamido] - 3 - (nitrogen - containing heterocyclic)thiomethyl - 3 - cephem - 4 - carboxylic acid.

Method 7.

In a mixture of 8 ml. of water and 4 ml. of tetrahydrofuran are dissolved 0.974 g. (2 m mol) of 7 - [2 - (2 - oxo - 4 - thiazolin - 4 - yl)acetamido] - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylic acid, 1.1 m mol of a nitrogen-containing heterocyclic thiol and 0.336 g. (4 m mol) of sodium hydrogen carbonate and

the resultant solution is stirred under heating at 60—65°C for 6-8 hours. After cooling, the reaction solution is adjusted pH 3.0 by adding phosphoric acid and extracted with ethyl acetate, followed by washing with water and drying. The dried extract is concentrated to dryness under reduced pressure and the residue is triturated with ether followed by standing. The precipitate is collected by filtration to give 7 - [2 - (2-oxo - 4 - thiazolin - 4 - yl)acetamido] - 3 - (nitrogen - containing heterocyclic)-thiomethyl - 3 - cephem - 4 - carboxylic acid as powder.

Method 8.

(1) In 4 ml. of tetrahydrofuran are dissolved 0.159 g. (1 m mol) of (2-oxo-4-thiazolin-4-yl)acetic acid, 0.115 g. (1 m mol) of N-hydroxysuccinimide and 0.206 g. of dicyclohexylcarbodiimide and the solution is stirred for one hour at room temperature. The reaction mixture is subjected to filtration under suction to remove the precipitate of N,N'-dicyclohexylurea.

The filtrate is added at a stroke to a solution of 1.2 m mol of a 7 - amino - 3 - (nitrogen - containing heterocyclic)thiomethyl - 3 - cephem - 4 - carboxylic acid and 0.15 g. (1.5 m mol) of triethylamine dissolved in 15 ml. of dichloromethane and the mixture is stirred for 2 hours at room temperature. The solvent is distilled off under suction from the reaction mixture and to the residue is added water, followed by adjusting to pH 2.5 with concentrated phosphoric acid. The resultant solution is extracted with ethyl acetate (3×60 ml.) and the extract is washed with water and dried, followed by concentration under suction. The residue is triturated with ether, and the mixture is allowed to stand. The precipitates are collected by filtration to obtain a 7 - [2 - (2 - oxo - 4 - thiazolin - 4 - yl)acetamido] - 3 - (nitrogen-containing heterocyclic)thiomethyl - 3 - cephem - 4 - carboxylic acid.

Method 9.

(1) In 10 ml. of dimethylformamide are dissolved 0.4 g. (2 m mol) of 2-(2-aminothiazol-4-yl)acetic acid hydrochloride, 0.25 g. (2.2 m mol) of N-hydroxysuccinimide and 0.412 g. (2 m mol) of dicyclohexylcarbodiimide and the solution is allowed to stand at room temperature for 3 hours. The reaction mixture is subjected to filtration under suction to remove the precipitate of N,N'-dicyclohexylurea.

(2) The filtrate is added at a stroke to a solution of 2 m mol of 7-aminocephalosporanic acid or a 7 - amino - 3 - (nitrogen - containing heterocyclic)thiomethyl - 3 - cephem - 4 - carboxylic acid and 0.404 g. (4 m mol) of triethylamine dissolved in 20 ml. of dichloromethane and the mixed solution is stirred for 24 hours at room temperature. The solvent is distilled off under reduced pressure and the residue is adjusted its pH to 7 by adding a 10% aqueous solution of sodium hydrogen carbonate. The resultant solution is chromatographed on column of polystyrene resin (Amberlite XAD-2) and developed with water and then with 5% ethanol. The fractions containing the desired product are pooled and freeze-dried to obtain the corresponding sodium 7 - [2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - acetoxymethyl or nitrogen-containing heterocyclic thiomethyl - 3 - cephem - 4 - carboxylate.

Method 10.

To 3 ml. of phosphorous oxychloride is added 0.35 g. of (2-thioxo-4-thiazolin-4-yl)acetic acid and the mixture is heated at 80—90°C for 15 minutes to give homogeneous solution, followed by distillation of excess phosphorous oxychloride under reduced pressure. The residue is dissolved in 5 ml. of acetone and the solution is added dropwise to a mixed solution of 2 m mol of 7-aminocephalosporanic acid or a 7 - amino - 3 - (nitrogen - containing heterocyclic)thiomethyl - 3 - cephem - 4 - carboxylic acid, 6 ml. of acetone and 10 ml. of water which is adjusted to pH 6.8 with a 10% aqueous solution of sodium hydrogen carbonate under ice-cooling and stirring, while the pH of the solution is maintained in the range from 6 to 7 by adding a 10% aqueous solution of sodium hydrogen carbonate. After stirring for further 2 hours, the mixture is subjected to the distillation under suction to remove acetone and the residue is chromatographed on a column of polystyrene resin (Amberlite XAD-2), followed by developing with water. The fractions containing desired product are pooled and freeze-dried to obtain the corresponding 7 - [2 - (2 - thioxo-4 - thiazolin - 4 - yl)acetamido] - 3 - acetoxymethyl or (nitrogen - containing heterocyclic)thiomethyl - 3 - cephem - 4 - carboxylic acid.

N#N=C1SC=CC1CC(=O)N2C(=O)NC(S2)C3=CC(=C(C=C3)CSC4=NC(=N5C(=S4)N=C5)S)C6=C(C=C6)R5

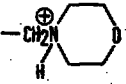
Compound No.	R ^s	M	UVλ _{max} (ε in water)	IR (KBr) cm ⁻¹	NMR δ ppm	Method No.
1	-SH	Na	—	1760	(60MHz, in D ₂ O): 3.4—3.7(m, 2×CH ₂), 3.9—4.31(ABq, J14Hz, 3—CH ₂), 5.08(d, J5Hz, 6—H), 5.64(d, J5Hz, 7—H), 6.50(s, thiazole 5—H).	3
2	-SCH ₃	Na	—	1760	(60MHz, in D ₂ O): 2.70(s, CH ₃), 3.45—3.70(m, 2×CH ₂) 3.95—4.34(ABq, J14Hz, 3—CH ₂), 5.10(d, J5Hz, 6—H), 5.70(d, J5Hz, 7—H), 6.55(s, thiazole 5—H).	3
3			262nm (1.53 ×10 ⁴)	1769	(100MHz, in D ₂ O) ² : 2.74(m, 4H), 3.53 & 3.87(ABq, J18Hz, 2—CH ₂), 3.70(s, CH ₂ CO), 3.88(m, 4H), 4.15(s, =NCH ₂), 4.20 & 4.59(ABq, J13Hz, 3—CH ₂), 5.20(d, J5Hz, 6—H), 5.76(d, J5Hz, 7—H), 6.58(s, thiazole 5—H).	1 4
4	-NH ₂	Na	260nm (1.61 ×10 ⁴)	1760	(100MHz, in D ₂ O): 3.44 & 3.88(ABq, J18Hz, 2—CH ₂), 3.70 (s, CH ₂ CO), 3.89 & 4.51(ABq, J13Hz, 3—CH ₂), 5.19(d, J5Hz, 6—H), 5.75 (d, J5Hz, 7—H), 6.60 (s, thiazole 5—H).	1 2 4

TABLE 1 (Continued)

