

PATENT SPECIFICATION

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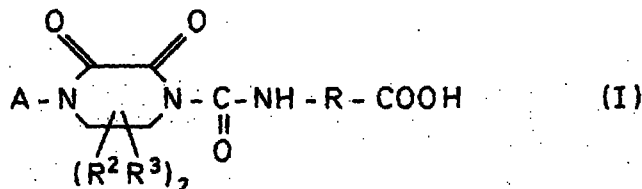


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(54) AMINO ACID DERIVATIVES

(71) We, TOYAMA CHEMICAL CO., LTD. a corporation organised under the laws of Japan of 1-18, Kayabacho, Nohonbashi, 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 amino acid derivatives, represented by the general formula (I), salts thereof, and reactive derivatives in the carboxyl group thereof,



wherein R represents an amino acid residue; R² and R³ are linked to the same carbon atom, and each of R² and R³, which may be the same or different, represents individually a hydrogen atom or an alkyl group; and A represents a hydrogen atom or an unsubstituted or substituted alkyl, alkenyl, aryl or aralkyl group.

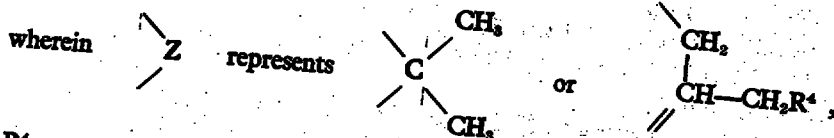
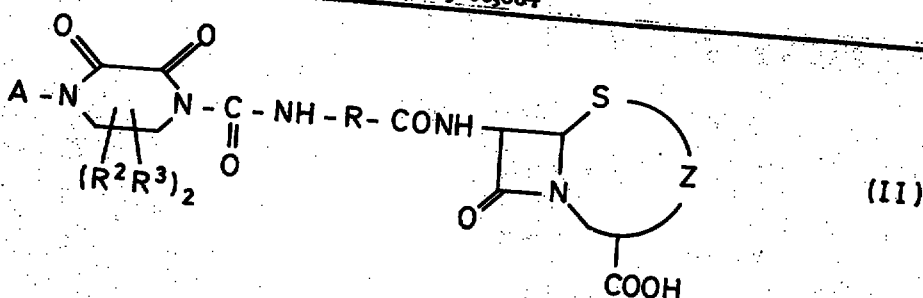
It is an object of this invention to provide amino acid derivatives mentioned above, which are useful as intermediates for the production of penicillins and cephalosporins having a broad and effective antibacterial activity against Gram-positive and Gram-negative bacteria, particularly against *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Proteus* species, which are significant at present from the clinical standpoint, and having high resistance to β -lactamase produced from bacteria.

The present inventors found that novel compounds of formula (II) and non-toxic salts thereof, which were prepared, for example, by acylating, with the compounds of the present invention, the amino group of 6-aminopenicillanic acid or 7-aminocephalosporanic acids, had the above-mentioned characteristics and extremely valuable therapeutic effects. (See British Patent Application No. 17557/75 (Serial No. 1,508,062) from which this application is divided).

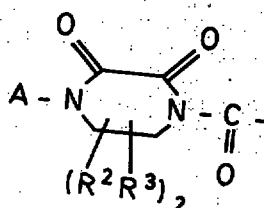
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where R^4 represents a hydrogen atom, a quaternary ammonium group or an unsubstituted or substituted alkoxy, aryloxy, aralkoxy, acyloxy, carbamoyloxy, thiocarbamoylthio, alkoxythiocarbonylthio, aryloxythiocarbonylthio, cycloalkoxythiocarbonylthio, amidinothio or heterocyclylthio, group and R , R^2 , R^3 and A are as defined above. Excellent characteristics of the compounds of formula (II) are derived from the following moiety in the molecule,

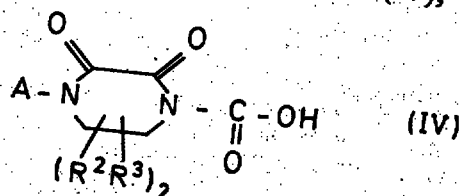


wherein R^2 , R^3 and A are as defined above. Therefore, the compounds of the present invention, which have the above-mentioned moiety, are quite significant as intermediates of the compounds of formula (II). The compounds of the present invention, wherein A is an ethyl group, are specially preferable.

The compounds of the present invention are prepared by the process comprising reacting an amino acid represented by the general formula (III),



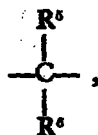
wherein R' represents a hydrogen atom or a salt-forming cation; and R is as defined above, with a reactive derivative in the carboxyl group of a 2,3-dioxopiperazino-carboxylic acids represented by the general formula (IV),



wherein R^2 , R^3 , and A are as defined above, and then, if desired, converting the obtained product to a salt thereof or a reactive derivative in the carboxyl group thereof by a conventional method.

In the above-mentioned general formulae (I) to (III), R represents an amino acid residue. The amino acid residue include residues of amino acids derived from various aliphatic, araliphatic, aromatic, alicyclic and heterocyclic compounds, which amino

acids may have the amino group at a position such as α , β or γ -position to the carboxyl group. Preferable as said R is an α -amino acid residue represented by the formula



wherein R⁵ is an alkyl group such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl or octyl; a cycloalkyl group such as cyclopentyl, cyclohexyl or cycloheptyl; a cycloalkenyl group such as cyclopentenyl or cyclohexenyl; a cycloalkadienyl group such as cyclopentadienyl or cyclohexadienyl; an aryl group such as phenyl, or naphthyl; an aralkyl group such as benzyl or phenethyl; an aryloxy group such as phenoxy or naphthoxy; an alkylthioalkyl group such as methylthiomethyl, ethylthiomethyl, methylthioethyl or ethylthioethyl or a heterocyclic group such as furyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, pyridyl, pirazyl, pyrimidyl, pyridazyl, quinolyl, isoquinolyl, quinazolyl, indolyl, indazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-thiadiazolyl or 1,2,4-thiadiazolyl; each group represented by said R⁵ may be substituted by various groups, for example, halogen, hydroxy, nitro, alkyl, alkoxy, alkylthio, acyl or alkylsulfonylamino; R⁶ represents a hydrogen atom; and R⁵ and R⁶ together with a common carbon atom may form a cycloalkane ring such as cyclohexane; or cycloalkyladiene such as cyclopentadiene or cyclohexadiene.

