

PATENT SPECIFICATION

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(54) NOVEL CEPHALOSPORINS AND PROCESS FOR PRODUCING THE SAME

(71) We, TOYAMA CHEMICAL CO. LTD., a corporation organized under the laws of Japan, of 1—18, Kayabacho, Nihonbashi, Chuo-ku, Tokyo, 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 cephalosporins and to a process for producing the same.

The compounds of this invention have various characteristics including a broad antibacterial spectrum against Gram-positive and Gram-negative bacteria, and effective antibacterial activity against *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Proteus* species. Furthermore, the compounds of this invention possess high stability to β -lactamase produced from bacteria, and effective antibacterial activity even against clinical isolates of bacteria which are significant at present from the clinical standpoint. In particular, the compounds of this invention are characterized in that they are very low in toxicity, they are well absorbed in living body, they are not inactivated in living body, they give a high maximum concentration in blood, they have no hemolytic activity, and the like. Accordingly, the compounds of this invention are quite effective as therapeutic drugs for human and animal infectious diseases derived from the above-mentioned pathogenic microorganisms.

It has heretofore been known that 7-acylaminocephalosporanic acids having an amino group at the α -position of the acyl group show strong antibacterial activity not only against Gram-positive bacteria but also against Gram-negative bacteria. However, there are the disadvantages that the known compounds described above show substantially no effective antibacterial activity against not only *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Proteus* species, which have been known as causes for clinically serious infectious diseases, but also resistant bacteria which are frequently isolated at present from many clinical hospitals. And they tend to be hydrolyzed with β -lactamase produced from many drug-resistant bacteria.

On the other hand, even if there are obtained the compounds having the above-mentioned properties, most of the compounds obtained cannot be commercialized because they have disadvantages such as high toxicity and a hemolytic activity. The compounds have further disadvantages that they are inactivated, that a high concentration in blood is not obtained and that the absorption in blood is low.

With an aim to obtain cephalosporins having no disadvantages mentioned above, the present inventors conducted extensive studies to find that the compounds of formula (I) can sufficiently satisfy the above-mentioned aim and have extremely valuable therapeutic effects.

The compound of this invention is characterized by having α -(4-ethyl-2,3-

dioxo-1-piperazinocarbonyl-amino)-p-hydroxyphenylacetamido group in the 7-position of the cephem ring, particularly having a hydroxy group in the p-position of the phenyl group, and the presence of p-hydroxy group results in a low toxicity, a good absorption in living body and the like. In addition, it is quite surprising and unexpected that only when the respective substituents are selected and combined the above-mentioned purpose can be achieved.

It is an object of this invention to provide cephalosporins having a broad antibacterial spectrum.

It is another object of this invention to provide cephalosporins having high stability to β -lactamase produced from bacteria.

It is a further object of this invention to provide cephalosporins having effective antibacterial activity against clinical isolates of bacteria.

It is a still further object of this invention to provide cephalosporins having a low toxicity.

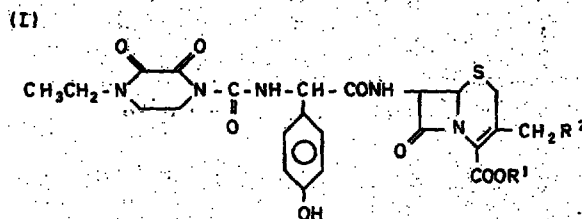
It is a still further object of this invention to provide cephalosporins which are well absorbed in living body, are not inactivated and give a high maximum concentration in blood.

It is a further object of this invention to provide cephalosporins having no hemolytic activity.

It is a still further object of this invention to provide a process for producing cephalosporins of the formula (I).

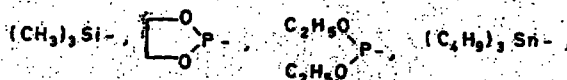
It is a still further object of this invention to provide a pharmaceutical composition containing cephalosporins of the formula (I) as active ingredient.

The compounds of this invention are cephalosporins represented by the general formula (I),



wherein R^1 represents a hydrogen atom, a salt-forming cation, or a blocking group, and R^2 represents an acetoxy, carbamoyloxy, 2-(5-methyl-1,3,4-thiadiazolyl)-thio, or 5-(1-methyl-1,2,3,4-tetrazolyl)thio group.

In the general formula (I), R^1 is a hydrogen atom, a blocking group or a salt-forming cation. The blocking group may be of any of those which have heretofore been used in the field of penicillin or cephalosporin type compounds. Concretely, the blocking group includes (1) ester-forming groups capable of being removed by catalytic reduction, chemical reduction or hydrolysis under mild conditions, e.g. arylsulfonylalkyl groups such as toluene-sulfonyl-ethyl; substituted or unsubstituted aralkyl groups such as benzyl, 4-nitrobenzyl, diphenylmethyl, trityl, or 3,5-di(tert.-butyl)-4-hydroxybenzyl; substituted or unsubstituted alkyl groups such as tert.-butyl or trichloroethyl; phenacyl group; alkoxyalkyl groups such as methoxymethyl; and unsubstituted or alkyl-substituted cyclic aminoalkyl groups such as piperidinoethyl, 4-methylpiperidinoethyl, morpholinoethyl, or pyrrolidinoethyl; (2) ester-forming groups capable of being easily removed owing to enzymes in a living body, e.g. acyloxyalkyl groups such as pivalolyloxymethyl; phthalidyl group; and indanyl group; (3) silicon-containing groups, phosphorus-containing groups and tin-containing groups which are capable of being easily removed by treating with H_2O or an alcohol, such as



or the like. The examples of the blocking groups mentioned in above (1), (2) and (3) are merely typical, and other examples are disclosed in U.S. Patents 3,499,909; 3,573,296; and 3,641,018, and DT-OS 2,301,014; 2,253,287 and 2,337,105, and may be used in this invention. The salt-forming cation includes cations which have heretofore been known in the field of penicillin or cephalosporin type compounds,

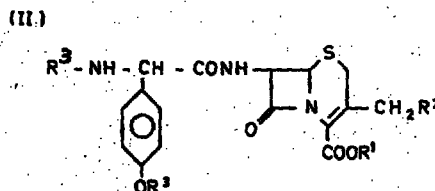
and preferable are those capable of forming non-toxic salts. The salts include alkali metal salts such as sodium salt or potassium salt, alkaline earth metal salts such as calcium salt or magnesium salt; ammonium salt; and salts with nitrogen-containing organic bases such as procaine, dibenzylamine, N-benzyl-β-phenethylamine, 1-phenamine, or N,N-dibenzylethylenediamine. In addition to the above cations, there may be used cations capable of forming the salts with other nitrogen-containing organic bases, such as trimethylamine, triethylamine, tributylamine, pyridine, dimethylaniline, N-methylpiperidine, N-methylmorpholine, diethylamine, or dicyclohexylamine.