Compound No.	R ^s	M	UVλ _{max} (ε in water)	IR (KBr) cm ⁻¹	NMR δ ppm	Method No.
5	-NHCOOCH ₃	Na	261nm (1.61 ×10 ⁴)	1760	(100MHz, in D ₂ O): 3.47 & 3.88(ABq, J18Hz, 2-CH ₂), 3.71 (s, CH ₂ CO), 3.89(s, OCH ₃), 3.90 & 4.51 (ABq, J13Hz, 3-CH ₂), 5.19(d, J5Hz, 6-H), 5.75(d, J5Hz, 7-H), 6.59(s, thiazole 5-H).	1 2 4
6	-SCH ₂ CH ₂ OH	Na	260nm (1.65 ×10 ⁴)	1765	(60MHz, in D ₂ O): 3.4-3.8(m, 3×CH ₂), 3.95(t, J6Hz, CH ₂ O), 4.00 & 4.40(ABq, J14Hz, 3-CH ₂), 5.05(d, J5Hz, 6-H), 5.62(d, J5Hz, 7-H), 6.52(s, thiazole 5-H).	1 2 3
7	-NHCOCH ₂ N(CH ₃) ₂	Na	261nm (1.62 ×10 ⁴)	1760	(60MHz, in D ₂ O): 2.95(s, 2×CH ₃), 3.40-4.10(m, 4×CH ₂), 5.02(d, J5Hz, 6-H), 5.59(d, J5Hz, 7-H), 6.42(s, thiazole 5-H).	1 2 3
8	-CH ₂ CON(CH ₃) ₂	Na	260nm (1.48 ×10 ⁴)	1757	(100MHz, in D ₂ O): 3.12 & 3.28(each s, N(CH ₃) ₂), 3.54 & 3.89(ABq, J18Hz, 2-CH ₂), 3.72(s, CH ₂ CO), 4.20 & 4.61(ABq, J14Hz, 3-CH ₂), 5.22(d, J5Hz, 6-H), 5.78 (d, J5Hz, 7-H), 6.61(s, thiazole 5-H).	1 2 4
9	-SCH ₂ CH ₂ N(CH ₃) ₂	Na	260nm (1.54 ×10 ⁴)	1768	(60MHz, in D ₂ O): 2.74(s, 2×CH ₃), 3.2-3.8(m, 4×CH ₂), 4.14 & 4.54(ABq, J14Hz, 3-CH ₂), 5.00(d, J5Hz, 6-H), 5.56(d, J5Hz, 7-H), 6.23(s, thiazole 5-H).	1 2 3

31

TABLE 1 (Continued)

Compound No.	R ^s	M	UVλ _{max} (ε in water)	IR (KBr) cm ⁻¹	NMR δ ppm	Method No.
10	-SCH ₂ CH ₂ OCOC ₆ H ₅	H	in 1% NaHCO ₃ : 233nm (2.14 × 10 ⁴) 260nm (1.71 × 10 ⁴)	1772	(60MHz, in D ₂ O): -d ₆ -DMSO): 3.3-3.8(m, 3×CH ₂), 4.12 & 4.52(ABq, J14Hz, 3-CH ₂), 4.58(t, J6Hz, CH ₂ O), 5.02(d, J5Hz, 6-H), 5.60(d, J5Hz, 7-H), 6.28(s, thiazole 5-H), 7.4-7.9(m, 5H).	5
11	-SCH ₂ CH ₂ OCOCH ₃	Na	260nm (1.68 × 10 ⁴)	260nm 1763	(60MHz, in D ₂ O): 2.00(s, CH ₃ CO), 3.2-3.7(m, 6H), 4.0-4.4(m, 4H), 5.00(d, J5Hz, 6-H), 5.57(d, J5Hz, 7-H), 6.46(s, thiazole 5-H).	3
12	-SCH ₂ CH ₂ SO ₃ Na	Na	261nm (1.70 × 10 ⁴)	1763	(60MHz, in D ₂ O): 3.0-3.8(m, 8H), 4.00 & 4.27(ABq, J13Hz, 3-CH ₂), 5.03(d, J5Hz, 6-H), 5.58(d, J5Hz, 7-H), 6.48(s, thiazole 5-H).	3
13	-SCH ₂ COOC ₂ H ₅	Na	261nm (1.75 × 10 ⁴)	1763	(60MHz, in D ₂ O): 1.23(t, J7Hz, CH ₃ , CH ₂), 3.4-4.5(m, 10H), 5.04(d, J5Hz, 6-H), 5.64(d, J5Hz, 7-H), 6.45(s, thiazole 5-H).	1 2 3
14	-SCH ₂ CON 	Na	260nm (1.73 × 10 ⁴)	1763	(60MHz, in D ₂ O): 3.3-4.5(m, 16H), 5.07(d, J5Hz, 6-H), 5.63(d, J5Hz, 7-H), 6.48(s, thiazole 5-H)	1 2 3

TABLE 1 (Continued)

Compound No.	R ^s	M	UVλ _{max} (ε in water)	IR (KBr) cm ⁻¹	NMR δ ppm	Method No.
15	-SCH ₂ COONa	Na	261nm (1.67 ×10 ⁴)	1763	(60MHz, in D ₂ O): 3.36 & 3.76(ABq, J16Hz, 2-CH ₂), 3.60 (s, CH ₂ CON), 3.96 & 4.40(ABq, J14Hz, 3-CH ₂), 5.08(d, J5Hz, 6-H), 5.63 (d, J5Hz, 7-H), 6.48(s, thiazole 5-H).	1 2 3
16	-SCH ₂ CONH ₂	Na	261nm (1.69 ×10 ⁴)	1768	(60MHz, in D ₂ O): 3.49 & 3.69(ABq, J18Hz, 2-CH ₂), 3.59(s, CH ₂ CO), 4.04(s, SCH ₂ CO), 4.00 & 4.42(ABq, J14Hz, 3-CH ₂), 5.03(d, J5Hz, 6-H), 5.60(d, J5Hz, 7-H), 6.47(s, thiazole 5-H).	1 2 4
17	-NHCH ₂ CH ₂ OH	Na	260nm (1.63 ×10 ⁴)	1765	(60MHz, in D ₂ O): 3.3-3.95(m, 8H), 4.32(ABq, 3-CH ₂), 4.97(d, J5Hz, 6-H), 5.53(d, J5Hz, 7-H), 6.40(s, thiazole 5-H).	1 2 3
18	-NHCH ₂ CH ₂ N(CH ₃) ₂	Na	255nm (2.12 ×10 ⁴)	1760	(60MHz, in D ₂ O): 2.95(s, 6H), 3.55 (m, 6H), 3.95(ABq, 2-CH ₂), 4.35(ABq, 3-CH ₂), 5.02(d, J5Hz, 6-H), 5.55 (d, J5Hz, 7-H), 6.38 (s, thiazole 5-H).	1 2 3
19	-CH ₂ COONa	Na	262nm (1.76 ×10 ⁴)	1761	(100MHz, in D ₂ O): 3.56 & 3.92(ABq, J18Hz, 2-CH ₂), 3.76 (s, CH ₂ CO), 4.16(s, CH ₂ CO), 4.20 & 4.62 (ABq, J13Hz, 3-CH ₂), 5.24(d, J5Hz, 6-H), 5.79(d, J5Hz, 7-H), 6.65(s, thiazole 5-H).	1 2 4

33

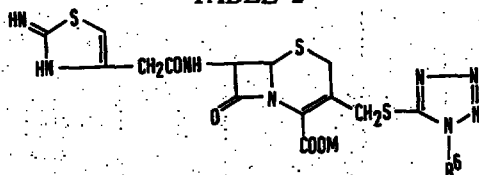
TABLE 1 (Continued)

