1 508 063

PATENT SPECIFICATION (11) 1 508 063

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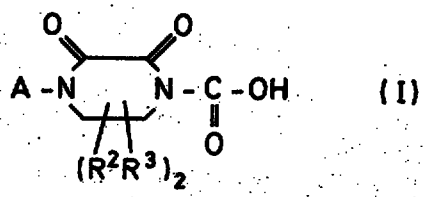
(19)



(54) 2,3-DIOXOPIPERAZINE DERIVATIVES

(71) We, TOYAMA CHEMICAL CO. LTD., a corporation organised 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 a 2,3-dioxo-piperazine derivative, which is a reactive derivative in the carboxyl group of the compound represented by the general formula (I),

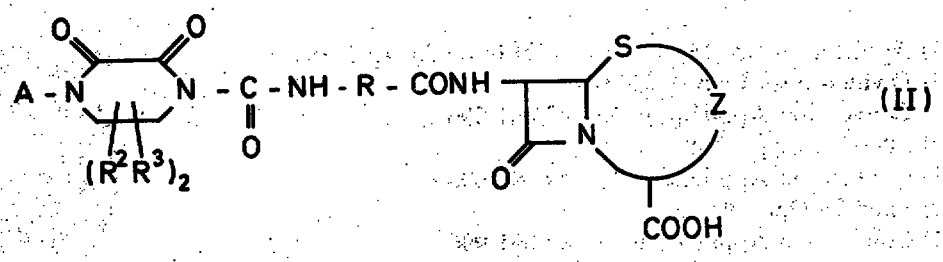


(I)

wherein 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, and reactive derivative represents acid halides, acid azides, acid cyanides, mixed acid anhydrides active esters, or active acid amides.

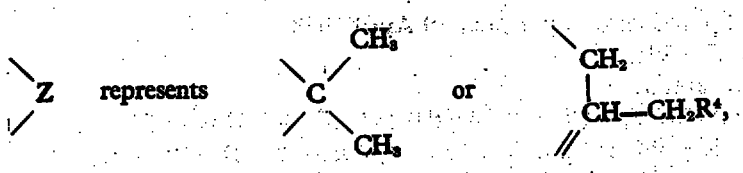
It is an object of this invention to provide novel 2,3-dioxo-piperazine derivatives, which are useful as intermediates of penicillins and cephalosporins having a broad and effective antibacterial activity against Gram-positive and Gram-negative bacteria, particularly against *Pseudomonas aeruginosa*, *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 compounds of formula (II) and non-toxic salts thereof, which were prepared, for example, by reacting 6-aminoacylaminopenicillanic acids or 7-aminoacylaminocephalosporanic acids with 2,3-dioxo-piperazine derivatives of the present invention, 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.).



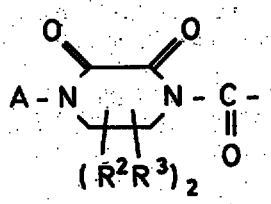
(II)

wherein R represents an amino acid residue;



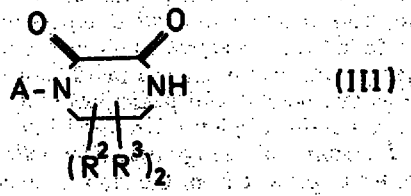
where R^4 represents a hydrogen atom, a quaternary ammonium group or an organic group linked through O, N or S; and R^2, R^3 and A are as defined above.

Excellent characteristics of the compounds of formula (II) and non-toxic salts thereof are derived from the following moiety in the molecule,



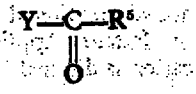
wherein R^2, R^3 and A are as defined above. Therefore, 2,3-dioxo-piperazine derivatives of the present invention, which have the above-mentioned moiety, are useful as intermediates for the compounds of formula (II) and non-toxic salts thereof. The reactive derivative in the carboxyl group of the compound of formula (I), wherein A is an ethyl group, is especially preferable.

The reactive derivative in the carboxyl group of the compound of formula (I) is prepared by the process comprising reacting a compound represented by the general formula (III),



(III)

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



(IV)

wherein Y represents a halogen atom, and R^5 represents a halogen atom or an ester residue, and then, if desired, converting

$$-C-R^5$$
$$\|$$
$$O$$

to different reactive derivative in the carboxyl group by a conventional method.

In the general formulae (I), (II) and (III), A represents a hydrogen atom; 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.