The above-mentioned compounds of formula (I) of this invention have their optical isomers, and all of D-isomers, L-isomers and racemic compounds thereof are involved in the scope of the present invention, and the present invention includes the compounds in all crystal forms and hydrate forms.

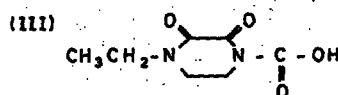
The compounds of formula (I) of the present invention are produced according to either the process (1), (2) or (3) described below.

Process (1):

A process comprising reacting a compound represented by the general formula (II),

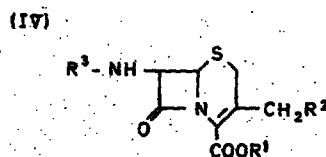


with a reactive derivative in the carboxyl group of a 4-ethyl-2,3-dioxo-1-piperazinocarboxylic acid represented by the formula (III),

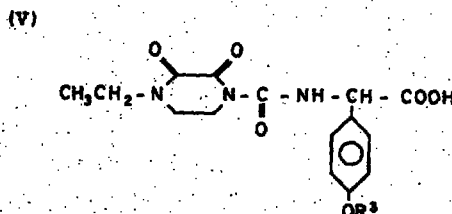


Process (2):

A process comprising reacting a compound represented by the general formula (IV),



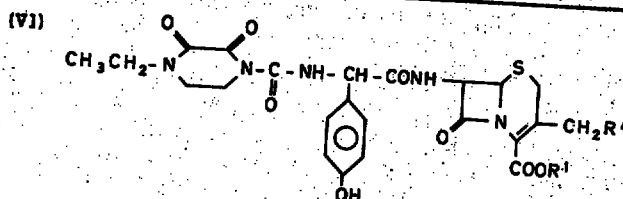
with a compound represented by the general formula (V),



or with a reactive derivative in the carboxyl group of the compound of formula (V).

Process (3):

A process comprising reacting a compound represented by the general formula (VI),



with a compound represented by the general formula (VII),

R_3M

(VII)

In the above-mentioned formulas (II), (IV), (V) and (VI), R^1 and R^2 are as defined above; and R^3 represents a hydrogen atom, a silicon-containing group or a phosphorus-containing group, these silicon-containing and phosphorus-containing groups having the same meanings as mentioned above for R^1 .

In the aforesaid formula (VI), R^4 represents a substituent capable of being easily replaced by a nucleophilic reagent, and includes, for example, halogen atoms such as chlorine and bromine; halo substituted or unsubstituted lower alkanoyloxy groups such as formyloxy, acetoxy, propionyloxy, butyryloxy, and pivaloyloxy; arylcarbonyloxy groups such as benzoyloxy and naphthoyloxy; arylcarbonylthio groups such as benzoylthio, and naphthoylthio; or carbamoyloxy groups. Each of the groups mentioned above for R^4 may be substituted by any of such substituents as, for example, halogen atoms, nitro groups, alkyl groups, alkoxy groups, alkylthio groups or acyl groups.

In the aforesaid formula (VII), R^1 represents a 2-(5-methyl-1,3,4-thiadiazolyl)thio, or 5-(1-methyl-1,2,3,4-tetrazolyl)thio group, and M represents a hydrogen atom, an alkali metal or an alkaline earth metal.

As the reactive derivative in the carboxyl group of the compound of formula (III), there is used a reactive derivative of a carboxylic acid which is ordinarily employed for the synthesis of acid amide compounds. Examples of the reactive derivative are acid halides, acid azides, acid cyanides, mixed acid anhydrides, active esters and active acid amides. Particularly preferable examples thereof are acid halides such as acid chlorides and acid bromides, and active esters such as cyanomethyl ester, trichloromethyl ester, etc.

The reactive derivative in the carboxyl group of the compound of formula (III) can easily be obtained by reacting, for example, 4-ethyl-2,3-dioxo-1-piperazine synthesized and according to the process of J. L. Riebsomer, J. Org. Chem., 15 68-73 (1950), with phosgene, trichloromethyl ester of chloroformic acid, or the like.

The compound represented by the general formula (V) can be easily obtained by reacting, for example, a salt with an alkali metal, an alkaline earth metal or a nitrogen-containing organic base of an α -amino-p-hydroxyphenylacetic acid (any of D-isomer, L-isomer and racemic compound), with a reactive derivative in the carboxyl group of a compound represented by the formula (III) in a solvent inert to the reaction in the presence of an acid-binding agent.

As the reactive derivative in the carboxyl group of the compound represented by the general formula (V), there is used a reactive derivative of a carboxylic acid which is ordinarily used in the synthesis of acid amides. Such reactive derivatives include, for example, acid halides, acid anhydrides, mixed acid anhydrides with organic or inorganic acids, active acid amides, acid cyanides and active esters. Particularly, acid chlorides, mixed acid anhydrides and active amides are preferable. Examples of the mixed acid anhydrides are mixed acid anhydrides with carbonic acids; examples of the active esters are cyanomethyl esters, substituted phenyl esters, substituted benzyl esters and substituted thienyl esters; and examples of the active acid amides are N-acyl saccharins, N-acyl imidazoles, N-acyl benzoylamides, N,N-dicyclohexyl-N'-acylureas and N-acyl sulfonamides.

Compounds of formula (VI) can be obtained by, for example, process (1) or (2). Some of the compounds obtained by process (3) can further be used as the starting compounds in process (3). Any of D-, L- and racemic compounds of formula (VI) may be used.