Compound No.	R ^s	M	UVλ _{max} (ε in water)	IR (KBr) cm ⁻¹	NMR δ ppm	Method No.
20	-CH ₂ COOCH ₂	Na	261nm (1.64 ×10 ⁴)	1757	(100MHz, in D ₂ O): 3.52 & 3.87(ABq, J18Hz, 2-CH ₂), 3.70 (s, CH ₂ CO), 3.91(s, OCH ₃), 4.18 & 4.58 (ABq, J13Hz, 3-CH ₂), 5.20(d, J5Hz, 6-H), 5.75(d, J5Hz, 7-H), 6.60(s, thiazole 5-H).	1 2 4
21	-CH ₂ CONH ₂	Na	260nm (1.64 ×10 ⁴)	1762	(100MHz, in D ₂ O): 3.51 & 3.86(ABq, J18Hz, 2-CH ₂), 3.70 (s, CH ₂ CO), 4.18 & 4.57(ABq, 3-CH ₂), 5.19(d, J5Hz, 6-H), 5.75(d, J5Hz, 7-H), 6.58(s, thiazole 5-H).	1 2 4
22	-NHCH ₂ CH ₂ SO ₃ Na	Na	260nm (1.67 ×10 ⁴)	1760	(60MHz, in D ₂ O): 3.23(t, J6Hz, CH ₂ SO ₃), 3.5-3.7(m, 3×CH ₂), 4.05 & 4.45(ABq, J13Hz, 3-CH ₂), 5.04 (d, J5Hz, 6-H), 5.58 (d, J5Hz, 7-H), 6.48 (s, thiazole 5-H).	3
23	-SCH ₂ COCH ₃	Na	260nm (1.58 ×10 ⁴)	1765	(69MHz, in D ₂ O): 2.40(s, CH ₃), 3.4- 3.8(m, 2×CH ₂), 4.05 & 4.35(ABq, J14Hz, 3-CH ₂), 4.30(s, CH ₂ CO), 5.08(d, J5Hz, 6-H), 5.62(d, J5Hz, 7-H), 6.42(s, thiazole 5-H).	3
24	-CH ₂ SCH ₃	Na	262nm (1.63 ×10 ⁴)	1762	(100MHz, in D ₂ O): 2.24(s, CH ₂ S), 3.53 & 3.85(ABq, J18Hz, 2-CH ₂), 3.72(s, CH ₂ CO), 4.21(s, CH ₂ S), 4.25 & 4.59(ABq, J14Hz, 3-CH ₂), 5.20 (d, J5Hz, 6-H), 5.78 (d, J5Hz, 7-H), 6.58 (s, thiazole 5-H).	1 2 4

TABLE 1 (Continued)

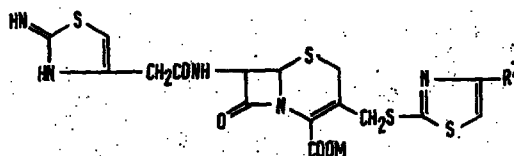
Compound No.	R ⁵	M	UVλ _{max} (ε in water)	IR (KBr) cm ⁻¹	NMR δ ppm	Method No.
25	-CH ₂ SO ₂ CH ₃	Na	261nm (1.64 × 10 ⁴)	1765	(100MHz, in D ₂ O): 3.32(s, CH ₂ SO ₂), 3.53 & 3.84(ABq, J18Hz, 2-CH ₂), 3.70 (s, CH ₂ CO), 4.23 & 4.59(ABq, J14Hz, 3-CH ₂), 5.19 & 5.74 (each d, J5Hz, 6- thiazole H).	1 2 4
26		Na	262nm (1.65 × 10 ⁴)	1770	(100MHz, in D ₂ O): 3.4-4.4(m, 12H), 5.21(d, J5Hz, 6-H), 5.77(d, J5Hz, 7-H), 6.60(s, thiazole 5-H).	1 2 4
27	-SCH ₂ CON(CH ₃) ₂	Na	260nm (1.70 × 10 ⁴)	1765	(60MHz, in D ₂ O): 2.95 & 3.14 (each s, 2×CH ₃), 3.5- 4.4(m, 4×CH ₂), 5.04 (d, J5Hz, 6-H), 5.64 (d, J5Hz, 7-H), 6.45 (s, thiazole 5-H).	1 2 3

TABLE 2



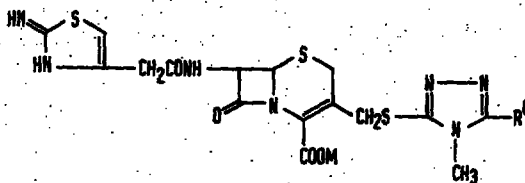
Compound No.	R ⁶	M	UVλ _{max} (ε in water)	IR (KBr) cm ⁻¹	NMR δ ppm	Method No.
28	-CH ₂ CH ₂ N(CH ₃) ₂	Na	261nm (1.71 × 10 ⁴)	1765	(60MHz, in D ₂ O): 2.79(s, 2×CH ₃), 3.5-4.8(m, 5×CH ₂), 5.09(d, J5Hz, 6-H), 5.65(d, J5Hz, 7-H), 6.48(s, thiazole 5-H).	1 2 3
29	-CH ₂ CONH ₂	Na	259nm (1.48 × 10 ⁴)	1765	(100MHz, in D ₂ O): 3.52 & 3.84(ABq, J18Hz, 2-CH ₂), 3.72(s, CH ₂ CO), 4.24 & 4.49(ABq, J13Hz, 3-CH ₂), 5.20 (d, J5Hz, 6-H), 5.42 (s, NCH ₂ CO), 5.76 (d, J5Hz, 7-H), 6.62 (s, thiazole 5-H).	1 2 4

TABLE 3



Compound No.	R ⁷	M	UVλ _{max} (ε in water)	IR (KBr) cm ⁻¹	NMR δ ppm	Method No.
30	-CH ₂ COONa	Na	259nm (1.66 × 10 ⁴)	1763	(100MHz, in D ₂ O): 3.44 & 3.83(ABq, J18Hz, 2-CH ₂), 3.69 (s, CH ₂ CO), 3.76(s, CH ₂ CO), 3.99 & 4.57(ABq, J14Hz, 3-CH ₂), 5.15(d, J5Hz, 6-H), 5.72 (d, J5Hz, 7-H), 6.58(s, 7 positioned thiazole 5-H), 7.35(s, 3 positioned thiazole 5-H).	1 4

TABLE 4

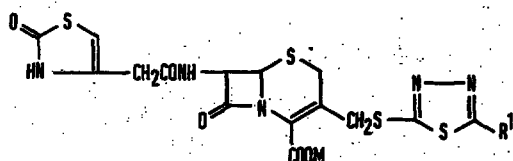


Compound No.	R ⁸	M	UVλ _{max} (ε in water)	IR (KBr) cm ⁻¹	NMR δ ppm	Method No.
31	-NH ₂	Na	257nm (1.43 × 10 ⁴)	1758	(100MHz, in D ₂ O): 3.45 & 3.95(ABq, J18Hz, 2-CH ₂), 3.57 (s, N-CH ₃), 3.68 & 4.36(ABq, J13Hz, 3-CH ₂), 3.70(s, CH ₂ CO), 5.17(d, J5Hz, 6-H), 5.17(d, J5Hz, 7-H), 6.60(s, thiazole 5-H).	4