In the general formula (III), R' is a hydrogen atom or a salt-forming cation. The salt-forming cation includes cations capable of forming the 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-phenylamine, N,N-dibenzylethylenediamine, trimethylamine, triethylamine, tributylamine, pyridine, dimethylaniline, N-methylpiperidine, N-methylmorpholine, diethylamine or dicyclohexylamine.

The salts of the compound of formula (I) include the above-mentioned salts.

In the general formulae (I), (II) and (IV), A represents a hydrogen atom or an alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, heptyl, octyl or dodecyl; an alkenyl group such as vinyl, propenyl or butenyl; an aralkyl group such as benzyl or phenethyl; or an aryl group such as phenyl or naphthyl. Each of the groups mentioned above for A may be substituted by any of such substituents as, for example, halogen atoms, hydroxyl groups, alkyl groups, alkoxy groups, alkylthio groups, nitro groups, cyano groups, carboxyl groups, acyl groups, dialkylamino groups or cyclic amino groups.

The reactive derivatives in the carboxyl group of the compound of formula (I) include, for example, acid halides, acid anhydrides, mixed acid anhydrides with organic or inorganic acids, active acid amides, acid cyanides or active esters. Particularly, acid chlorides, mixed acid anhydrides and active acid amides are preferable as an intermediate. Examples of the mixed acid anhydrides are mixed acid anhydrides with substituted acetic acids, alkyl carbonic acids, aryl carbonic acids and aralkyl/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.

The above-mentioned amino acids of formula (III) and the compounds of formula (I), salts thereof or reactive derivatives in the carboxyl group thereof have their optical isomers, and all of D-isomers, L-isomers and racemic compounds thereof are involved in the scope of the present invention.

As the reactive derivative in the carboxyl group of the compound of formula (IV), 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 with organic or inorganic acids, active esters or active amides. Particularly preferable examples thereof are acid halides such as acid chlorides, acid bromides, etc., and active esters such as cyanomethyl ester and trichloromethyl ester.

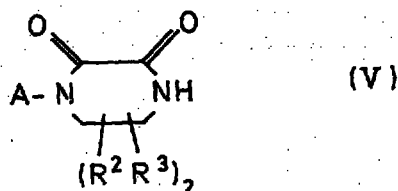
The reactive derivative in the carboxyl group of the compound of formula (IV) can be easily obtained by reacting 2,3-dioxopiperazines of formula (V) synthesized according to the process of the literature reference described below, with phosgene or the trichloromethyl ester of chloroformic acid,

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wherein A and R² are as defined previously.

Literature reference:

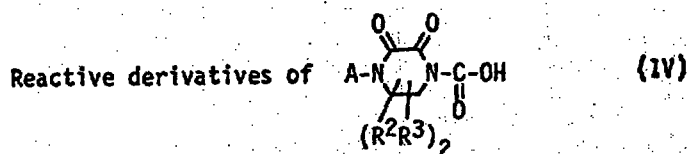
J. L. Riebsomer, J. Org. Chem., 15 68—73 (1950).

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Concrete examples of the reactive derivative of the compound of formula (IV) are as set forth in Table 1.

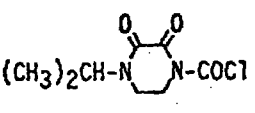
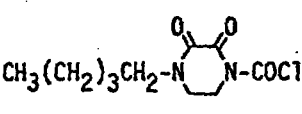
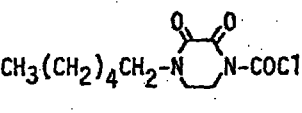
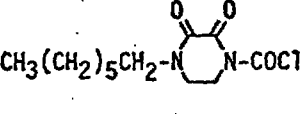
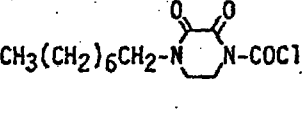
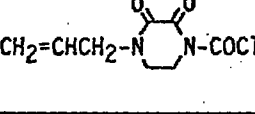
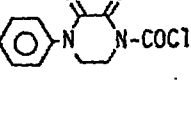
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Table 1