The modes of practice of the processes (1), (2) and (3) are explained below. The processes (1) and (2) may be carried out under substantially the same conditions. That is, the compound of formula (II) or (IV) is dissolved or suspended

in at least one inert solvent selected from, for example, water, acetone, tetrahydrofuran, dioxane, acetonitrile, dimethylformamide, methanol, ethanol, methoxyethanol, diethyl ether, isopropyl ether, benzene, toluene, methylene chloride, chloroform, ethyl acetate, methyl isobutyl ketone and the like. The resulting solution or suspension is reacted with a reactive derivative of the compound of formula (III) or with the compound of formula (V) or a reactive derivative in the carboxyl group of the compound of formula (V) in the presence or absence of a base at a temperature in the range from -60°C to 80°C , preferably from -40°C to 30°C . The reaction time is ordinarily 5 minutes to 5 hours. Examples of the base used in the above reaction are inorganic bases such as alkali hydroxides, alkali hydrogencarbonates, alkali carbonates and alkali acetates; tertiary amines such as trimethylamine, triethylamine, tributylamine, pyridine, N-methylpiperidine, N-methylmorpholine, lutidine and collidine; and secondary amines such as dicyclohexylamine and diethylamine. When the compound of formula (V) is used in the form of a free acid or salt in the process (2), the reaction of the process (2) may be effected in the presence of a dehydrating condensing agent such as N,N'-dicyclohexyl carbodiimide, N-cyclohexyl-N'-morpholinethyl carbodiimide, N,N'-diethylcarbodiimide, N,N'-carbonyl di(2-methylimidazole), a trialkyl ester of phosphorous acid, ethyl ester of polyphosphoric acid, phosphorus oxychloride, phosphorus trichloride, 2-chloro-1,2,3-dioxaphospholane or oxazoyl chloride. The salt of the compound of formula (V) includes alkali metal salts, alkaline earth metal salts, ammonium salts, and salts with organic bases such as triethylamine, dicyclohexylamine and the like.

The process (3) is carried out in the manner described below.

The compound of formula (VI) is reacted with the compound of formula (VII) in at least one solvent selected from, for example, water, methanol, ethanol, propanol, isopropanol, butanol, acetone, methyl ethyl ketone, methyl isobutyl ketone, tetrahydrofuran, dioxane, acetonitrile, ethyl acetate, methoxyethanol, dimethoxyethane, dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform, a dichloroethane, and the like. The above-mentioned reaction is preferably effected in a strongly polar solvent such as water or the like. In this case, the pH of the reaction solution is advantageously maintained at 2 to 10, preferably 4 to 8. The desired pH may be attained by addition of a buffer solution such as sodium phosphate. The reaction conditions are not particularly limited, though the reaction is ordinarily conducted at 0° to 100°C over a period of several hours to several tens hours.

The reaction conditions to be adopted in the processes (1), (2) and (3) are not limited to those mentioned above, and can be properly varied depending upon the kinds of reaction reagents.

Further, the non-toxic salts of the general formula (1), in which R^1 is a salt-forming cation, can be easily obtained according to an ordinary procedure from compounds of the general formula (I), in which R^1 is a hydrogen atom or a blocking group.

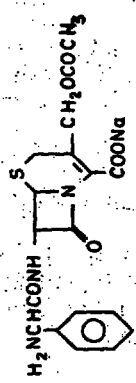
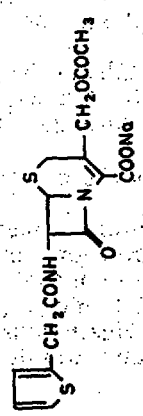
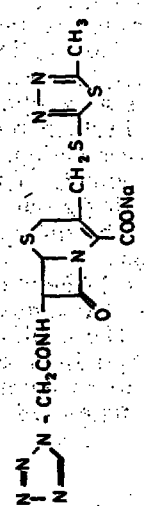
The susceptible tests of the compounds of the present invention are shown below.

(1) The minimum inhibitory concentrations (MIC) of the compounds against different standard strains are shown in Table 1.

The minimum inhibitory concentration (MIC) was determined by the plate method disclosed in "Chemotherapy" (Japan), Vol. 16, (1968), pages 98-99. The culture medium used was a Heart Infusion agar (pH 7.4). The number of the cells per plate used in the inoculum was 10^4 (10^6 cells/ml).

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TABLE 1

Compound No.	Compound	Staphylococcus aureus 209p	Escherichia coli NIHJ	Pseudomonas aeruginosa I.F.O.	Klebsiella pneumoniae	Proteus vulgaris 3027
1	 (Sodium Cephaloglycin)	<1.57	<1.57	>200	<1.57	100
2	 (Sodium Cephalothin)	<1.57	<1.57	>200	<1.57	100
3	 (Sodium Cephaezolin)	<1.57	<1.57	>200	1.57	200

Control

TABLE 1 (Continued)

Compound No.	Compound	<i>Staphylococcus aureus</i> 209P	<i>Escherichia coli</i> NIHJ	<i>Pseudomonas aeruginosa</i> I.F.O.	<i>Klebsiella pneumoniae</i>	<i>Proteus vulgaris</i> 3027
A		<1.57	<0.1	6.25	<0.1	0.4
B		1.57	<0.4	50	0.79	3.13
C		<1.57	<1.57	12.5	<1.57	<1.57
D		<1.57	<1.57	25	<1.57	<1.57

(2) The minimum inhibitory concentrations (MIC) of the compounds against clinical isolates of bacteria are shown in Tables 2-1 and 2-2. The MIC was determined in the same manner as in the preceding paragraph (1).

TABLE 2-1

Compound		<i>Escherichia coli</i>							
		GN 3481	GN 3435	GN 345 2	GN 3465	K-1	K-2	K-3	K-4
Control	Sodium Cephaloglycin	3.13	1.56	3.13	12.5	1.56	1.56	25	12.5
	Sodium Cephalothin	12.5	6.25	12.5	25	6.25	6.25	100	25
	Sodium Cephezolin	1.56	1.56	1.56	6.25	1.56	1.56	>200	3.13
Present compound	Compound A	-	0.1	0.2	1.56	-	0.39	-	0.39
	Compound B	-	0.39	0.39	6.25	-	0.78	12.5	0.78
	Compound C	-	0.78	0.78	12.5	-	3.13	50	1.56

TABLE 2-2

		<i>Pseudomonas aeruginosa</i>									
Compound		GN 1035	GN 376	GN 82	GN 221	GN 1091	GN 2565	GN 2987	GN 163	GN 244	GN 383
Control	Sodium Cephaloglycin	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200
	Sodium Cephalothin	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200
	Sodium Cephalozin	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200
Present compound	Compound A	25	6.25	6.25	6.25	6.25	25	—	—	12.5	12.5
	Compound B	25	12.5	25	12.5	12.5	50	—	—	12.5	12.5
	Compound C	25	12.5	12.5	6.25	12.5	50	—	—	25	25

(3) Stability of each cephalosporin compound against β -lactamase.
The stability of each cephalosporin compound against β -lactamase was measured in the manner described below.