NC(=S)C=CNC(=O)CC1C(=O)NC(C(=O)O)S1CC2=NC=CC=C2R

Compound No.	R ₂	M	IR (KBr) cm ⁻¹	NMR δ ppm	Method No.
32	4-NH ₂ , 5-CH ₃	Na	1758	(100MHz, in D ₂ O): 2.04(s, CH ₃), 3.43 & 3.74(ABq, J18Hz, 2-CH ₂), 3.66(s, CH ₂ CO), 3.91 & 4.57(ABq, J14Hz, 3-CH ₂), 5.12(d, J5Hz, 6-H), 5.73(d, J5Hz, 7-H), 6.52(s, thiazole 5-H), 7.79(s, pyrimidine-H).	4
33	4-NH ₂ , 6-OH	Na	1758	(100MHz, in D ₂ O): 3.52 & 3.80(ABq, J18Hz, 2-CH ₂), 3.69(s, CH ₂ CO), 4.10 & 4.59(ABq, 3-CH ₂), 5.17(d, J5Hz, 6-H), 5.75(d, J5Hz, 7-H), 6.55(s, thiazole-H).	4
34	4-OH, 6-CH ₃	Na	1760	(100MHz, in D ₂ O): 2.31(s, CH ₃), 3.58 & 3.82(ABq, J18Hz, 2-CH ₂), 3.67(s, CH ₂ CO), 4.13 & 4.56(ABq, J14Hz, 3-CH ₂), 5.22(d, J5Hz, 6-H), 5.75(d, J5Hz, 7-H), 6.08(s, pyrimidine-H), 6.52(s, thiazole-H).	4

37



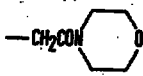
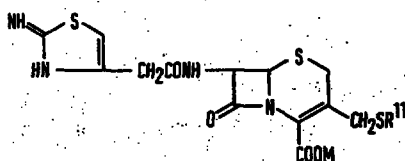
Compound No.	R ¹⁰	M	UVλ _{max} (ε in water)	IR (KBr) cm ⁻¹	NMR δ ppm	Method No.
35	-NHCH ₃	H	in 5% NaHCO ₃ , 253nm (1.28 × 10 ⁴)	1780	(100MHz, in d ₆ -DMSO): 2.85(s, NCH ₃), 3.32(s, CH ₂ CO), 3.52 & 3.75 (ABq, J18Hz, 2-CH ₂), 4.04 & 4.24(ABq, J13Hz, 3-CH ₂), 5.04 & 5.65 (each d, J4.5Hz, 6- & 7-H), 6.00(s, thiazoline H), 8.89(d, J8Hz, NHCO).	6 7 8
36	-SCH ₂ CONH ₂	H	-	1785	(100MHz, in d ₆ -DMSO): 3.32(s, CH ₂ CO), 3.4-3.7(m, 2-CH ₂), 3.96 (s, SCH ₂), 4.20 & 4.48 (ABq, J13Hz, 3-CH ₂), 5.07(d, J4.5Hz, 6-H), 5.67(dd, J4.5 & 8.0Hz, 7-H), 6.00(s, thiazoline H), 7.22 & 7.62(CONH ₂).	6 7 8
37		H	-	1786	(100MHz, in d ₆ -DMSO): 3.31(s, CH ₂ CO), 3.4-3.8(m, 5-CH ₂), 4.23 & 4.52 (ABq, J13Hz, 3-CH ₂), 4.29(s, CH ₂ CO), 5.06(d, J4.5Hz, 6-H), 5.66 (dd, J4.5 & 8.0Hz, 7-H), 6.0(s, thiazoline H), 8.96(d, J8.0Hz, NH).	6 7 8

TABLE 7



Compound No.	R ¹¹	M	UVλ _{max} (ε in water)	IR (KBr) cm ⁻¹	NMR δ ppm	Method No.
38		Na	258nm (1.56 × 10 ⁴)	1763	(100MHz, in D ₂ O): 2.57(s, oxadiazole CH ₃), 3.42 & 3.82 (ABq, J18Hz, 2-CH ₂), 3.62(s, CH ₂ CO), 3.97 & 4.51(ABq, J13Hz, 3-CH ₂), 5.10(d, J5Hz, 6-H), 5.67 (d, J5Hz, 7-H), 6.51(s, thiazole 5-H).	4 9
39		Na	261nm (1.49 × 10 ⁴)	1765	(100MHz, in D ₂ O): 3.47 & 3.90(ABq, 17Hz, 2-CH ₂), 3.67(s, CH ₂ CO), 3.80(s, triazole CH ₃), 3.83 & 4.37(ABq, J14Hz, 3-CH ₂), 5.15(d, J5Hz, 6-H), 5.70(d, J5Hz, 7-H), 6.56 (s, thiazole 5-H), 8.58 (s, triazole 5-H).	4
40		Na	—	1750	(100MHz, in D ₂ O): 2.47 (s, pyridazine CH ₃), 3.58(ABq, 2-CH ₂), 3.59 (s, CH ₂ CO), 4.20(ABq, 3-CH ₂), 5.10(d, 6-H), 5.65(d, 7-H), 6.46(s, thiazole 5-H), 7.35 & 7.74(each d, pyridazine 4 & 5-H).	3 9
41		Na	259nm (1.46 × 10 ⁴)	1768	(100MHz, in D ₂ O): 3.45 & 3.77(ABq, J18Hz, 2-CH ₂), 3.62(s, CH ₂ CO), 4.03 & 4.27(ABq, J14Hz, 3-CH ₂), 5.12(d, 5Hz, 6-H), 5.67 (d, 5Hz, 7-H), 6.50(s, triazole 4-H), 8.36 (s, triazole 5-H).	4
42		Na	250nm (1.60 × 10 ⁴)	1760	(100MHz, in D ₂ O): 2.52 (s, triazole 5-CH ₃), 3.43 & 3.95(ABq, J18Hz, 2-CH ₂), 3.68(s, CH ₂ CO & triazole 4-CH ₃), 3.74 & 4.41(ABq, J14Hz, 3-CH ₂), 5.14(d, J4Hz, 6-H), 5.70 (d, J4Hz, 7-H), 6.57(s, thiazole 5-H).	3 4

TABLE 7 (Continued)