Preferable examples of a reactive derivative in the carboxyl group of the compound of formula (I) are acid halides such as acid chlorides or acid bromides, and active esters such as cyanomethyl ester or trichloromethyl ester.

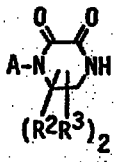
The compound of formula (III) can be easily obtained by reacting N-substituted ethylenediamine with diester of oxalic acid according to the process of the literature reference described below.

Literature reference:

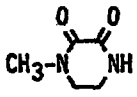
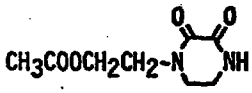
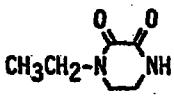
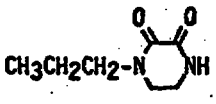
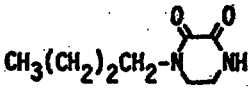
J. L. Riebsomer, J. Org. Chem., *15* 68—73 (1950).

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

Table 1



(III)

Compound	m.p. (recrystallization solvent)	I.R. (cm^{-1})
	158°C (IPA)	$\nu_{C=O}$ 1695, 1660 ν_{NH} 3220
	Oily material	$\nu_{C=O}$ 1730 - 1650 ν_{NH} 3300 - 3200
	124°C ()	$\nu_{C=O}$ 1680, 1650 ν_{NH} 3250
	98 - 100°C ()	$\nu_{C=O}$ 1680, 1650 ν_{NH} 3200, 3100
	111 - 113°C (CCl_4)	$\nu_{C=O}$ 1695, 1670 ν_{NH} 3240, 3150

- cont'd -

Table 1 (Cont'd)

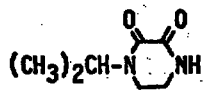
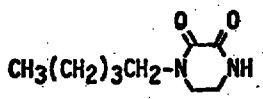
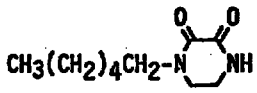
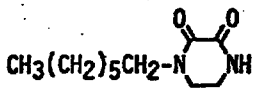
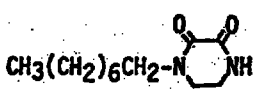
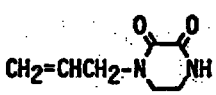
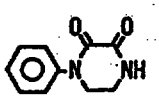
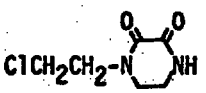
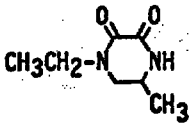
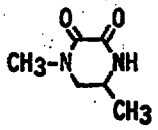
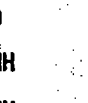
	166 - 167°C ()	$\nu_{C=O}$ 1650 ν_{NH} 3300 - 3200
	104 - 106°C (IPE)	$\nu_{C=O}$ 1700, 1660 ν_{NH} 3200, 3100
	111 - 115°C (IPE)	$\nu_{C=O}$ 1700, 1660 ν_{NH} 3200, 3100
	112 - 115°C (IPE)	$\nu_{C=O}$ 1700, 1660 ν_{NH} 3200, 3100
	116 - 120°C (IPE)	$\nu_{C=O}$ 1700, 1660 ν_{NH} 3225, 3100
	136 - 137°C (Acetone)	$\nu_{C=O}$ 1680, 1655 ν_{NH} 3200, 3100
	202 - 204°C (IPA)	$\nu_{C=O}$ 1690, 1645 ν_{NH} 3260
	128 - 129°C (EtOH)	$\nu_{C=O}$ 1700 - 1650 ν_{NH} 3200 - 3100

Table 1 (Cont'd)

	127 - 128°C (AcOEt)	$\nu_{C=O}$ 1660 ν_{NH} 3200, 3080
	146 - 147°C ()	$\nu_{C=O}$ 1660 ν_{NH} 3200, 3100

Note: IPA = $(CH_3)_2CHOH$

IPE = $(CH_3)_2CHOCH(CH_3)_2$

AcOEt = $CH_3COOCH_2CH_3$

EtOH = CH_3CH_2OH

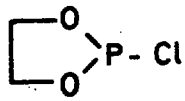
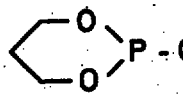
The ester residue for R^5 includes those which are capable of being reacted with the amino group in the acyl group of 6-aminoacylaminopenicillanic acids and 7-aminoacylaminocephalosporanic acids. Particularly, preferable examples thereof are substituted alkoxy group such as trichloromethoxy or cyanomethoxy.