β -Lactamase was prepared from each bacterium in Table 3. 10 ml of overnight culture in Heart Infusion broth was diluted with 100 ml of a medium containing 2 g of yeast extract, 10 g of polypeptone, 2 g of glucose, 7 g of disodium hydrogen phosphate, 2 g of potassium dihydrogen phosphate, 1.2 g of ammonium sulfate and 0.4 g of magnesium sulfate, per liter, and incubated with shaking at 37°C. After incubation for 2 hrs., Penicillin G (50 μ g/ml) was added as the inducer, and further incubated for 2 hrs. The resulting cells were collected by centrifugation (5,000 r.p.m. x 10 min), washed two times with 0.1 M phosphate buffer (pH 7.0). Subsequently, the cells were subjected to sonication (20 KHz, 5 min) and then centrifuged at 15,000 r.p.m. for 60 min. By using the supernatant of enzyme fluid, the stability of each compound against β -lactamase was determined by the

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iodometric assay method. The results obtained were as set forth in Table 3. Each numeral shown in Table 3 is a relative activity value calculated by assuming as 100 the activity of the control Cephaloridine.

TABLE 3

Comparison of stability against β -lactamase

Compound	Relative rate of hydrolysis (%)				
	<i>Pseudomonas aeruginosa</i> GN 918	<i>Proteus vulgaris</i> GN 76	<i>Escherichia coli</i> GN 5482	<i>Escherichia freundii</i> GN 346	<i>Escherichia coli</i> GN 5484
Control	Cephaloridine	100	100	100	136
	Cephalexine	13	150	14	2
	Cephalothin	91	105	100	11
	Cephazolin	410	440	130	40
	Penicillin G	—	8	—	15
Present compound	Ampicillin	—	8	—	0.06
	Compound A	1	7	0.6	0.2
	Compound B	7	11	4	1
	Compound C	10	6	2	0.4
	Compound D	—	10	—	1

(4) Acute toxicity

Each of the compounds shown in Table 4 was administered by intravenous injection one time to a group of five male ICR mice (weight 19 ± 1 g), and the number of survived mice after one week was determined to obtain the results shown in Table 4.

TABLE 4

Compound	Dose (g/Kg)			
	2	3	4	5
Compound A	—	5	5	5
Compound B	—	5	5	4
Compound C	—	5	5	5

(5) Protection from infection

A bacterium liquid of *Klebsiella* Y—3 or *Pseudomonas aeruginosa* GN 1035 having added thereto mucin in a final concentration of 5% was inoculated into the peritoneum of a male ICR mouse (weight 19 ± 1 g). One hour after the inoculation, each of the compounds shown in Table 5 was administered one time under the skin of dorsum of the mouse, and the mouse was observed after one week to obtain the results shown in Table 5.

TABLE 5

ED₅₀ value (mg/mouse)

Compound	<i>Klebsiella</i> Y—3	<i>Pseudomonas aeruginosa</i> GN 1035
Compound A	<0.04	1.6
Compound B	0.18	3.6
Compound C	0.36	1.5
Cephazolin	0.16	>25

Note: ED₅₀ values were calculated by the Van der Waenden method.

(6) Concentration in blood

Each of the compounds shown in Table 6 was administered by intramuscular injection to a wister rat (weight about 300 g) at a rate of 20 mg/kg, and after 15 min, 30 min, 60 min, 120 min and 180 min, the concentration of the compound in blood was measured to obtain the results shown in Table 6. The inspection bacteria were *Sarcina* and *Pseudomonas*, and the results obtained by measurement with *Pseudomonas* are indicated in parentheses.

TABLE 6

(g/ml)

Compound	TIME				
	15 min	30 min	60 min	120 min	180 min
Compound A	11.0 (11.6)	8.2 (7.1)	3.4 (<3.13)	1.4 (<3.13)	0.46 (<3.13)
Compound B	8.2 (6.4)	8.1 (7.0)	6.9 (6.7)	3.5 (3.7)	1.1 (1.7)
Compound C	11.5 (13.8)	7.0 (10.0)	3.3 (3.85)	0.95 (<3.13)	0.43 (<3.13)

(7) Hemolytic test

The test was effected by the Akaish et al. method (observation with the naked eye) to obtain the results shown in Table 7.

TABLE 7

Compound	Concentration (mg/ml)				
	250	167	125	62.5	41.8
Cephaloridine	+++	++	+	-	-
Cephazolin	-	-	-	-	-
Cephalothin	+	-	-	-	-
Compound A	-	-	-	-	-
Compound B	-	-	-	-	-
Compound C	-	-	-	-	-

Note: "-" refers to no hemolysis

"+" refers to weak hemolysis (rose and clear).

"++" refers to hemolysis (red and clear)

"+++" refers to hemolysis (red and turbid).

From tables 1 and 2, it is understood that the compounds of this invention have a broader antibacterial spectrum and more excellent antibacterial activity against not only *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Proteus* species but also many drug-resistant bacteria than the control drugs. It is also understood from Table 3 that the compounds of this invention are far higher in stability to β -lactamase than the control drugs. From Table 4, it is understood that the compounds of this invention are very low in toxicity, and from Tables 5 and 6, it is understood that the compounds of this invention are well absorbed in living

body, are not inactivated, and give a high maximum concentration in blood. Moreover, it is understood from Table 7 that the compounds of this invention have no hemolytic activity.

The compounds of formula (I) of this invention may be administered not only in the form of free acids but also in the form of non-toxic salts or physiologically acceptable esters. Further, the compounds which are in the form of physiologically unacceptable esters, are ordinarily put into use after bringing them to the form of free acids or non-toxic salts by removing the ester-forming group according to a conventional procedure known in this technical field.

The compounds of this invention can be administered to humans and animals by oral or non-oral administration after formulating them into a physiological form such as tablet, capsule, syrup, injection or the like which is usually adopted in the case of penicillin and cephalosporin type drugs. *

When the compound of this invention is administered to humans, it is usually preferable to administer the compound in a dose of 250 mg to 5 g per adult (60 kg) 1 to 4 times a day.

Procedures for producing the compounds of the present invention are shown below with reference to examples.

Example 1.