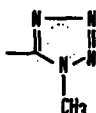
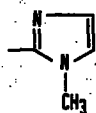
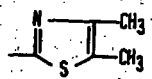
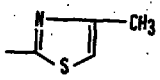
Compound No.	R ¹¹	M	UVλ _{max} (ε in water)	IR (KBr) cm ⁻¹	NMR δ ppm	Method No.
43		H	—	1762, 1662	(100MHz, in d ₆ -DMSO): 3.39(s, CH ₂ CO), 3.35 & 3.77(ABq, J18Hz, 2-CH ₂), 3.90(s, tetrazole 1-CH ₃), 4.21 & 4.36(ABq, J14Hz, 3-CH ₂), 5.03(d, J5Hz, 6-H), 5.66(dd, J9 & 5Hz, 7-H), 6.23(s, thiazole 5-H), 6.2-7.1(m, NH ₂), 8.85(d, J9Hz, CONH).	1 2
44		Na	250nm (1.57 ×10 ⁴)	1758	(100MHz, in D ₂ O): 3.32 & 3.85(ABq, J18Hz, 2-CH ₂), 3.68(s, CH ₂ CO), 3.65 & 4.35(ABq, J13Hz, 3-CH ₂), 3.79(s, 1,3-diazole 1- CH ₃), 5.13(d, J5Hz, 6-H), 5.69(d, J5Hz, 7-H), 6.57 (s, thiazole 5-H), 7.14 & 7.30(each d, J1Hz, 1,3- diazole 4- & 5-H).	4
45		Na	261nm (1.59 ×10 ⁴)	1763	(100MHz, in D ₂ O): 3.56 & 3.89(ABq, J18Hz, 2-CH ₂), 3.71 (s, CH ₂ CO), 4.32 & 4.70(ABq, J13Hz, 3- CH ₂), 5.21(d, J5Hz, 6-H), 5.78(d, J5Hz, 7-H), 6.58(s, thiazole 5-H).	4 9
46		Na	258nm (1.61 ×10 ⁴)	1757	(100MHz, in D ₂ O): 2.35 & 2.77(each s, thiazole 4- & 5-CH ₃), 3.40 & 3.82(ABq, J18Hz, 2-CH ₂), 3.69(s, CH ₂ CO), 3.89 & 4.51(ABq, J13Hz, 3-CH ₂), 5.15(d, J5Hz, 6-H), 5.75 (d, J5Hz, 7-H), 6.56(s, thiazole 5-H).	4 9
47		H	(in 2% NaHCO ₃) 259nm (1.61 ×10 ⁴)	1759	(100MHz, in d ₆ -DMSO): 2.32(s, thiazole 4-CH ₃), 3.99(s, CH ₂ CO), 3.50 & 3.77(ABq, J18Hz, 2-CH ₂), 4.10 & 4.48(ABq, J13Hz, 3-CH ₂), 5.05(d, J5Hz, 6-H), 5.67(q, J5 & 8Hz, 7-H), 6.23(s, thiazole 5-H), 6.85(broad s, NH ₂), 7.15(s, thiazole 5-H), 8.82(d, J8Hz, CONH).	4 9

TABLE 7 (Continued)

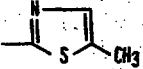
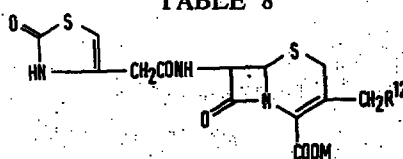
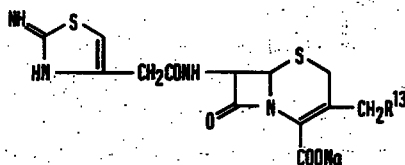
Compound No.	R ¹¹	M	UVλ _{max} (ε in water)	IR (KBr) cm ⁻¹	NMR δ ppm	Method No.
48		Na	258nm (1.73 ×10 ⁴)	1758	(100MHz, in D ₂ O): 2.55(s,thiazole 5-CH ₃), 3.42 & 3.85(ABq,J18Hz, 2-CH ₂), 3.70(s, CH ₂ CO), 3.90 & 4.56(ABq,J14Hz, 3-CH ₂), 5.15(d, J4.5Hz, 6-H), 5.73 (d,J4.5Hz,7-H), 6.58(s,thiazole 5-H), 7.51(s,thiazole 4-H).	4 9
49		Na	—	1765	(60MHz, in D ₂ O): 3.28 & 3.64(ABq, J18Hz,2-CH ₂), 3.50 (s, CH ₂ CO), 3.80 & 3.64(ABq,J14Hz, 3-CH ₂), 4.95(d, J4.5Hz,6-H), 5.54 (d,J4.5Hz,7-H), 6.41(s,thiazole 5-H), 7.0-7.9(m, pyridine 3,4,5-H), 8.28(m,pyridine 6-H).	4
50		Na	—	1763	(60MHz, in D ₂ O): 3.63(s,CH ₂ CO), 3.42 & 3.95(ABq,J18Hz, 2-CH ₂), 3.85 & 4.35 (ABq,J14Hz,3-CH ₂) 5.01(d,J5Hz,6-H), 5.60(d,J5Hz,7-H), 6.40(s,thiazole 5-H), 7.15(t,J5.5Hz, pyrimidine 5-H), 8.47(d,J5.5Hz, pyrimidine 4- & 6-H).	4

TABLE 8



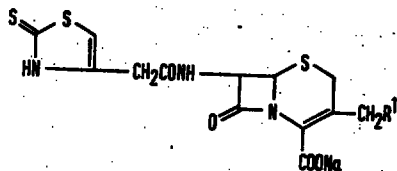
Compound No.	R ¹²	M	UVλ _{max} (ε in water)	IR (KBr) cm ⁻¹	NMR δ ppm	Method No.
51		Na	—	1760	(100MHz, in D ₂ O): 2.48(s, pyridazine-CH ₃), 3.61(s, CH ₂ CO), 3.64(ABq, 2-CH ₂), 4.20(ABq, 3-CH ₂), 5.10(d, 6-H), 5.64 (d, 7-H), 6.25(s, thiazoline 5-H), 7.37 & 7.71(each d, pyridazine 4 & 5-H).	4
52		Na	—	1760	(100MHz, in D ₂ O): 2.48(s, thiazole 4-CH ₃), 3.43 & 3.86(ABq, J18Hz, 2-CH ₂), 3.70(s, CH ₂ CO), 3.95 & 4.59(ABq, J13Hz; 3-CH ₂), 5.15(d, J4.5Hz, 6-H), 5.72(d, J4.5Hz, 7-H), 6.34(s, thiazoline 5-H), 7.21(s, thiazole 5-H).	4
53	-O-COCH ₃	H	identical with those of Example 1			8
54		H	identical with those of Example 6			8
55		H	identical with those of Example 9			8
56		H	identical with those of Example 4			8
57		H	identical with those of Example 2			8

TABLE 9



Compound No.	R ¹³	UVλ _{max} (ε in water)	IR (KBr) cm ⁻¹	NMR δ ppm	Method No.
58		255nm (1.87 ×10 ⁴)	1757	(100MHz, in D ₂ O): 2.14 & 2.34 (each s, oxazole 4- & 5-CH ₃), 3.42 & 3.87(ABq, J18Hz, 2-CH ₂), 3.70(s, CH ₂ CO), 3.91 & 4.57(ABq, J14Hz, 3-CH ₂), 5.16(d, J5Hz, 6-H), 5.75(d, J5Hz, 7-H), 6.58(s, thiazole 5-H).	9
59	-OCOCH ₃	identical with those of Example 11			9
60		identical with those of Example 16			9
61		identical with those of Example 18			9
62		identical with those of Example 14			9

TABLE 10



Compound No.	R ¹⁴	UVλ _{max} (ε in water)	NMR δ ppm	Method No.
63	-OCOCH ₃	250nm (8.39 ×10 ³) 310nm (1.16 ×10 ⁴)	(100MHz, in D ₂ O): 2.8 (s, CH ₃ CO), 3.44 & 3.76 (ABq, J18Hz, 2-CH ₂), 3.76 (s, CH ₂ CO), 4.78 & 4.98 (ABq, J13Hz, 3-CH ₂), 5.10 (d, J5Hz, 6-H), 5.75(d, J5Hz, 7-H), 6.87(s, thiazoline 5-H).	10
64		270nm (1.03 ×10 ⁴) 310nm (8.80 ×10 ³)	(100MHz, in D ₂ O): 3.48 & 3.81(ABq, J18Hz, 2-CH ₂), 3.75(s, CH ₂ CO), 4.09(s, tetrazole CH), 4.39(ABq, J13Hz, 3-CH ₂), 5.13(d, J5Hz, 6-H), 5.67(d, J5Hz, 7-H), 6.84(s, thiazoline 5-H).	10

TABLE 11

Antibacterial spectra

(mcg./ml., agar dilution method)