The mode of practice of process of the present invention is explained below.

That is, the compound of formula (III) is reacted with the compound of formula (IV) in at least one inert solvent in the presence or absence of an acid-binding agent. The solvent includes, for example, methylenechloride, chloroform, tetrahydrofuran, dioxane, acetonitrile, methyl acetate, acetone, methyl ethyl ketone, 1,2-dimethoxyethane and benzene. Further, the examples of the acid-binding agent are nitorogen-containing organic bases such as triethylamine, tributylamine, N-methylpiperidine, N-methylmorpholine, pyridine, and diazabicycloundecene. The reaction is ordinarily carried out at a temperature of −60° to 50°C, and the reaction time is ordinarily 30 minutes to 4 hours. In the above reaction, after the addition of a silylating agent or phosphorylating agent to the compound of formula (III) in the presence or absence of an above acid-binding agent, the reaction may be conducted. In this case,



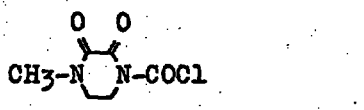
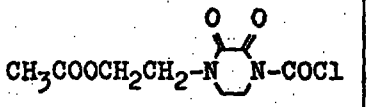
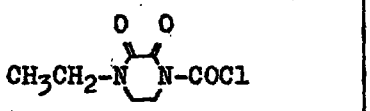
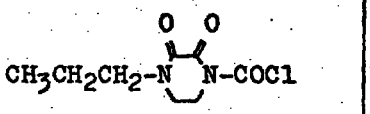
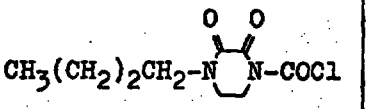
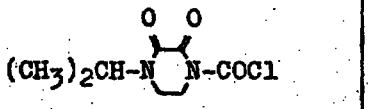
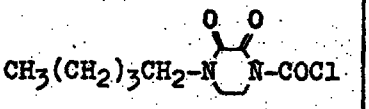
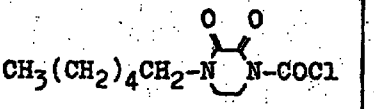
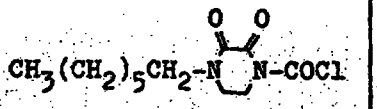
group of the 2,3-dioxopiperazine ring is protected by silylating agent or phosphorylating agent. Example of silylating agents are an organo silylating agent known in the field of penicillin and cephalosporin compound such as $(CH_3)_3SiCl$, $(CH_3)_2SiCl_2$, $(CH_3O)_3SiCl$, or hexamethyldisilazane, and examples of phosphorylating agents are an organic phosphorylating agent known in the field of penicillin and cephalosporin compounds such as

 ,  and $(C_2H_5)_2PCl$

R^5 in the general formula (IV), can be easily converted to a reactive group of different reactive derivatives by a conventional method. After the reaction, the objective compound can be easily obtained according to an ordinary procedure from the reaction solution. The thus obtained product may be, if necessary, recrystallized from or washed with a solvent, for example, acetone, isopropyl alcohol, methylene chloride or ethyl ether, to obtain the pure product.

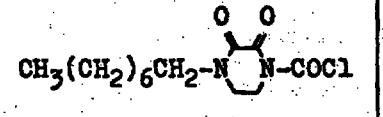
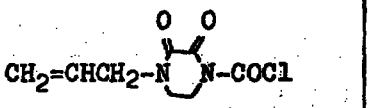
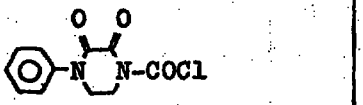
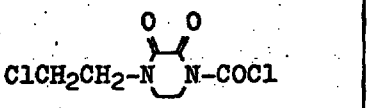
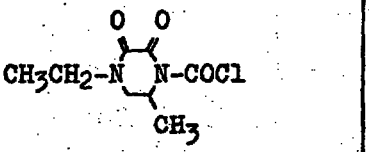
Concrete examples of the compound of the present invention are as set forth in Table 2, but it is needless to say that these are not limitative.