Compound	Physical property	I.R. (cm ⁻¹)
$ \begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{CH}_3-\text{N} \quad \text{N}-\text{COCl} \\ \quad \\ \text{---} \text{C} \text{---} \text{C} \text{---} \\ \quad \\ \text{---} \text{C} \text{---} \text{C} \text{---} \\ \quad \\ (\text{R}^2 \text{R}^3)_2 \end{array} $	m.p. 94 - 95° C (decomp.) (from CH ₂ Cl ₂ -Et ₂ O)	ν _{C=O} 1790, 1680
$ \begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{CH}_3\text{COOCH}_2\text{CH}_2-\text{N} \quad \text{N}-\text{COCl} \\ \quad \\ \text{---} \text{C} \text{---} \text{C} \text{---} \\ \quad \\ (\text{R}^2 \text{R}^3)_2 \end{array} $	Oily material	ν _{C=O} 1790, 1720, 1670
$ \begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{CH}_3\text{CH}_2-\text{N} \quad \text{N}-\text{COCl} \\ \quad \\ \text{---} \text{C} \text{---} \text{C} \text{---} \\ \quad \\ (\text{R}^2 \text{R}^3)_2 \end{array} $	m.p. 95 - 96° C (decomp.) (from AcOBu)	ν _{C=O} 1780, 1660
$ \begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{CH}_3\text{CH}_2\text{CH}_2-\text{N} \quad \text{N}-\text{COCl} \\ \quad \\ \text{---} \text{C} \text{---} \text{C} \text{---} \\ \quad \\ (\text{R}^2 \text{R}^3)_2 \end{array} $	Oily material	ν _{C=O} 1780, 1710 - 1640
$ \begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{CH}_3(\text{CH}_2)_2\text{CH}_2-\text{N} \quad \text{N}-\text{COCl} \\ \quad \\ \text{---} \text{C} \text{---} \text{C} \text{---} \\ \quad \\ (\text{R}^2 \text{R}^3)_2 \end{array} $	"	ν _{C=O} 1780, 1660

Table 1 (Cont'd)

 <chem>ClCC1CC(=O)N(CCCl)C1=O</chem>	m.p. 130 - 131° C (decomp.)	$\nu_{C=O}$ 1780, 1660
 <chem>ClCCC1CC(=O)N(CCCC1=O)C1=O</chem>	Oily material	$\nu_{C=O}$ 1790, 1720 - 1665
 <chem>ClCCCC1CC(=O)N(CCCCC1=O)C1=O</chem>	"	$\nu_{C=O}$ 1780, 1720 - 1640
 <chem>ClCCCCC1CC(=O)N(CCCCC1=O)C1=O</chem>	"	$\nu_{C=O}$ 1780, 1720 - 1640
 <chem>ClCCCCCC1CC(=O)N(CCCCCC1=O)C1=O</chem>	"	$\nu_{C=O}$ 1780, 1720 - 1640
 <chem>ClCC1CC(=O)N(CCCl)C1=O</chem>	Crystal	$\nu_{C=O}$ 1775, 1660 - 1620
 <chem>ClCC1CC(=O)N(CCCl)C1=O</chem>	"	$\nu_{C=O}$ 1785, 1720 - 1650

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TABLE 1 (Cont'd)

$\text{ClCH}_2\text{CH}_2\text{-N}\begin{array}{c} \text{O} \\ \parallel \\ \text{C} \end{array}\text{N-COCl}$	Oily material	$\nu_{\text{C=O}}$ 1790, 1730, 1680
$\text{CH}_3\text{CH}_2\text{-N}\begin{array}{c} \text{O} \\ \parallel \\ \text{C} \end{array}\text{N-COCl}$ CH_3	m.p. 65 - 70° C (decomp.)	$\nu_{\text{C=O}}$ 1785, 1680

Note: $\text{Et}_2\text{O} = \text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3$
 $\text{AcOB}_4 = \text{CH}_3\text{COO}(\text{CH}_2)_3\text{CH}_3$

The mode of practice of the process of the present invention is explained below.
 Thus the compound of formula (III) is dissolved or suspended in at least one inert solvent selected from, for example, water, acetone, tetrahydrofuran, dioxane, acetonitrile, dimethylformamide, methanol, ethanol, methoxyethanol, ethyl acetate, or methylene chloride. The resulting solution or suspension is reacted with a reactive derivative in the carboxyl group of the compound of formula (IV), preferably in the presence of a base. Examples of the base are inorganic bases such as alkali metal hydroxides, alkali metal hydrogencarbonates or alkali metal carbonates; and organic bases such as trimethylamine, N-methylpiperidine or diethylamine.

The reaction is ordinarily carried out at a temperature of 0° to room temperature, and concluded within 2 hours. After the reaction, the objective compound can be easily obtained according to an ordinary procedure from the reaction solution.

Further, the salts of the compound of formula (I) can be easily obtained according to an ordinary procedure from the compound of formula (I).

Furthermore, the reactive derivatives in the carboxyl group of the compound of formula (I) can be easily obtained according to an ordinary procedure from the compound of formula (I) or the salt thereof.

Concrete examples of the compound of formula (I) are as follows.

- α -(4-Methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid
- α -(4-Acetoxyethyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid
- α -(4-Ethyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid
- α -(4-n-Propyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid
- α -(4-n-Butyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid
- α -(4-Isopropyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid
- α -(4-n-Pentyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid
- α -(4-n-Hexyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid
- α -(4-n-Heptyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid
- α -(4-n-Octyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid
- α -(4-Allyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid
- α -(4-Phenyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid
- α -(4- β -Chloroethyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid
- α -(4-Pyrrolidinoethyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid
- α -(4-Methyl-2,3-dioxo-1-piperazinocarbonylamino)-p-hydroxyphenylacetic acid
- α -(4-Ethyl-2,3-dioxo-1-piperazinocarbonylamino)-p-hydroxyphenylacetic acid
- α -(6-Methyl-4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid
- α -(4,6-Dimethyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid
- α -(4-Methyl-2,3-dioxo-1-piperazinocarbonylamino)-1,4-cyclohexadienylacetic acid
- α -(4-Ethyl-2,3-dioxo-1-piperazinocarbonylamino)-1,4-cyclohexadienylacetic acid
- α -(4-n-Propyl-2,3-dioxo-1-piperazinocarbonylamino)-1,4-cyclohexadienylacetic acid
- α -(4-n-Butyl-2,3-dioxo-1-piperazinocarbonylamino)-1,4-cyclohexadienylacetic acid
- α -(4-Methyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid
- α -(4-Ethyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid

α -(4-n-Propyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid
 α -(4-n-Butyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid

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

Example 1.