Compound No.	Gram-positive bacteria		Gram-negative bacteria					
	<i>S. aureus</i> 209P	<i>S. aureus</i> 1840	<i>E. coli</i> NIHJ JC-2	<i>E. coli</i> O-111	<i>E. coli</i> T-7	<i>K. pneumoniae</i> DT	<i>P. vulgaris</i> IFO 3988	<i>P. morganii</i> Eb53
Cephalexidine	≤0.2	0.39	3.13	1.56	>100	1.56	6.25	>100
Cephazolin	≤0.2	0.78	1.56	0.78	50	1.56	6.25	100
4	0.2	0.78	0.78	0.1	100	0.2	0.2	50
6	≤0.2	0.78	0.78	≤0.2	12.5	≤0.2	0.39	6.25
7	0.78	3.13	0.78	≤0.2	25	≤0.2	0.39	12.5
8	0.39	0.78	0.78	≤0.2	12.5	≤0.2	0.39	<0.2
9	≤0.2	0.78	1.56	0.39	50	≤0.2	6.25	<0.2
12	0.39	1.56	0.78	≤0.2	50	≤0.2	≤0.2	25
15	0.78	1.56	0.78	≤0.2	25	≤0.2	≤0.2	3.13
16	≤0.2	0.78	0.39	≤0.2	12.5	≤0.2	≤0.2	1.56
17	0.39	3.13	0.39	≤0.2	12.5	≤0.2	0.39	0.78
18	1.56	3.13	0.78	≤0.2	6.25	≤0.2	1.56	1.56
19	0.78	3.13	0.78	≤0.2	25	≤0.2	≤0.2	0.78
21	≤0.2	1.56	0.39	≤0.2	25	≤0.2	≤0.2	0.78
22	0.78	3.13	0.78	≤0.2	25	≤0.2	≤0.2	0.78
23	≤0.2	0.78	1.56	0.39	25	≤0.2	0.39	3.13
24	≤0.2	0.78	1.56	0.39	25	≤0.2	0.39	25
25	0.39	0.78	0.39	≤0.2	100	≤0.2	0.39	25
28	0.39	1.56	0.39	≤0.2	3.13	≤0.2	0.78	≤0.2
29	0.78	1.56	0.39	≤0.2	3.13	≤0.2	≤0.2	≤0.2
30	0.39	1.56	1.56	0.39	100	≤0.05	0.2	50
31	0.78	1.56	0.2	≤0.1	3.13	≤0.1	0.2	1.56
32	0.2	1.56	1.56	0.78	50	0.39	0.78	100

TABLE 11 (Continued)

Compound No.	Gram positive bacteria		Gram-negative bacteria					
	<i>S. aureus</i> 209P	<i>S. aureus</i> 1840	<i>E. coli</i> NIHJ JC-2	<i>E. coli</i> O-111	<i>E. coli</i> T-7	<i>K. pneumoniae</i> DT	<i>P. vulgaris</i> IFO 3988	<i>P. morganii</i> Eb53
38	0.39	0.78	1.56	0.39	—	0.39	—	25
39	0.78	1.56	0.2	<0.05	25	0.1	—	25
40	0.2	0.78	0.39	0.2	—	0.1	—	3.125
51	0.2	0.78	1.56	0.78	—	1.56	—	12.5
41	0.39	0.78	0.78	0.78	—	0.2	—	25
42	0.39	1.56	0.2	0.1	—	0.1	—	1.56
44	0.39	1.56	0.78	0.39	6.25	0.39	0.39	—
45	≤0.2	0.78	3.13	0.78	25	0.78	0.78	—
47	≤0.2	0.78	1.56	0.78	12.5	0.39	0.39	—
55	0.2	0.78	1.56	0.78	—	1.56	—	—
64	≤0.78	1.56	—	1.56	—	<0.78	—	—

TABLE 12
Protective Effect (ED₅₀*, mg/kg) on Infected Mice

Compound No.	ED ₅₀ * mg/kg
9	0.812
11	<0.625
19	<0.625
21	<0.625
Cephaloridine	2.81

TABLE 13

Compound No.	ED ₅₀ * mg/kg
12	<0.625
15	<0.625
16	<0.625
17	<0.625
18	<0.625
Cephaloridine	1.94

TABLE 14

Compound No.	ED ₅₀ * mg/kg
40	0.28
42	0.38
43	0.73
60	0.89
62	2.38
Cephaloridine	3.57
Cephazolin	3.1

*Test animals: male mice (ICR/SLC)
5 mice per group per single dose

Infection: intraperitoneally with *Escherichia coli*
0-111

Administration: a single subcutaneous dose immediately
after challenge

Observation period: 7 days

Example 24.

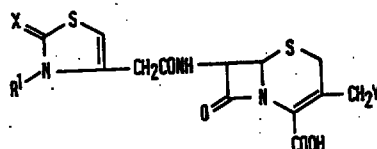
(1) A solution of 0.263 g. of (2 - thioxo - 4 - thiazolin - 4 - yl) acetic acid dissolved in 3 ml. of dimethylformamide is cooled with ice and to the solution are added 0.173 g. of N-hydroxysuccinimide and 0.309 g. of dicyclohexylcarbodiimide, followed by stirring for 25 minutes. The reaction mixture is subjected to filtration under suction to remove the precipitate of N,N'-dicyclohexylurea and 1 ml. each of dimethylformamide and dichloromethane are added to the filtrate.

(2) The mixed solution is added at a stroke to a solution of 0.49 g. of 7-aminocephalosporanic acid and 0.252 ml. of triethylamine dissolved in 5 ml. of dichloromethane and the mixture is stirred for 3 hours at room temperature. The solvent is distilled off under reduced pressure and water is added to the residue. The pH of the resultant mixture is adjusted to 2.5 by adding concentrated phosphoric acid under ice-cooling, followed by extracting with ethyl acetate (60 ml. x 3). The combined ethyl acetate layer is dried and concentrated to dryness under reduced pressure. The

residue is dissolved in a solution of 0.168 g. of sodium hydrogen carbonate dissolved in 5 ml. of water and the solution is chromatographed on a column of polystyrene resin (Amberlite XAD-2), followed by development with water. The fractions containing the desired product are pooled and freeze-dried to obtain sodium 7 - [2 - (2-thioxo - 4 - thiazolin - 4 - yl)acetamido] - 3 - acetoxymethyl - 3 - cephem - 4-carboxylate, which is in good agreement with the Compound No. 64 of Example 21 in IR, UV and NMR spectra. Yield 0.302 g. (45%).

WHAT WE CLAIM IS:—

1. A compound of general formula:



or a tautomeric form thereof, wherein R¹ is a hydrogen atom or an alkyl group, X is an oxygen or sulphur atom or a group of formula =NR² wherein R² is a hydrogen atom or an alkyl group, or R¹ and R² can together form an alkylene group, and Y is an acetoxy group or a group of formula—SR³ wherein R³ is a nitrogen-containing heterocyclic group, or a pharmaceutically acceptable salt thereof.

2. 7 - [2 - (2 - Amino - thiazol - 4 - yl)acetamido] - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylic acid.

3. 7 - [2 - (2 - Oxo - 4 - thiazolin - 4 - yl)acetamido] - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylic acid.

4. 7 - [2 - (2 - Thioxo - 4 - thiazolin - 4 - yl)acetamido] - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylic acid.

5. A compound according to claim 1, wherein the heterocyclic group is a 5- or 6-membered heterocyclic group.

6. A compound according to claim 5, wherein the heterocyclic group contains up to four ring nitrogen atoms.

7. A compound according to claim 6, wherein the heterocyclic group is a pyridyl, N-oxido-pyridyl, pyrimidyl, pyridazinyl, N-oxido-pyridazinyl, pyrazolyl, diazolyl, triazolyl or tetrazolyl group.