(1) To a solution of 3.01 g of sodium D(-)- α -N-(1-methoxycarbonyl-1-propen-2-yl)amino-p-hydroxyphenyl acetate in a mixed solution comprising 25 ml of anhydrous methylene chloride and 6 ml of dimethylformamide was added a drop of N-methylmorpholine. To the resulting solution was added 1.14 g of ethyl chloro-carbonate at -15° to -10°C over a period of 5 minutes, and then the mixture was reacted at -15° to -10°C for one hour. After the reaction, to the reaction mixture was added 1.22 ml of N,O-bis(trimethylsilyl)acetamide, and the resulting mixture was cooled to -20°C . On the other hand, 3.66 ml of N,O-bis(trimethylsilyl)acetamide was added to a suspension of 3.28 g of 7-amino-3-[5-(1-methyl-1,2,3,4-tetrazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid to form a solution, and the solution was cooled to -20°C , and poured into the aforesaid solution. Subsequently, the resulting mixture was reacted at -5° to -10°C for two hours, and at -5° to -0°C for two hours. After the reaction, to the reaction mixture was added 5 ml of methanol, and the resulting mixture was stirred for 30 minutes. Thereafter, insolubles were separated by filtration, and to the filtrate was added 10 ml of water. The resulting solution was adjusted to a pH of 1.5 by addition of 6N hydrochloric acid, and then subjected to hydrolysis for 30 minutes. The solution was adjusted to a pH of 5 by addition of triethylamine, and then stirred at 5° to 10°C over a period of a night to deposit crystals. The deposited crystals were collected by filtration, and the crystals were suspended in 50 ml of ethanol, and then the resulting suspension was stirred for one hour. Thereafter, the crystals were collected by filtration, and washed with ethanol, and then dried to obtain 3.0 g of 7-[D(-)- α -amino-p-hydroxyphenylacetamido]-3-[5-(1-methyl-1,2,3,4-tetrazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid, m.p. $161-163^{\circ}\text{C}$ (decomp.), yield 63.0%.

IR (KBr) cm^{-1} : $\nu_{\text{C=O}}$ 1760, 1685, 1600

(2) To a suspension of 3.0 g of 7-[D(-)- α -amino-p-hydroxyphenylacetamido]-3-[5-(1-methyl-1,2,3,4-tetrazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid in 29 ml of water was added 0.95 g of anhydrous potassium carbonate. After the solution was formed, 15 ml of ethyl acetate was added to the solution, and 1.35 g of 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride was added to the resulting solution at 0° to 5°C over a period of 15 minutes, and then the mixture was reacted at 0° to 5°C for 30 minutes. After the reaction, an aqueous layer was separated off, 40 ml of ethyl acetate and 10 ml of acetone were added to the aqueous layer, and then the resulting solution was adjusted to a pH of 2.0 by addition of dilute hydrochloric acid. Thereafter, an organic layer was separated off, the organic layer was washed with two times with 10 ml of water, dried over anhydrous magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was dissolved in 10 ml of acetone, and 60 ml of 2-propanol was added to the solution to deposit crystals. The deposited crystals were collected by filtration, washed with 2-propanol, and then dried to obtain 3.27 g of 7-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)-p-hydroxyphenylacetamido]-3-[5-(1-methyl-1,2,3,4-tetrazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid, yield 80.7%.

IR (KBr) cm^{-1} : $\nu_{\text{C=O}}$ 1775 (lactam), 1705 ($-\text{COOH}$),
1680, 1670 ($-\text{CON}<$).

In a mixed solvent comprising 20 ml of acetone and 5 ml of n-butanol was dissolved 3.0 g of the above-obtained product. To the resulting solution was added a solution of 20 ml of n-butanol containing 0.77 g of a sodium salt of 2-ethylhexanoic acid. Then the mixed solution was stirred for one hour to deposit crystals, which were collected by filtration, washed with acetone and then dried to obtain 2.6 g of a sodium salt of 7-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)-p-hydroxyphenylacetamido]-3-[5-(1-methyl-1,2,3,4-tetrazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid, yield 83.9%.

Example 2.

Using 7-[D(-)- α -amino-p-hydroxyphenylacetamido]-3-carbamoyloxymethyl- Δ^3 -cephem-4-carboxylic acid and 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride, the same procedure as in Example 1 was repeated to obtain 7-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)-p-hydroxyphenylacetamido]-3-carbamoyloxymethyl- Δ^3 -cephem-4-carboxylic acid, m.p. 178—182°C (decomp.), yield 79.3%.

IR (KBr) cm^{-1} : $\nu_{\text{C=O}}$ 1778, 1710, 1670

Example 3.

Using 7-[D(-)- α -amino-p-hydroxyphenylacetamido]-3-acetoxymethyl- Δ^3 -cephem-4-carboxylic acid and 3-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride, the same procedure as in Example 1 was repeated to obtain 7-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)-p-hydroxyphenylacetamido]-3-acetoxymethyl- Δ^3 -cephem-4-carboxylic acid, m.p. 168—174°C (decomp.), yield 84.0%.

IR (KBr) cm^{-1} : $\nu_{\text{C=O}}$ 1770 (lactam), 1710 ($-\text{COOH}$),
1680, 1670 ($-\text{CON}<$)

Example 4.

Using 7-[D(-)- α -amino-p-hydroxyphenylacetamido]-3-[2-(5-methyl-1,3,4-thiadiazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid and 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride, the same procedure as in Example 1 was repeated to obtain 7-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)-p-hydroxyphenylacetamido]-3-[5-(5-methyl-1,3,4-thiadiazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid, m.p. 172—177°C (decomp.), yield 82.5%.

IR (KBr) cm^{-1} : $\nu_{\text{C=O}}$ 1780 (lactam), 1710 ($-\text{COOH}$),
1685, 1672 ($-\text{CON}<$)

Example 5.

To a solution of 3.36 g of D(-)- α -(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)-p-hydroxyphenyl-acetic acid in 20 ml of anhydrous methylene chloride and 5 ml of dimethylformamide was added 1.33 g of N,N-dimethylaniline. The resulting mixture was cooled to -15° to -10°C, and a solution of 1.14 g of ethyl chloro-carbonate in 5 ml of anhydrous methylene chloride was dropped into said mixture over a period of 5 minutes. The mixture was reacted at said temperature for 60 minutes.

On the other hand, to a suspension of 2.72 g of 7-amino-3-acetoxymethyl- Δ^3 -cephem-4-carboxylic acid in 65 ml of anhydrous acetonitrile was added 3.04 g of N,O-bis(trimethylsilyl)acetamide to obtain a solution. The solution was cooled to -20°C and poured into the aforesaid reaction mixture. Subsequently, the mixture was reacted at -10° to -5°C for 60 minutes, and at 5° to 10°C for 60 minutes. After the reaction, 5 ml of methanol was added to the reaction mixture, and the mixture was freed from insolubles by filtration. Thereafter, the solvent was removed by distillation under reduced pressure. The residue was dissolved in a mixed solvent comprising 100 ml of water and 50 ml of ethyl acetate, and the resulting solution was adjusted to a pH of 7.5 to 8.0 by addition of sodium hydrogencarbonate, and then the aqueous layer was separated off and added to a mixed solvent comprising 80 ml of ethyl acetate and 20 ml of acetone. The

resulting solution was adjusted to a pH of 1.5 by addition of dilute hydrochloric acid. Subsequently, the organic layer was separated off, sufficiently washed with water and then the solvent was removed from ethyl acetate layer by distillation under reduced pressure. The residue was dissolved in 10 ml of acetone, and to this solution was added 60 ml of 2-propanol with stirring to deposit white crystals. The deposited crystals were collected by filtration, sufficiently washed with 2-propanol and then dried to obtain 4.94 g of 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 piperazinocarbonylamino) - p - hydroxyphenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, m.p. 168—174°C (decomp.), yield 84.0%.