(1) To a solution of 8.7 g of a sodium salt of D(-)- α -phenylglycine in 50 ml of water were added 50 ml of ethyl acetate and 5.05 g of triethylamine. To the resulting mixture was gradually added 9.5 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride at 0° to 5° C. over a period of 15 minutes, and then the mixture was reacted at 5° to 15° C. for 30 minutes. After the reaction, the aqueous layer was separated off, washed with diethyl ether, and then adjusted to a pH of 1.5 by addition of dilute hydrochloric acid to deposit crystals. The deposited crystals were collected by filtration, washed with water and dried to obtain 14.1 g of D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid, m.p. 138—141° C. (decomp.), yield 8%. Recrystallization from hydrous butanol gave white crystals, m.p. 140—142° C. (decomp.).

Elementary analysis (for $C_{14}H_{16}N_2O_5 \cdot H_2O$):

Calculated (%) C: 52.01 H: 5.30 N: 13.00
Found (%) C: 52.24 H: 5.32 N: 12.87
IR (KBr) cm^{-1} ; $\nu_{O=O}$ 1710, 1700, 1660, ν_{NH} 3280,
NMR (d_6 -DMSO) τ values: 0.1 (1H, d), 2.65 (5H, s), 4.60 (1H, d), 6.10 (2H, bs) 6.50 (2H, bs), 7.0 (3H, s)

In the same manner as above, the following objective compound were obtained.
D(-)- α -(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid,

(2) Into a solution of 10 g of the above-mentioned D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid in 200 ml of acetone was dropped a solution of 5.2 g of a sodium salt of 2-ethylhexanoic acid in 50 ml of acetone with stirring to deposit crystals. The deposited crystals were collected by filtration and then washed with acetone to obtain 9.6 g of a sodium salt of D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid, m.p. 165° C. (decomp.), yield 95%.

(3) To a suspension of 8.8 g of the above-mentioned sodium salt of D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid in 80 ml of methylene chloride was added 20 mg of N-methylmorpholine. Into the resulting mixture was dropped a solution of 3.1 g of ethyl chlorocarbonate in 20 ml of methylene chloride at -20° to -50° C. over a period of 5 minutes, and the mixture was reacted at said temperature for 1 hour to form the mixed acid anhydride of D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid. Into this reaction liquid was dropped a solution of 9.4 g of a triethylamine salt of 6-aminopenicillanic acid in 40 ml of methylene chloride at -40° to -30° C. over a period of 10 minutes, and the resulting mixture was reacted at -40° to -20° C. over a period of 1 hour. After the reaction, the temperature of the reaction liquid was gradually elevated to 0° C. over a period of 1 hour, and the mixture was then subjected to extraction with 100 ml of water. Subsequently, the aqueous layer was separated off, and the methylene chloride layer was further subjected to extraction with 50 ml of water, and the resulting aqueous layer was combined with the aforesaid aqueous layer. The combined aqueous layer was adjusted to a pH of 2 by addition of dilute hydrochloric acid with ice-cooling to deposit crystals. The deposited crystals were collected by filtration, sufficiently washed with water, dried and then dissolved in 200 ml of acetone. Into the resulting solution was dropped a solution of 4 g of a sodium salt of 2-ethylhexanoic acid in 40 ml of acetone over a period of 10 minutes to deposit crystals. The deposited crystals were collected by filtration, washed with acetone and then dried to obtain 11.4 g of a sodium salt of 6-[D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 170° C. (decomp.), yield 80.8%. The structure of this compound was confirmed by IR and NMR.

Example 2.

To a suspension of 0.9 g of D(-)- α -alanine in 15 ml of water was added 2.05 g of triethylamine to dissolve D(-)- α -alanine in water, and the resulting solution was cooled to 0° C. To the solution was added 2.3 g of 4-methyl-2,3-dioxo-1-piperazino-

carbonyl chloride over 15 minutes, after which reaction was effected for 30 minutes with ice-cooling. Dilute hydrochloric acid was then added to the reaction product to adjust the pH thereof to 2.0. The water was removed by distillation under reduced pressure, and 30 ml of acetone was added to the residue, after which insolubles were filtered off. To the resulting acetone solution was added 10 ml of an acetone solution of 1.6 g of a sodium salt of 2-ethylhexanoic acid, and the deposited crystals were collected by filtration, and dried to obtain 2.1 g of a sodium salt of D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)propionic acid having a melting point of 115–118° C. (decomp.), yield 78.5%.

IR (KBr) cm^{-1} : $\nu_{\text{C=O}}$ 1700, 1680, 1600 ($-\text{CONH}-$, $-\text{COO}^-$)

Example 3.

(1) To a solution of 2.28 g of D(-)- α -amino-1,4-cyclohexadienylacetic acid in 15 ml of N NaOH were added 20 ml of ethyl acetate and 2.1 ml of triethylamine, and the resulting mixture was cooled to 0° C. To this mixture was gradually added 1.69 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride over a period of 10 minutes. Subsequently, the mixture was reacted for 30 minutes with ice-cooling, and then the aqueous layer was separated off. To the aqueous layer was further added 20 ml of ethyl acetate. The resulting mixture was adjusted to a pH of 2 by addition of 2N hydrochloric acid with ice-cooling, and the ethyl acetate layer was separated off. The organic layer was sufficiently washed with water, dried over anhydrous magnesium sulfate, freed from the solvent by distillation under reduced pressure and then incorporated with isopropyl alcohol to deposit crystals. The deposited crystals were collected by filtration to obtain 2.5 g of white crystals of D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-1,4-cyclohexadienylacetic acid, m.p. 140–145° C. (decomp.), yield 74%.