Table 2

	m.p. 94 - 95°C (decomp.) (from CH_2Cl_2-Et_2O)	$\nu_{C=O}$ 1790, 1680
	Oily material	$\nu_{C=O}$ 1790, 1720, 1670
	m.p. 95 - 96°C (decomp.) (from AcOBu)	$\nu_{C=O}$ 1780, 1660
	Oily material	$\nu_{C=O}$ 1780, 1710 - 1640
	"	$\nu_{C=O}$ 1780, 1660
	m.p. 130 - 131°C (decomp.)	$\nu_{C=O}$ 1780, 1660
	Oily material	$\nu_{C=O}$ 1790, 1720 - 1665
	"	$\nu_{C=O}$ 1780, 1720 - 1640
	"	$\nu_{C=O}$ 1780, 1720 - 1640

- cont'd -

Table 2 (Cont'd)

	"	$\nu_{C=O}$ 1780, 1720 - 1640
	Crystal	$\nu_{C=O}$ 1775, 1660 - 1620
	Crystal	$\nu_{C=O}$ 1785, 1720 - 1650
	Oily material	$\nu_{C=O}$ 1790, 1720, 1680
	m.p. 65 - 70°C (decomp.)	$\nu_{C=O}$ 1785, 1680

Note: $Et_2O = CH_3CH_2OCH_2CH_3$

$AcOBu = CH_3COO(CH_2)_3CH_3$

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

Example 1.

(1) Into a mixture comprising 8 g of a diethyl ester of oxalic acid and 8 ml of ethanol was dropped at room temperature 4.4 g of N-ethyl ethylenediamine. The resulting mixture was allowed to react for 3 hours, and then heated to remove the ethanol. Subsequently, the residue was recrystallized from 10 ml of dioxane to obtain 5.4 g of 1-ethyl-2,3-dioxo-piperazine, m.p. 124°C, yield 76.0%.

(2) To a suspension of 0.71 g of the above-mentioned 1-ethyl-2,3-dioxo-piperazine in 15 ml of anhydrous dioxane were added with stirring 0.70 g of trimethylsilyl chloride and 0.83 ml of triethylamine. The resulting mixture was stirred at room temperature for 20 hours to deposit triethylamine hydrochloride. This hydrochloride was separated by filtration, and the filtrate was dropped at 5° to 10°C into a solution of 0.70 g of phosgene in 10 ml of anhydrous tetrahydrofuran. Subsequently, the resulting mixture was reacted at 5° to 10°C for 30 minutes and at room temperature for 2 hours, and then the solvent was removed by distillation under reduced pressure to obtain 1.0 g of pale yellow crystals of 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1780, 1660

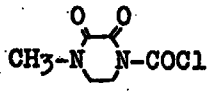
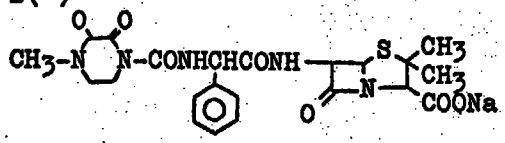
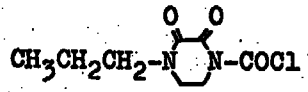
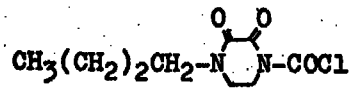
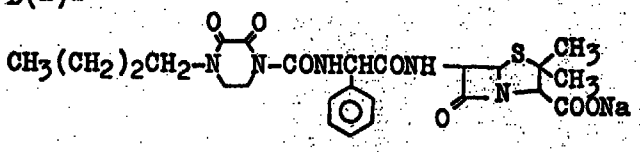
(3) A suspension of 1.75 g of 6-[D(−)-α-aminophenylacetamido]penicillanic acid in 50 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by addition of triethylamine with stirring to form a solution. This solution was cooled to 0° to 5°C, and then 7 ml of an anhydrous tetrahydrofuran solution containing 1.0 g of the aforesaid 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride

was dropped into the solution. During this period, the pH of the reaction solution was maintained at 7.5 to 8.0 by gradual addition of triethylamine. The resulting mixed solution was reacted at said temperature for 30 minutes and then at 5° to 10°C for 1 hour, while maintaining the pH thereof at 7.5 to 8.0. After the reaction, the tetrahydrofuran was removed by distillation under reduced pressure, and the residue was dissolved in 20 ml of water and then washed two times with 20 ml of ethyl acetate. To the aqueous layer was again added 50 ml of ethyl acetate, and the resulting mixture was adjusted to a pH of 1.5 by gradual addition of dilute hydrochloric acid with ice-cooling. Subsequently, the ethyl acetate layer was separated off, sufficiently washed with water, and then dried over anhydrous magnesium sulfate. Into the thus treated layer was dropped 10 ml of an ethyl acetate solution containing 0.83 g of sodium 2-ethylhexanoate to deposit white crystals. The deposited crystals were collected by filtration, sufficiently washed with ethyl acetate, washed with diethyl ether, and then dried to obtain 2.4 g of a sodium salt of 6-[D(−)-α-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 183—185°C (decomp.), yield 89%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1765 (lactam), 1720—1670 (—CON<), 1600 ($—COO^{\ominus}$)
NMR ($(CD_3)_2SO + D_2O$) τ values: 2.62 (5H), 4.31 (1H), 4.50 (1H), 4.70 (1H), 6.05 (1H), 6.35—6.65 (6H), 8.49 (3H), 8.60 (3H), 8.91 (3H)

The above-mentioned operation was repeated, except that the 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of 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

Reactive derivative of compound of formula (I)	compound of formula (II)
	D(-)-  m.p. (decomp.) 170°C, yield 84 %
	D(-)-  m.p. (decomp.) 170°C, yield 86 %
	D(-)-  m.p. (decomp.) 190°C, yield 87 %

- cont'd -

Table 3 (Cont'd)

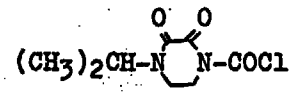
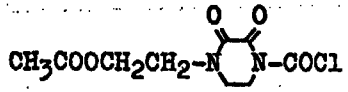
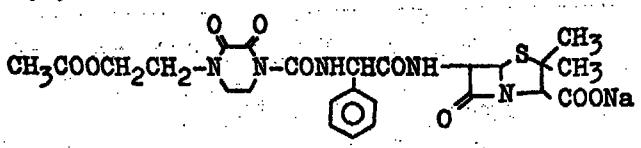
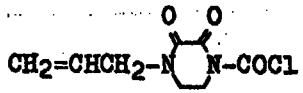
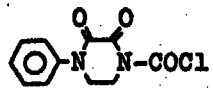
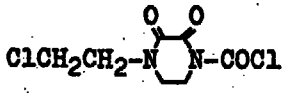
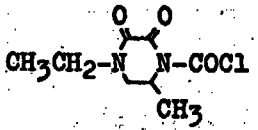
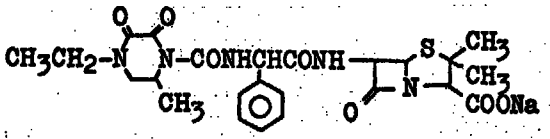
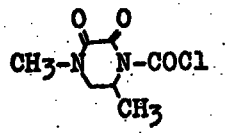
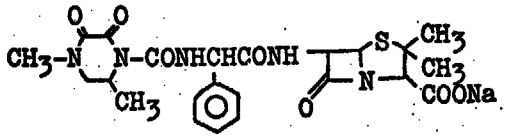
	D(-)-  m.p. (decomp.) 186°C, yield 85 %
	D(-)-  m.p. (decomp.) 175°C, yield 79 %
	D(-)-  m.p. (decomp.) 198 - 200°C, yield 75 %

Table 3 (Cont'd)

	D(-)-  m.p. (decomp.) 185 - 187°C, yield 88 %
	D(-)-  m.p. (decomp.) 210°C, yield 83 %
	D(-)-  m.p. (decomp.) 175 - 177°C, yield 76 %

- cont'd -

Table 3 (Cont'd)

	D(-)-  m.p. (decomp.) 177 - 178°C, yield 79 %

Example 2.

(1) To a solution of 0.92 g of 1-n-pentyl-2,3-dioxo-piperazine in 15 ml of anhydrous dioxane were added 1.1 ml of triethylamine and 1.08 g of trimethylsilyl chloride. The resulting mixture was stirred at room temperature for 20 hours to form triethylamine hydrochloride. This hydrochloride was separated by filtration, and the filtrate was dropped at 0° to 5°C into a solution of 0.6 g of phosgene in 10 ml of anhydrous tetrahydrofuran. Subsequently, the resulting mixture was reacted at 5° to 10°C for 30 minutes and then at room temperature for 2 hours. Thereafter, the solvent was removed by distillation under reduced pressure to obtain 1.21 g of pale yellow, oily 4-n-pentyl-2,3-dioxo-1-piperazinocarbonyl chloride.