8. A compound according to claim 5, wherein the heterocyclic group contains a ring oxygen atom.

9. A compound according to claim 8, wherein the heterocyclic group is an oxadiazolyl group.

10. A compound according to claim 5, wherein the heterocyclic group contains a ring sulphur atom.

11. A compound according to claim 10, wherein the heterocyclic group is a thiazolyl or thiadiazolyl group.

12. A compound according to claim 5, wherein the heterocyclic group is substituted with at least one halogen atom or C₁ or C₂ alkyl, C₁ or C₂ alkoxy, amino, mercapto, hydroxy, carboxy, carbamoyl, or substituted C₁ or C₂ alkyl, mercapto or amino group.

13. A compound according to claim 12, wherein the C₁ or C₂ alkyl group is substituted with a hydroxy, mercapto, amino, morpholino, carboxy, sulpho, carbamoyl, mono-, di- or tri-(C₁ or C₂ alkyl)amino, mono- or di-(C₁ or C₂ alkyl)carbamoyl, alkoxy, alkylthio, alkylsulphonyl, acyloxy or morpholinocarbonyl group.

14. A compound according to claim 12, wherein the mercapto group is substituted with a C₁ or C₂ alkyl group or a C₁ or C₂ alkyl group substituted with a hydroxy, mercapto, amino, morpholino, carboxy, sulpho, carbamoyl, mono-, di-, or tri-(C₁ or C₂ alkyl)amino, mono-, di- or tri-(C₁ or C₂ alkyl)carbamoyl, alkoxy, alkylthio, alkylsulphonyl, acyloxy or morpholinocarbonyl group.

15. A compound according to claim 12, wherein the amino group is substituted with a C₁ or C₂ alkyl group, an alkoxy-carbonyl group, an acyl or carbamoyl group, a (C₁ or C₂ alkyl)carbamoyl group, or a C₂ or C₂ alkyl group substituted with a hydroxy, mercapto, amino, morpholino, carboxy, sulpho, carbamoyl, mono-, di- or tri-(C₁ or C₂ alkyl)amino, mono- or di-(C₁ or C₂ alkyl)carbamoyl, alkoxy, alkylthio, alkylsulphonyl, acyloxy or morpholinocarbonyl group.

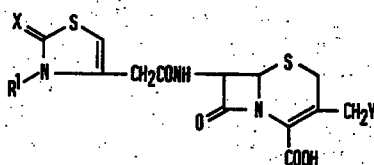
16. 7 - [2 - (2 - Amino-thiazol - 4 - yl)acetamido] - 3 - [1 - (2 - N,N - dimethylaminoethyl) - tetrazol - 5 - yl]thiomethyl - 3 - cephem - 4 - carboxylic acid.



residue is dissolved in a solution of 0.168 g. of sodium hydrogen carbonate dissolved in 5 ml. of water and the solution is chromatographed on a column of polystyrene resin (Amberlite XAD-2), followed by development with water. The fractions containing the desired product are pooled and freeze-dried to obtain sodium 7 - [2 - (2-thioxo - 4 - thiazolin - 4 - yl)acetamido] - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylate, which is in good agreement with the Compound No. 64 of Example 21 in IR, UV and NMR spectra. Yield 0.302 g. (45%).

WHAT WE CLAIM IS:—

1. A compound of general formula:



or a tautomeric form thereof, wherein R^1 is a hydrogen atom or an alkyl group, X is an oxygen or sulphur atom or a group of formula $=NR^2$ wherein R^2 is a hydrogen atom or an alkyl group, or R^1 and R^2 can together form an alkylene group, and Y is an acetoxy group or a group of formula $-SR^3$ wherein R^3 is a nitrogen-containing heterocyclic group, or a pharmaceutically acceptable salt thereof.

2. 7 - [2 - (2 - Amino - thiazol - 4 - yl)acetamido] - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylic acid.

3. 7 - [2 - (2 - Oxo - 4 - thiazolin - 4 - yl)acetamido] - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylic acid.

4. 7 - [2 - (2 - Thioxo - 4 - thiazolin - 4 - yl)acetamido] - 3 - acetoxymethyl - 3 - cephem - 4 - carboxylic acid.

5. A compound according to claim 1, wherein the heterocyclic group is a 5- or 6- membered heterocyclic group.

6. A compound according to claim 5, wherein the heterocyclic group contains up to four ring nitrogen atoms.

7. A compound according to claim 6, wherein the heterocyclic group is a pyridyl, N-oxido-pyridyl, pyrimidyl, pyridazinyl, N-oxido-pyridazinyl, pyrazolyl, diazolyl, triazolyl or tetrazolyl group.

8. A compound according to claim 5, wherein the heterocyclic group contains a ring oxygen atom.

9. A compound according to claim 8, wherein the heterocyclic group is an oxadiazolyl group.

10. A compound according to claim 5, wherein the heterocyclic group contains a ring sulphur atom.

11. A compound according to claim 10, wherein the heterocyclic group is a thiazolyl or thiadiazolyl group.

12. A compound according to claim 5, wherein the heterocyclic group is substituted with at least one halogen atom or C_1 or C_2 alkyl, C_1 or C_2 alkoxy, amino, mercapto, hydroxy, carboxy, carbamoyl, or substituted C_1 or C_2 alkyl, mercapto or amino group.

13. A compound according to claim 12, wherein the C_1 or C_2 alkyl group is substituted with a hydroxy, mercapto, amino, morpholino, carboxy, sulphy, carbamoyl, mono-, di- or tri- $(C_1$ or C_2 alkyl)amino, mono- or di- $(C_1$ or C_2 alkyl)carbamoyl, alkoxy, alkylthio, alkylsulphonyl, acyloxy or morpholinocarbonyl group.

14. A compound according to claim 12, wherein the mercapto group is substituted with a C_1 or C_2 alkyl group or a C_1 or C_2 alkyl group substituted with a hydroxy, mercapto, amino, morpholino, carboxy, sulphy, carbamoyl, mono-, di-, or tri- $(C_1$ or C_2 alkyl)amino, mono-, di- or tri- $(C_1$ or C_2 alkyl)carbamoyl, alkoxy, alkylthio, alkylsulphonyl, acyloxy or morpholinocarbonyl group.

15. A compound according to claim 12, wherein the amino group is substituted with a C_1 or C_2 alkyl group, an alkoxycarbonyl group, an acyl or carbamoyl group, a $(C_1$ or C_2 alkyl)carbamoyl group, or a C_2 or C_2 alkyl group substituted with a hydroxy, mercapto, amino, morpholino, carboxy, sulphy, carbamoyl, mono-, di- or tri- $(C_1$ or C_2 alkyl)amino, mono- or di- $(C_1$ or C_2 alkyl)carbamoyl, alkoxy, alkylthio, alkylsulphonyl, acyloxy or morpholinocarbonyl group.

16. 7 - [2 - (2 - Amino - thiazol - 4 - yl)acetamido] - 3 - [1 - (2 - N,N - dimethylaminoethyl) - tetrazol - 5 - yl]thiomethyl - 3 - cephem - 4 - carboxylic acid.