IR (KBr) cm^{-1} : ν_{NH} 3300, $\nu_{\text{C=O}}$ 1715, 1660

NMR (d_6 -DMSO) τ values: 0.57 (1H, d), 4.26 (1H, s), 4.36 (2H, s), 5.29 (1H, d), 6.07–6.18 (2H, m), 6.38–6.49 (2H, m), 7.05 (3H, s), 7.35 (4H, s)

In the same manner as above, the following objective compounds were obtained.

D(-)- α -(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)-1,4-cyclohexadienylacetic acid.

D(-)- α -(4-n-propyl-2,3-dioxo-1-piperazinocarbonylamino)-1,4-cyclohexadienylacetic acid.

D(-)- α -(4-n-butyl-2,3-dioxo-1-piperazinocarbonylamino)-1,4-cyclohexadienylacetic acid.

(2) To a suspension of 0.45 g of the above-mentioned D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-1,4-cyclohexadienylacetic acid in 15 ml of anhydrous methylene chloride was added 0.24 ml of N-methylmorpholine with stirring to form a solution. After cooling the solution to -10° C., 3 ml of an anhydrous methylene chloride solution containing 0.24 g of ethyl chlorocarbonate was dropped into the solution, and the resulting mixture was reacted at said temperature for 90 minutes to form the mixed acid anhydride of D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-1,4-cyclohexadienylacetic acid. Subsequently, the reaction liquid was cooled to -20° C., and 5 ml of a methylene chloride solution containing 0.70 g of a triethylamine salt of 6-aminopenicillanic acid and 0.31 ml of triethylamine was gradually dropped into the reaction liquid. The resulting mixture was reacted at -20° C. for 1 hour, at -20° to 0° C. for 1 hour, and 0° to 5° C. for 1 hour. Thereafter, the reaction liquid was freed from the solvent by distillation under reduced pressure. The residue was dissolved in 10 ml of water and then washed with 10 ml of ethyl acetate. The aqueous layer was again incorporated with 15 ml of ethyl acetate, and then adjusted to a pH of 2.0 by addition of 2N HCl with ice-cooling. Subsequently, the ethyl acetate layer was separated off, washed with water, dried over anhydrous magnesium sulfate, and freed from the solvent by distillation under reduced pressure to obtain 0.74 g of white crystals of 6-[D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-1,4-cyclohexadienylacetamido]penicillanic acid, m.p. 84–87° C. (decomp.), yield 87%. The structure of this compound was confirmed by IR and NMR.

Example 4.

(1) To a solution of 2.2 g of DL- α -amino-2-thienylacetic acid in 14 ml of a N sodium hydroxide solution was added at 0° C. 2.2 g of triethylamine. To the resulting

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mixture was further added 3.6 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride little by little at said temperature. Subsequently, the mixture was reacted at 0° C. for 30 minutes, and then at room temperature for 30 minutes. After the reaction, the reaction liquid was adjusted to a pH of 1.0 by addition of dilute hydrochloric acid to deposit crystals. The deposited crystals were collected by filtration, washed with water and then dried to obtain 3.5 g of DL- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid, m.p. 214–215° C. (decomp.), yield 80.5%.

IR (KBr) cm^{-1} : $\nu_{\text{C=O}}$ 1710, 1680–1660

In the same manner as above, the following objective compounds were obtained.

DL- α -(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid
DL- α -(4-n-propyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid
DL- α -(4-n-butyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid

(2) Into a solution of 3.5 g of the above-mentioned DL- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid in 100 ml of acetone was dropped a solution of 1.86 g of a sodium salt of 2-ethylhexanoic acid in 50 ml of acetone, upon which crystals were deposited. The deposited crystals were collected by filtration and then washed with acetone to obtain 3.5 g of a sodium salt of DL- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid, m.p. 175–176° C. (decomp.).

(3) To a suspension of 3.3 g of the above-mentioned sodium salt of DL- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid in 50 ml of methylene chloride was added 30 mg of N-methylmorpholine, and the resulting mixture was then cooled to –20° to –15° C. Into the resulting mixture was dropped a solution of 1.3 g of ethyl chlorocarbonate in 20 ml of methylene chloride over a period of 5 minutes, and the mixture was stirred at said temperature for 90 minutes to form the mixed acid anhydride of DL- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid. Subsequently, a solution of 3.3 g of a triethylamine salt of 6-aminopenicillanic acid in 50 ml of methylene chloride was dropped into the mixture at –50° to –40° C. over a period of 20 minutes, and the resulting mixture was reacted with stirring at –40° to –30° C. for 30 minutes, at –30° to –20° C. for 30 minutes, and then at –20° to 0° C. for 30 minutes. After the reaction, the solvent was removed by distillation under reduced pressure, and the residue was dissolved in water. The resulting aqueous solution was adjusted to a pH of 2.0 by addition of dilute hydrochloric acid with ice-cooling to deposit crystals. The deposited crystals were collected by filtration, sufficiently washed with water and then dried to obtain 4.1 g of 6-[DL- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetamido]-penicillanic acid, m.p. 185° C. (decomp.), yield 80.5%. The structure of this compound was confirmed by IR and NMR.

Example 5.

(1) To a solution of 28.2 g of a sodium salt of D(–)- α -phenylglycine in 150 ml of water were added 200 ml of ethyl acetate and 18.2 g of triethylamine, and the resulting mixture was cooled to 0° C. To this mixture was added 34.3 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride over a period of 15 minutes, and the mixture was reacted at 5° to 10° C. for 15 minutes. Thereafter, the aqueous layer was separated off and adjusted to a pH of 0.5 by addition of 2N hydrochloric acid with ice-cooling to deposit crystals. The deposited crystals were collected by filtration and then dried to obtain 42 g of white crystals of D(–)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid.