IR (film) cm^{-1}: $\nu_{C=O}$ 1790, 1720—1665

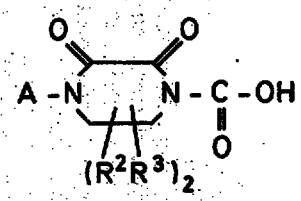
(2) A suspension of 1.70 g of a monohydrate of 7-[D(−)-α-aminophenylacetamido]-3-methyl-Δ^3-cephem-4-carboxylic acid in 50 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by addition of triethylamine with stirring to form a solution. This solution was cooled to 0° to 5°C, and 7 ml of an anhydrous tetrahydrofuran solution containing 1.21 g of the 4-n-pentyl-2,3-dioxo-1-piperazinocarbonyl chloride obtained in (1) was dropped into the solution. During this period, the pH of the solution was maintained at a pH of 7.5 to 8.0 by addition of triethylamine. Subsequently, the resulting mixed solution was reacted at 0° to 5°C for 1 hour and then at 5° to 10°C for 2 hours while maintaining the pH thereof at 7.5 to

8.0. After the reaction, the tetrahydrofuran was removed by distillation under reduced pressure, and the residue was dissolved in 20 ml of water and then washed two times with 20 ml of ethyl acetate. The aqueous layer was again charged with 40 ml of ethyl acetate, and then adjusted to a pH of 1.5 by gradual addition of dilute hydrochloric acid with ice-cooling. Subsequently, the ethyl acetate layer was separated off, washed with water, and then dried over anhydrous magnesium sulfate. Thereafter, 10 ml of an ethyl acetate solution containing 0.75 g of sodium 2-ethylhexanoate was dropped into the layer at 0° to 5°C to deposit white crystals. The deposited crystals were collected by filtration, and washed with ethyl acetate and then with diethyl ether to obtain 1.95 g of a sodium salt of 7-[D(−)-α-(4-n-pentyl-2,3-dioxo-1-piperazinocarbonylamino)-phenylacetamido]-3-methyl-Δ³-cephem-4-carboxylic acid, m.p. 164—166°C (decomp.), yield 75%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1750 (lactam), 1720—1660 (—CON<), 1590 ($—COO^{\ominus}$)
NMR (d_6-DMSO + D_2O) τ values: 2.58 (5H, s), 4.33 (1H, s), 4.49 (1H, d), 5.17 (1H, d), 6.10 (2H, bs), 6.42—6.87 (6H, m), 8.09 (3H, s), 8.60—8.90 (6H, bs), 9.12 (3H, t)

WHAT WE CLAIM IS:—

1. A reactive derivative in the carboxyl group of the compound represented by the general formula (I),



(I)

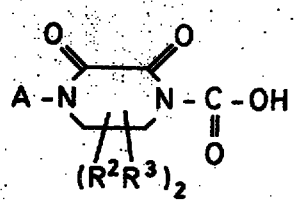
wherein R^2 and R^3 are linked to the same carbon atom, and each of R^2 and R^3, which may be the same or different, represents individually a hydrogen atom or an alkyl group; and A represents a hydrogen atom or an unsubstituted or substituted alkyl, alkenyl, aryl or aralkyl group, and a reactive derivative represents acid halides, acid azides, acid cyanides, mixed acid anhydrides active esters or active acid amides.

2. A compound according to Claim 1, wherein A is a methyl or ethyl group; R^2 and R^3 are individually a hydrogen atom or a methyl group; and a reactive derivative is an acid halide or trichloromethyl ester.

3. 4-Ethyl-2,3-dioxo-1-piperazinocarbonyl chloride.

4. 4-Ethyl-1-trichloromethoxycarbonyl-2,3-dioxo-piperazine.