IR (KBr) cm^{-1} : $\nu_{\text{C=O}}$ 1770 (lactam), 1710 (—COOH), 1680, 1670 (—CON<)

In a mixed solvent comprising 25 ml of acetone and 10 ml of n-butanol was dissolved 3.5 g of the above-obtained product. To the resulting solution was added a solution of 20 ml of n-butanol containing 1.0 g of a sodium salt of 2-ethylhexanoic acid. Then the mixed solution was stirred for one hour to deposit crystals, which were collected by filtration, washed with acetone and then dried to obtain 3.3 g of a sodium salt of 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p - hydroxyphenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, yield 90.0%.

Example 6.

(1) To a suspension of 1 g of D(-)- α -(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)-p-hydroxyphenylacetic acid in 20 ml of methylene chloride were added 0.6 g of triethylamine and 0.65 g of trimethylsilyl chloride at 15° to 20°C, and the resulting mixture was reacted at the same temperature for 30 minutes. Subsequently, the reaction liquid was cooled to 0° to 5°C, and 0.95 g of oxalyl chloride and a drop of dimethylformamide were added to the reaction liquid at the same temperature. After the resulting mixture was reacted at the same temperature for 30 minutes, the solvent was removed by distillation under reduced pressure. Thereafter, the residue was dissolved in 8 ml of dioxane, the insolubles were separated off, and the filtrate was concentrated to dryness to obtain 1.15 g (yield 90.6%) of trimethylsilyl derivative of D(-)- α -(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)-p-hydroxyphenylacetyl chloride.

IR (KBr) cm^{-1} : $\nu_{\text{C=O}}$ 1790, 1715, 1685

(2) To a suspension of 0.27 g of 7-amino-3-carbamoyloxymethyl- Δ^3 -cephem-4-carboxylic acid in 5 ml of acetonitrile were added 0.22 g of trimethylsilyl chloride and 0.3 g of triethylamine, and the resulting mixture was reacted at 15° to 20°C for one hour. Subsequently, to the reaction liquid was added a solution of 2 ml of acetonitrile containing 0.5 g of trimethylsilyl derivative of D(-)- α -(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)-p-hydroxyphenylacetyl chloride, which was obtained in the above reaction, and the resulting mixture was reacted at the above-mentioned temperature for two hours. After the reaction, the same procedure as in Example 5 was repeated to obtain 0.38 g of 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p - hydroxyphenylacetamido] - 3 - carbamoyloxymethyl - Δ^3 - cephem - 4 - carboxylic acid, m.p. 178—182°C (decomp.), yield 65%.

IR (KBr) cm^{-1} : $\nu_{\text{C=O}}$ 1778, 1710, 1670

The thus obtained product was adjusted to a pH of 7.0 by neutralization with an aqueous sodium hydrogencarbonate solution, and then subjected to filtration and freeze-drying to obtain a sodium salt thereof.

Example 7.

In the same manner as in Example 5, 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p - hydroxyphenylacetamido] - 3 - [5 - 1 - methyl - 1,2,3,4 - tetrazolyl]thiomethyl - Δ^3 - cephem - 4 - carboxylic acid, yield 75.5%, was obtained from 7 - amino - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl)thiomethyl) - Δ^3 - cephem - 4 - carboxylic acid and D(-)- α -(4-ethyl-2,3,3-dioxo-1-piperazinocarbonylamino)-p-hydroxyphenylacetic acid.

IR (KBr) cm^{-1} : $\nu_{\text{C=O}}$ 1775 (lactam), 1705 ($-\text{COH}$),
1680, 1670 ($-\text{CON}<$)

Thus thus obtained product was adjusted to a pH of 7.0 by neutralization with an aqueous sodium hydrogencarbonate solution, and then subjected to filtration and freeze-drying to obtain a sodium salt thereof.

Example 8.

Using 1.5 g of D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonyl - amino) - p - hydroxyphenylacetic acid and 1.5 g of 7 - amino - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, the same procedure as in Example 5 was repeated to obtain 2.3 g of 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p - hydroxyphenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl)thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, m.p. 172—177°C (decomp.), yield 79.8%.

IR (KBr) cm^{-1} : $\nu_{\text{C=O}}$ 1780 (lactam), 1710 ($-\text{COOH}$),
1685, 1672 ($\text{CON}<$)

The thus obtained product was adjusted to a pH of 7.0 by neutralization with an aqueous sodium hydrogencarbonate solution, and then subjected to filtration and freeze-drying to obtain a sodium salt thereof.

Example 9.

In the same manner as in Example 5, 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p - hydroxyphenylacetamido] - 3 - carbamoyloxymethyl - Δ^3 - cephem - 4 - carboxylic acid, m.p. 178—182°C, (decomp.), yield 76.4%, was obtained from 7 - amino - 3 - carbamoyloxymethyl - Δ^3 - cephem - 4 - carboxylic acid and D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonyl - amino) - p - hydroxyphenylacetic acid.

IR (KBr) cm^{-1} : $\nu_{\text{C=O}}$ 1778, 1710, 1670

In 10 ml of a phosphoric acid buffer solution of a pH of 6.3 was suspended 0.58 g of 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p - hydroxyphenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, and 0.07 g of sodium hydrogen-carbonate was dissolved therein. To the resulting solution was then added 0.13 g of 5-methyl-2-mercapto-1,3,4-thiadiazole to dissolve the latter in the former, and the solution was subjected to reaction at 45° to 55°C for 24 hours while maintaining the pH of the solution at 6.0—6.5 by using dilute hydrochloric acid and sodium hydrogencarbonate. After the reaction, the reaction liquid was cooled, and then adjusted to a pH of 5.0 by adding dilute hydrochloric acid. The reaction liquid was sufficiently washed with ethyl acetate, and then the aqueous layer was separated off, and added to a mixed solvent comprising 16 ml of ethyl acetate and 4 ml of acetone. The resulting solution was adjusted to a pH of 1.5 by adding dilute hydrochloric acid. Subsequently, the organic layer was separated off, sufficiently washed with water, and then the solvent was removed by distillation under reduced pressure. The residue was dissolved in 3 ml of acetone, and 12 ml of 2-propanol was added to this solution with stirring to deposit white crystals. The deposited crystals were collected by filtration, sufficiently washed with 2-propanol and then dried to obtain 0.39 g of 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p - hydroxyphenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl)thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, m.p. 172—177°C (decomp.), yield 69.2%.