(2) To a suspension in 15 ml of anhydrous methylene chloride of 0.31 g of the D(–)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid obtained in the above-mentioned item (1) was added 0.11 g of N-methylmorpholine with stirring to form a solution, which was then cooled to –20° C. To this solution was added 3 ml of an anhydrous methylene chloride solution containing 0.13 g of ethyl chlorocarbonate, and the resulting mixture was reacted at –10° to 20° C. for 60 minutes to form a mixed acid anhydride. Into the thus formed acid anhydride was dropped a solution formed by adding 0.50 ml of triethylamine to a suspension in 5 ml of methanol of 0.41 g of 7-amino-3-[2-(5-methyl-1,3,4-thiadiazolyl)-thiomethyl]- Δ^3 -cephem-4-carboxylic acid. After the dropping, the resulting mixture was reacted at –50° to –30° C. for 30 minutes, at –30° to –20° C. for 60 minutes, at –20° to 0° C. for 60 minutes, and then at room temperature for 30 minutes. Thereafter, the reaction liquid was concentrated under reduced pressure, and the concentrate was dissolved in 10 ml of water, washed with 5 ml of ethyl acetate, again charged with 15 ml of ethyl acetate, and then

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adjusted to a pH of 1.5 by addition of 2N hydrochloric acid with ice-cooling. Subsequently, insolubles were separated by filtration, and the ethyl acetate layer was separated off, successively washed with water and a saturated sodium chloride solution, dried over magnesium sulfate, and then freed from the solvent by distillation under reduced pressure to obtain 0.58 g of pale yellow crystals of 7-[D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido]-3-[2-(5-methyl-1,3,4-thiadiazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid, m.p. 160° C. (decomp.), yield 91 %.

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IR (KBr) cm^{-1} : $\nu_{\text{C=O}}$ 1780 (lactam), 1650—1720 ($-\text{CON}-$, $-\text{COOH}$)
NMR (d_6 -DMSO) τ values: 0.2 (1H, d), 0.6 (1H, d), 2.60 (5H, s), 4.35 (1H, q), 4.40 (1H, d), 5.0 (1H, d), 5.70 (2H, q), 6.10 (2H, bs), 6.25—6.55 (2H, 2H, bs), 7.0 (3H, s), 7.30 (3H, s)

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The above-mentioned operation was repeated, except that the D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid was replaced by each of the compounds of formula (I) shown in Table 2, to obtain respective compounds of formula (II) as shown in Table 2. The structure of each compound of formula (II) was confirmed by IR and NMR.

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Table 2

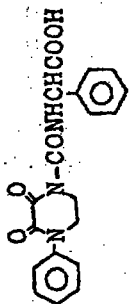
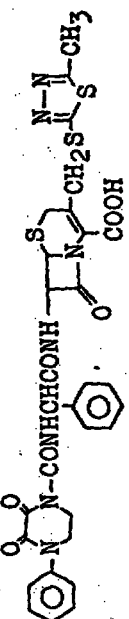
Compound of formula (I)	Compound of formula (II)
D(-)- <chem>CC1CC(=O)N(C1)C(=O)Cc2ccccc2C(=O)O</chem>	D(-)- <chem>CC1CC(=O)N(C1)C(=O)Cc2ccccc2C(=O)Nc3cc(C(=O)O)sc(C)c3</chem> m.p. (decomp.) 150°C, yield 91 %
D(-)- <chem>CC1CC(=O)N(C1)C(=O)Cc2ccccc2C(=O)O</chem>	D(-)- <chem>CC1CC(=O)N(C1)C(=O)Cc2ccccc2C(=O)Nc3cc(C(=O)O)sc(C)nn3</chem> m.p. (decomp.) 147°C, yield 85.4 %
D(-)- <chem>CC1CC(=O)N(C1)C(=O)Cc2ccccc2C(=O)O</chem>	D(-)- <chem>CC1CC(=O)N(C1)C(=O)Cc2ccccc2C(=O)Nc3cc(C(=O)O)sc(C)nn3</chem> m.p. (decomp.) 144°C, yield 84.3 %

- cont'd -

(19) (10)

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Table 2 (Cont'd)

D(-)- 	D(-)-  m.p. (decomp.) 167°C, yield 93 %
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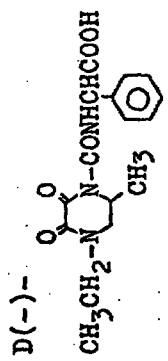
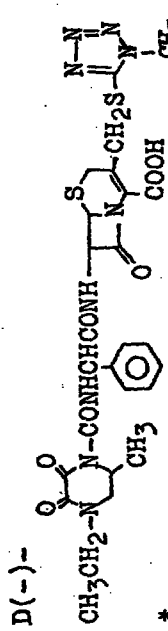
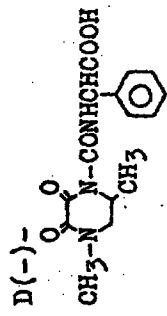
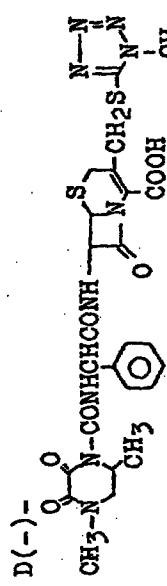
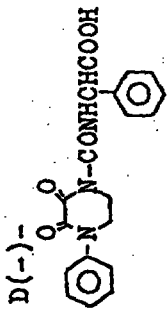
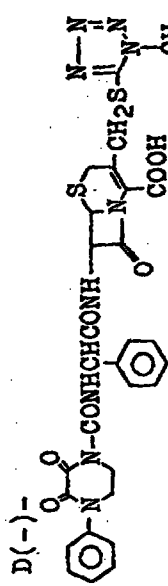
Example 6.