5. A process for producing a reactive derivative in the carboxyl group of the compound represented by the general formula (I),



(I)

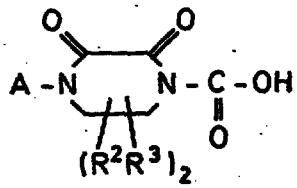
wherein R^2 and R^3 are linked to the same carbon atom, and each of R^2 and R^3 which may be the same or different, represent individually a hydrogen atom or an alkyl group; A represents a hydrogen atom, an unsubstituted or substituted alkyl, alkenyl, aryl or aralkyl group; and a reactive derivative represents acid halides, aicd azides, acid cyanides, mixed acid anhydrides, active esters, and active acid amides, which comprises reacting a compound represented by the general formula (III),

8.0. After the reaction, the tetrahydrofuran was removed by distillation under reduced pressure, and the residue was dissolved in 20 ml of water and then washed two times with 20 ml of ethyl acetate. The aqueous layer was again charged with 40 ml of ethyl acetate, and then adjusted to a pH of 1.5 by gradual addition of dilute hydrochloric acid with ice-cooling. Subsequently, the ethyl acetate layer was separated off, washed with water, and then dried over anhydrous magnesium sulfate. Thereafter, 10 ml of an ethyl acetate solution containing 0.75 g of sodium 2-ethylhexanoate was dropped into the layer at 0° to 5°C to deposit white crystals. The deposited crystals were collected by filtration, and washed with ethyl acetate and then with diethyl ether to obtain 1.95 g of a sodium salt of 7-[D(−)-α-(4-n-pentyl-2,3-dioxo-1-piperazinocarbonylamino)-phenylacetamido]-3-methyl-Δ^3-cephem-4-carboxylic acid, m.p. 164—166°C (decomp.), yield 75%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1750 (lactam), 1720—1660 (—CON<), 1590 ($—COO^{\ominus}$)
NMR (d_6-DMSO + D_2O) τ values: 2.58 (5H, s), 4.33 (1H, s), 4.49 (1H, d), 5.17 (1H, d), 6.10 (2H, bs), 6.42—6.87 (6H, m), 8.09 (3H, s), 8.60—8.90 (6H, bs), 9.12 (3H, t)

WHAT WE CLAIM IS:—

1. A reactive derivative in the carboxyl group of the compound represented by the general formula (I),



(I)

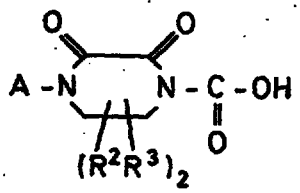
wherein R^2 and R^3 are linked to the same carbon atom, and each of R^2 and R^3, which may be the same or different, represents individually a hydrogen atom or an alkyl group; and A represents a hydrogen atom or an unsubstituted or substituted alkyl, alkenyl, aryl or aralkyl group, and a reactive derivative represents acid halides, acid azides, acid cyanides, mixed acid anhydrides active esters or active acid amides.

2. A compound according to Claim 1, wherein A is a methyl or ethyl group; R^2 and R^3 are individually a hydrogen atom or a methyl group; and a reactive derivative is an acid halide or trichloromethyl ester.

3. 4-Ethyl-2,3-dioxo-1-piperazinocarbonyl chloride.

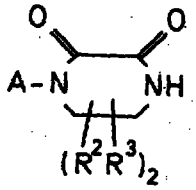
4. 4-Ethyl-1-trichloromethoxycarbonyl-2,3-dioxo-piperazine.

5. A process for producing a reactive derivative in the carboxyl group of the compound represented by the general formula (I),



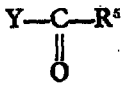
(I)

wherein 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, represent individually a hydrogen atom or an alkyl group; A represents a hydrogen atom, an unsubstituted or substituted alkyl, alkenyl, aryl or aralkyl group; and a reactive derivative represents acid halides, aicd azides, acid cyanides, mixed acid anhydrides, active esters, and active acid amides, which comprises reacting a compound represented by the general formula (III),



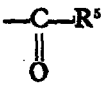
(III)

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



(IV)

wherein Y represents a halogen atom, and R^5 represents a halogen atom or an ester residue, in inert solvents in the presence or absence of an acid-binding agent at a temperature of −60° to 50°C, and then, if desired, converting



to different reactive derivative in the carboxyl group by a conventional method.

6. A process according to Claim 1, wherein the reaction in conducted after the addition of a silylating agent or a phosphorylating agent to the compound of formula (III) in the presence or absence of an acid-binding agent.

7. A process according to Claim 1 or 2, wherein a reactive derivative in the carboxyl group of the compound of formula (I) is an acid halide or an active ester of the compound of formula (I) which A is an ethyl group.

8. A process according to Claim 3, wherein a reactive derivative in the carboxyl group of the compound of formula (I) is 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride or 4-ethyl-1-trichloromethoxycarbonyl-2,3-dioxo-piperazine.

9. A reactive derivative as claimed in Claim 1 and substantially as hereinbefore set forth.

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