IR(KBr) cm^{-1} : $\nu_{\text{C=O}}$ 1780 (lactam), 1710 ($-\text{COOH}$),
1685, 1672 ($-\text{CON}<$)

Example 11.

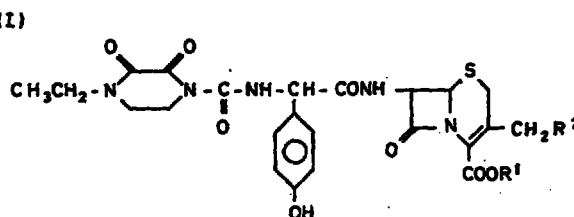
Using 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p - hydroxyphenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid and 1-methyl-5-mercapto-1,2,3,4-tetrazole, the same procedure as in Example 10 was repeated to obtain 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p - hydroxyphenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4-tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, yield 59.0%.

IR (KBr) cm^{-1} : $\nu_{\text{C=O}}$ 1775 (lactam), 1705 ($-\text{COOH}$),
1680, 1670 ($-\text{CON}<$)

The thus obtained product was adjusted to a pH of 7.0 by neutralization with an aqueous sodium hydrogencarbonate solution, and then subjected to filtration and freeze-drying to obtain a sodium salt thereof.

WHAT WE CLAIM IS:—

1. A compound represented by the general formula (I),



wherein R^1 represents a hydrogen atom, a salt-forming cation, or a blocking group; and R^2 represents an acetoxy, carbamoyloxy, 2-(5-methyl-1,3,4-thiadiazolyl)-thio, or 5-(1-methyl-1,2,3,4-tetrazolyl)thio group.

2. 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p-hydroxyphenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid and its non-toxic salts.

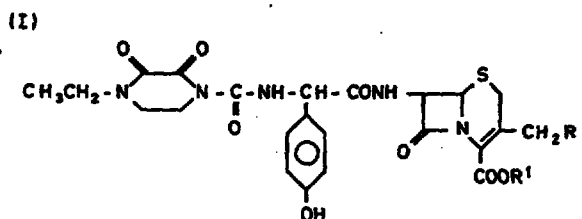
3. 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p-hydroxyphenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl)thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid and its non-toxic salts.

4. 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p-hydroxyphenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl)thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid and its non-toxic salts.

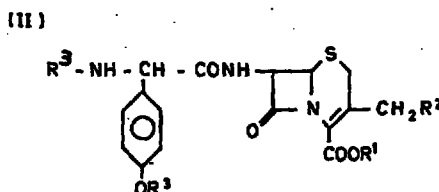
5. 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p-hydroxyphenylacetamido] - 3 - carbamoyloxy - methyl - Δ^3 - cephem - 4 - carboxylic acid and its non-toxic salts.

6. A process for producing a compound represented by the general formula

(I).



wherein R^1 represents a hydrogen atom, a salt-forming cation or a blocking group; and R^2 represents an acetoxy, carbamoyloxy, 2-(5-methyl-1,3,4-thiadiazolyl)-thio, or 5-(1-methyl-1,2,3,4-tetrazolyl)thio group, which comprises [A] reacting a compound represented by the general formula (II),



wherein R^1 and R are the same as defined above; and R^3 represents a hydrogen atom, a silicon-containing group or a phosphorus-containing group, with a reactive derivative in the carboxyl group of a 4-ethyl-2,3-dioxo-1-piperazinocarboxylic acid represented by the formula (III),



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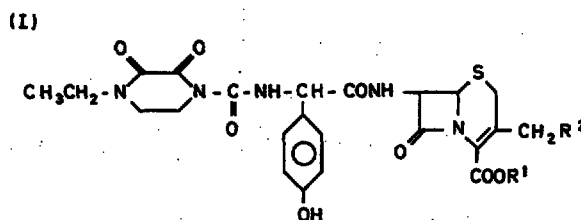
17

IR (KBr) cm^{-1} : $\nu_{\text{C=O}}$ 1775 (lactam), 1705 ($-\text{COOH}$),
1680, 1670 ($-\text{CON}<$)

The thus obtained product was adjusted to a pH of 7.0 by neutralization with an aqueous sodium hydrogencarbonate solution, and then subjected to filtration and freeze-drying to obtain a sodium salt thereof.

WHAT WE CLAIM IS:—

1. A compound represented by the general formula (I),



wherein R^1 represents a hydrogen atom, a salt-forming cation, or a blocking group; and R^2 represents an acetoxy, carbamoyloxy, 2-(5-methyl-1,3,4-thiadiazolyl)-thio, or 5-(1-methyl-1,2,3,4-tetrazolyl)thio group.

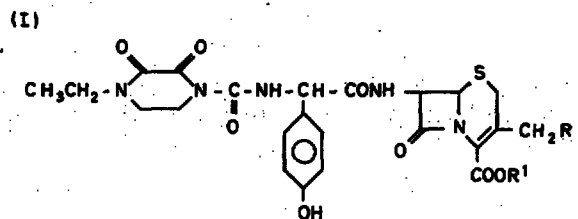
2. 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p-hydroxyphenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid and its non-toxic salts.

3. 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p-hydroxyphenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl)thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid and its non-toxic salts.

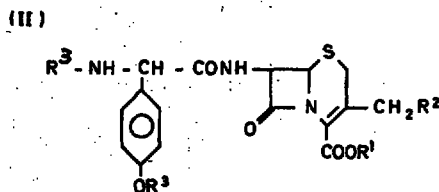
4. 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p-hydroxyphenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl)thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid and its non-toxic salts.

5. 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p-hydroxyphenylacetamido] - 3 - carbamoyloxy - methyl - Δ^3 - cephem - 4 - carboxylic acid and its non-toxic salts.