Using 0.3 g of D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid and 0.33 g of 7-amino-3-[5-(1-methyl-1,2,3,4-tetrazolyl)-thiomethyl]- Δ^8 -cephem-4-carboxylic acid, the same operation as in Example 5 was repeated, to obtain 0.5 g of 7-[D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido]-3-[5-(1-methyl-1,2,3,4-tetrazolyl)-thiomethyl]- Δ^8 -cephem-4-carboxylic acid, m.p. 161-163°C. (decomp.), yield 76%.

IR (Nujol) cm^{-1} : $\nu_{\text{C=O}}$ 1775 (lactam), 1720-1660 (CONH , COOH)
 NMR (d_6 -DMSO) τ values: 0.02 (1H, d), 0.34 (1H, d), 2.48 (5H, s), 4.17 (1H, q), 4.26 (1H, d), 4.92 (1H, d), 5.66 (2H, s), 6.01 (5H, s), 6.35 (4H, s), 7.0 (3H, s)

The above-mentioned operation was repeated, except that the D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid was replaced by each of the compounds of formula (I) shown in Table 3, to obtain respective compounds of formula (II) as shown in Table 3. The structure of each compound of formula (II) was confirmed by IR and NMR.

Table 3

Compound of formula (I)	Compound of formula (II)
D(-)-  CH₃CH₂-N-CONHCHCOOH	D(-)-  CH₃CH₂-N-CONHCHCOOH * m.p. (decomp.) 170°C, yield 63.6 %
D(-)-  CH₃-N-CONHCHCOOH	D(-)-  CH₃-N-CONHCHCOOH m.p. (decomp.) 173°C, yield 68 %
D(-)-  CH₃-N-CONHCHCOOH	D(-)-  CH₃-N-CONHCHCOOH m.p. (decomp.) 163°C, yield 74.8 %

* Anhydrous methylene chloride was substituted for the methanol used in Example 5

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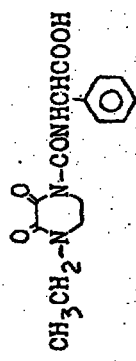
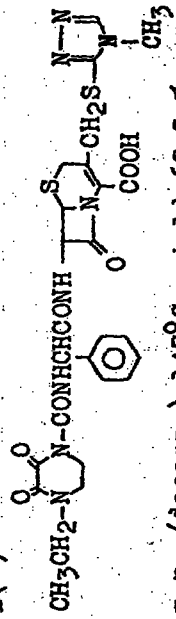
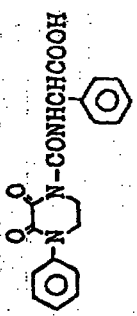
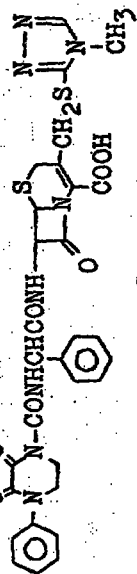
Example 7.

Using 0.31 g of D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-phenylacetic acid and 0.39 g of 7-amino-3-[2-(1-methyl-1,3,4-triazolyl)thiomethyl]- Δ^6 -cephem-4-carboxylic acid, the same operation as in Example 5 was repeated, except that the methanol was replaced by anhydrous methylene chloride, to obtain 0.43 g of 7-[D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-phenylacetamido]-3-[2-(1-methyl-1,3,4-triazolyl)-thiomethyl]- Δ^6 -cephem-4-carboxylic acid, yield 70%.

IR (Nujol; Registered Trade Mark) cm^{-1} : $\nu_{\text{C=O}}$ 1780 (lactam), 1720-1650 ($-\text{CONH}-$, $-\text{COOH}$)

The above-mentioned operation was repeated, except that the D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid was replaced by each of the compounds of formula (I) shown in Table 4, to obtain respective compounds of formula (II) as shown in Table 4. The structure of each compound of formula (II) was confirmed by IR and NMR.

Table 4

Compound of formula (I)	Compound of formula (II)
D(-)- 	D(-)-  m.p. (decomp.) 147°C, yield 68.5 %
D(-)- 	D(-)-  m.p. (decomp.) 158°C, yield 74.5 %

Example 8.

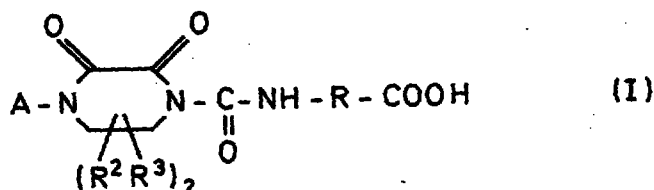
In the same manner as in Example 7, 7-[D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-p-hydroxyphenylacetamido]-3-[5-(1-methyl-1,2,3,4-tetrazolyl)-thiomethyl]- Δ^3 -cephem-4-carboxylic acid was obtained from 7-amino-3-[5-(1-methyl-1,2,3,4-tetrazolyl)-thiomethyl]- Δ^3 -cephem-4-carboxylic acid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

Melting point (decomp.), 147—9° C.; yield, 62.0%.

IR (KBr) cm^{-1} : $\nu_{\text{C=O}}$ 1765 (lactam), 1720—1660 ($-\text{CON}-$, $-\text{COOH}$)

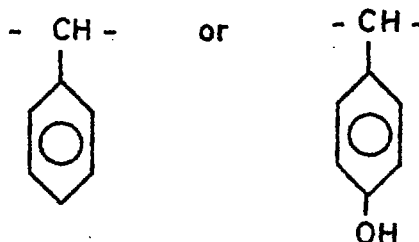
WHAT WE CLAIM IS:—

1. A compound represented by the general formula (I), a salt thereof, or a reactive derivative in the carboxyl group thereof,



wherein R represents an amino acid residue; R^2 and R^3 are linked to the same carbon atom, and each of R^2 and R^3 , which may be the same or different, represents individually a hydrogen atom or an alkyl group; and A represents a hydrogen atom or an unsubstituted or substituted alkyl, alkenyl, aryl or aralkyl group.