* C L M S *

1,491,018

42

42

5

10

15

20

25

30

35

40

45

50

55

60

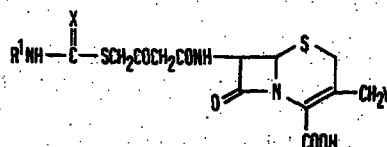
17. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - (1 - carbamoylmethyl-tetrazol - 5 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid.
18. 7 - [2 - (2 - Amino - thiazol - 4 - yl)acetamido] - 3 - (1 - methyl - tetrazol - 5 - yl) - thiomethyl - 3 - cephem - 4 - carboxylic acid.
19. 7 - [2 - (2 - Amino - thiazol - 4 - yl)acetamido] - 3 - [1 - (2 - hydroxyethyl)tetrazol - 5 - yl] - thiomethyl - 3 - cephem - 4 - carboxylic acid.
20. 7 - [2 - (2 - Oxo - 4 - thiazolin - 4 - yl) - acetamido] - 3 - (1 - methyl-tetrazol - 5 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid.
21. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - (4 - carboxylmethyl-1,3 - thiazol - 2 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid.
22. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - (4 - methyl - 1,3-thiazol - 2 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid.
23. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - (2 - amino - 1,3,4-thiadiazol - 5 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid.
24. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - [2 - (2 - hydroxyethyl-thio) - 1,3,4 - thiadiazol - 5 - yl]thiomethyl - 3 - cephem - 4 - carboxylic acid.
25. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - [2 - (2 - acetoxyethyl-thio) - 1,3,4 - thiadiazol - 5 - yl]thiomethyl - 3 - cephem - 4 - carboxylic acid.
26. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - [2 - (2 - capryloxyethylthio) - 1,3,4 - thiadiazol - 5 - yl]thiomethyl - 3 - cephem - 4 - carboxylic acid.
27. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - [2 - (N,N - dimethylaminomethylcarbonyl)amino - 1,3,4 - thiadiazol - 5 - yl]thiomethyl - 3 - cephem - 4 - carboxylic acid.
28. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - [2 - N,N - dimethylaminocarbonyl)methyl - 1,3,4 - thiadiazol - 5 - yl]thiomethyl - 3 - cephem - 4 - carboxylic acid.
29. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - [2 - (2 - N,N - dimethylaminoethyl)thio - 1,3,4 - thiadiazol - 5 - yl]thiomethyl - 3 - cephem - 4 - carboxylic acid.
30. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - [2 - (2 - sulphoethyl)-thio - 1,3,4 - thiadiazol - 5 - yl]thiomethyl - 3 - cephem - 4 - carboxylic acid.
31. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - (2 - carboxylmethyl-thio - 1,3,4 - thiadiazol - 5 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid.
32. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - (2 - ethoxycarbonylmethylthio - 1,3,4 - thiadiazol - 5 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid.
33. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - (2 - hexyloxycarbonylmethylthio - 1,3,4 - thiadiazol - 5 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid.
34. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - (2 - carbamoylmethyl-thio - 1,3,4 - thiadiazol - 5 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid.
35. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - [2 - (2 - hydroxyethyl)-amino - 1,3,4 - thiadiazol - 5 - yl]thiomethyl - 3 - cephem - 4 - carboxylic acid.
36. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - [2 - (2 - N,N - dimethylaminoethyl)amino - 1,3,4 - thiadiazol - 5 - yl]thiomethyl - 3 - cephem - 4 - carboxylic acid.
37. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - (2 - carboxymethyl-1,3,4 - thiadiazol - 5 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid.
38. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - (2 - carbamoylmethyl-1,3,4 - thiadiazol - 5 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid.
39. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - [2 - (2 - sulphoethyl)-amino - 1,3,4 - thiadiazol - 5 - yl]thiomethyl - 3 - cephem - 4 - carboxylic acid.
40. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - (2 - methyl - 1,3,4-thiadiazol - 5 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid.
41. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - (1,3,4 - thiadiazol - 2 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid.
42. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - (2 - methylthiomethyl-1,3,4 - thiadiazol - 5 - yl) - thiomethyl - 3 - cephem - 4 - carboxylic acid.
43. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - (3 - amino - 4 - methyl-1,2,4 - triazol - 5 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid.
44. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - (4 - methyl - 1,2,4-triazol - 5 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid.
45. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - 1,2,4 - triazol - 5 - yl)-thiomethyl - 3 - cephem - 4 - carboxylic acid.
46. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - (3,4 - dimethyl - 1,2,4-triazol - 5 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid.



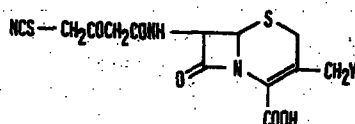
429

47. 7 - [2 - (2 - Aminothiazol - 4 - yl)acetamido] - 3 - (1 - methyl - 1,3-diazol - 2 - yl)thiomethyl - 3 - cephem - 4 - carboxylic acid.

48. A process for preparing a compound according to any one of claims 1 to 47, the process comprising (1) subjecting a compound of general formula (II)



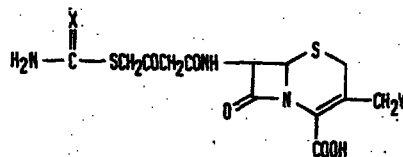
wherein R¹, X and Y are as defined in claim 1, or a salt or ester thereof, to a ring closure reaction with elimination of water, (2) reacting a compound of general formula (III)



10 wherein Y is as defined in claim 1, or a salt or ester thereof, with a compound of the formula (IV) 10



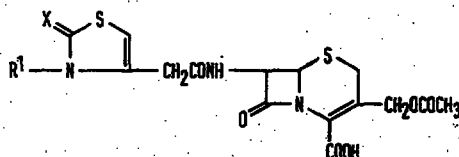
wherein X is as defined in claim 1, to give a compound of general formula (V)



15 wherein X and Y are as defined in claim 1 and subjecting the compound so obtained to a ring closure reaction with the elimination of water, (3) reacting a compound of general formula (VI) as hereinbefore defined or a salt or ester thereof, with a compound of general formula (VII) 15



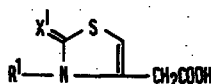
20 wherein R¹ and X are as defined in claim 1, or a salt thereof, to give a compound of general formula (II) and subjecting the compound so obtained to a ring closure reaction with the elimination of water, (4) reacting a compound of general formula (IX) 20



25 wherein R¹ and X are as defined above or a salt thereof, with a compound of general formula (X) 25



30 wherein R³ is as defined in claim 1 or a salt thereof, to give a compound of general formula (I) wherein Y is a group of formula -SR³, or (5) reacting a compound of general formula (XII) as hereinbefore defined, or salt or ester thereof, with a compound of general formula (XIII) 30





44

1,491,018

44

wherein X^1 is an oxygen or sulphur atom or an optionally protected imino group and R^1 is as defined in claim 1 or a reactive derivative thereof, and, if desired, removing the protecting group of the imino group, to give a compound of general formula (I) wherein Y is a group of formula $-SR^2$.

5

49. A process according to claim 48 substantially as described herein.

5

50. A compound of general formula (I) or a salt thereof prepared by a process according to claim 48 or 49.

10

51. A pharmaceutical composition comprising a compound according to any one of claim 1 to 47 and 50, or a salt thereof, and a pharmaceutically acceptable carrier or diluent.

10

52. A composition according to claim 51 substantially as described herein.

J. A. KEMP & CO.,
Chartered Patent Agents,
14, South Square,
Gray's Inn, London, W.C.1.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1977.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.

ERRATUM

SPECIFICATION No. 1,491,018

Page 1, line 3, *for* Doshamachi *read* Dosho-
machi

THE PATENT OFFICE
29th December, 1980