6. A process for producing a compound represented by the general formula (I).



wherein R^1 represents a hydrogen atom, a salt-forming cation or a blocking group; and R^2 represents an acetoxy, carbamoyloxy, 2-(5-methyl-1,3,4-thiadiazolyl)-thio, or 5-(1-methyl-1,2,3,4-tetrazolyl)thio group, which comprises [A] reacting a compound represented by the general formula (II),



wherein R^1 and R are the same as defined above; and R^3 represents a hydrogen atom, a silicon-containing group or a phosphorus-containing group, with a reactive derivative in the carboxyl group of a 4-ethyl-2,3-dioxo-1-piperazinocarboxylic acid represented by the formula (III),



wherein R^1 , R^2 and R^3 are the same as defined above, with a compound represented by the general formula (V),

wherein R³ is the same as defined above, or with a reactive derivative in the carboxyl group of the compound of formula (V), or [C] reacting a compound represented by the general formula (VI),

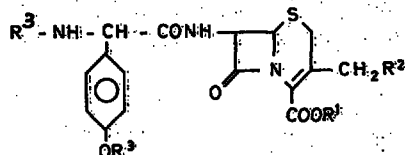
wherein R¹ is the same as defined above; and R⁴ represents a substituent capable of being easily replaced by a nucleophilic reagent, with a compound represented by the general formula (VII),

15 wherein R³ represents a 2-(5-methyl-1,3,4-thiadiazolyl)-thio or 5-(1-methyl-1,2,3,4-tetrazolyl)thio group; and M represents a hydrogen atom, an alkali metal or an alkaline earth metal.

7. A process for producing a compound represented by the general formula (I),

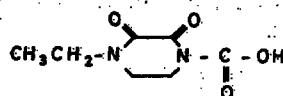
wherein R¹ represents a hydrogen atom, a salt-forming cation or a blocking group; R² represents an acetoxy, carbamoyloxy, 2-(5-methyl-1,3,4-thiadiazolyl)thio or 5-(1-methyl-1,2,3,4-tetrazolyl)thio group, which comprises reacting a compound represented by the general formula (II),

(III)



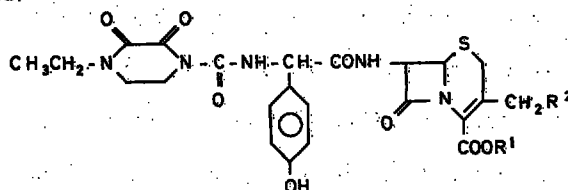
wherein R^1 and R^2 are the same as defined above; and R^3 represents a hydrogen atom, a silicon-containing group or a phosphorus-containing group, with a reactive derivative in the carboxyl group of a 4-ethyl-2,3-dioxo-1-piperazinocarboxylic acid represented by the formula (III),

(III)



8. A process for producing a compound represented by the general formula (I),

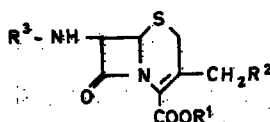
(I)



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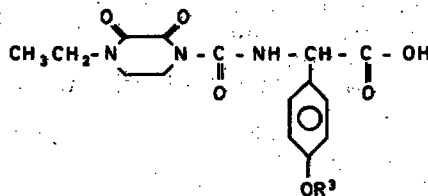
wherein R^1 and R^2 are the same as defined in Claim 7, which comprises reacting a compound represented by the general formula (IV),

(IV)



wherein R^1 , R^2 and R^3 are the same as defined in Claim 7, with a compound represented by the general formula (V),

(V)

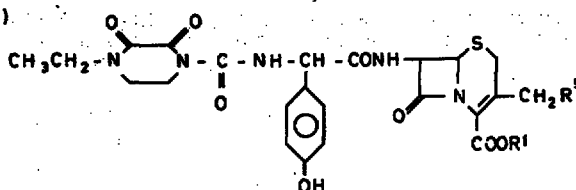


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wherein R^3 is the same as defined in Claim 7, or with a reactive derivative in the carboxyl group of the compound of formula (V).

9. A process for producing a compound represented by the general formula (I-a).

(I-a)



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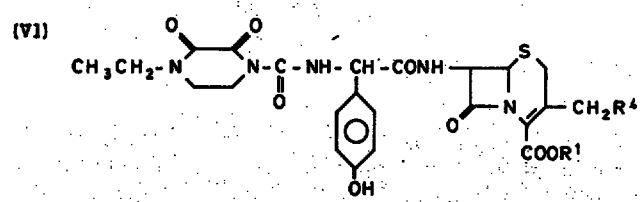
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wherein R¹ is the same as defined above; and R⁵ represents a 2-(5-methyl-1,3,4-thiadiazolyl)thio or 5-(1-methyl-1,2,3,4-tetrazolyl)thio group, which comprises reacting a compound represented by the general formula (VI),



5 wherein R¹ is the same as defined above; and R⁴ represents a substituent capable of being easily replaced by a nucleophilic reagent, with a compound represented by the general formula (VII),



10 wherein R⁵ is the same as defined above; M represents a hydrogen atom, an alkali metal or an alkaline earth metal.

10 10. A process according to Claim 7 or 8, wherein R² is an acetoxy, 2-(5-methyl-1,3,4-thiadiazolyl)thio or 5-(1-methyl-1,2,3,4-tetrazolyl)thio group.

11. A process according to Claim 9, wherein R³ is a 2-(5-methyl-1,3,4-thiadiazolyl)thio group.

15 12. A process according to Claim 9, wherein R³ is a 5-(1-methyl-1,2,3,4-tetrazolyl)thio group.

13. A process according to Claim 7, 8 or 9, wherein R¹ is a cation capable of forming a salt.

14. A process according to Claim 13, wherein the salt is a non-toxic salt.

20 15. A process according to Claim 7 or 8, wherein at least one of R¹ and R³ is a silicon-containing group or a phosphorus-containing group.

16. A process according to Claim 7, wherein the reactive derivative in the carboxyl group of a compound of formula (III) is an acid halide.

25 17. A process according to Claim 8, wherein the reactive derivative in the carboxyl group of a compound of formula (V) is a mixed acid anhydride, or an acid halide.

18. A process according to Claim 7 or 8, wherein the reaction is carried out in the presence of a base.

30 19. A process according to Claim 8, wherein the reaction is carried out in the presence of a dehydrating condensing agent.

20. A process according to Claim 7 or 8, wherein the reaction is carried out at a temperature of -60° to +80°C.

35 21. A process according to Claim 9, wherein R⁴ is a halo-substituted or unsubstituted lower alkanoyloxy group.

22. A process according to Claim 9, wherein R⁴ is an acetoxy group.

23. A process according to Claim 9, wherein the reaction is carried out in a polar solvent at a pH of 2 to 10.

40 24. A process according to Claim 9, wherein the reaction is carried out at a temperature of 0° to 100°C.

25. A pharmaceutical composition containing as an active ingredient the compound as claimed in Claim 1.

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