2. A compound according to Claim 1, wherein A is a methyl or ethyl group; R^2 and R^3 are individually represent a hydrogen atom or a methyl group; and R is

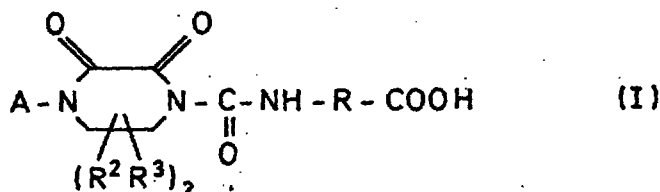


3. A compound according to Claim 2, wherein a reactive derivative in the carboxyl group is an acid halide or mixed acid anhydride.

4. D(-)- α -(4-Ethyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid, its salt or its reactive derivative.

5. D(-)- α -(4-Ethyl-2,3-dioxo-1-piperazinocarbonylamino)-p-hydroxyphenylacetic acid, its salt or its reactive derivative.

6. A process for producing a compound represented by the general formula (I), a salt thereof, or a reactive derivative in the carboxyl group thereof,



wherein R, A, R^2 and R^3 are as defined in claim 1, which comprises reacting an amino acid represented by the general formula (III),



wherein R' represents a hydrogen atom or a salt-forming cation; and R is as defined



* C L M S *

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Example 8.

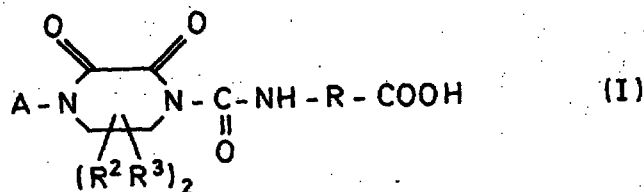
In the same manner as in Example 7, 7-[D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-p-hydroxyphenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4-tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid was obtained from 7 - amino - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl]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

Melting point (decomp.), 147-9° C.; yield, 62.0%

IR (KBr) cm^{-1} : $\nu_{\text{C=O}}$ 1765 (lactam), 1720-1660 ($-\text{CON}<$, $-\text{COOH}$)

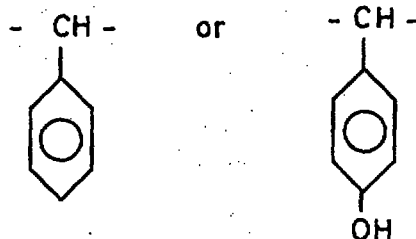
WHAT WE CLAIM IS:—

1. A compound represented by the general formula (I), a salt thereof, or a reactive derivative in the carboxyl group thereof,



wherein R represents an amino acid residue; R^2 and R^3 are linked to the same carbon atom, and each of R^2 and R^3 , which may be the same or different, represents individually a hydrogen atom or an alkyl group; and A represents a hydrogen atom or an unsubstituted or substituted alkyl, alkenyl, aryl or aralkyl group.

2. A compound according to Claim 1, wherein A is a methyl or ethyl group; R^2 and R^3 are individually represent a hydrogen atom or a methyl group; and R is

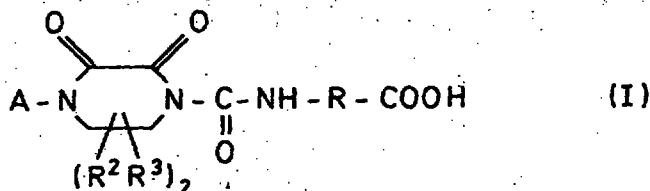


3. A compound according to Claim 2, wherein a reactive derivative in the carboxyl group is an acid halide or mixed acid anhydride.

4. D(-)- α -(4-Ethyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid, its salt or its reactive derivative.

5. D(-)- α -(4-Ethyl-2,3-dioxo-1-piperazinocarbonylamino)-p-hydroxyphenylacetic acid, its salt or its reactive derivative.

6. A process for producing a compound represented by the general formula (I), a salt thereof, or a reactive derivative in the carboxyl group thereof,



wherein R, A, R^2 and R^3 are as defined in claim 1, which comprises reacting an amino acid represented by the general formula (III),



wherein R' represents a hydrogen atom or a salt-forming cation; and R is as defined

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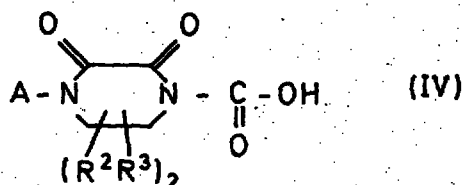


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above, with a reactive derivative in the carboxyl group of a 2,3-dioxopiperazinocarboxylic acid represented by the general formula (IV),



wherein R^2 , R^3 and A are as defined above, an inert solvents in the presence or absence of a base at a temperature of -30° to 40° C., and then, if desired, converting the obtained product to a salt thereof or a reactive derivative in the carboxyl group thereof by a conventional method.

7. A process according to claim 6, wherein A is an ethyl group.

8. A process according to claim 6, wherein R is



A is an ethyl group; and R^2 and R^3 are hydrogen atoms.

9. A process according to claim 6, wherein R is



A is an ethyl group; and R^2 and R^3 are hydrogen atoms.

10. A compound according to claim 1 and substantially as hereinbefore described.

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