

PATENT SPECIFICATION

(11) 1 517 098

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- (21) Application No. 32136/76 (22) Filed 2 Aug. 1976
 (31) Convention Application No. 50/104 046
 (32) Filed 29 Aug. 1975
 (31) Convention Application No. 50/104 046
 (32) Filed 18 Feb. 1976 in
 (33) Japan (JP)
 (44) Complete Specification published 12 July 1978
 (51) INT CL² C07D 499/48, 501/20
 (52) Index at acceptance

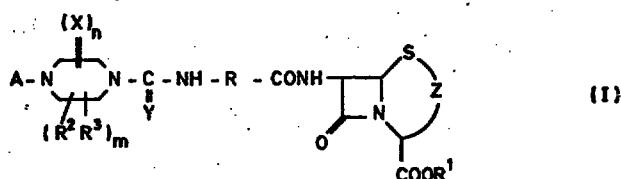


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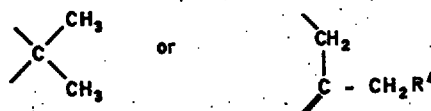
(54) A PROCESS FOR PRODUCING NOVEL PENICILLINS AND CEPHALOSPORINS

(71) We, TOYOMA 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 process for producing a compound represented by the general formula (I).



wherein R represents an amino acid residue; R¹ represents a hydrogen atom, a carboxyl-protecting group or a salt forming cation; n represents 1 or 2; X represents an oxygen atom, and is linked to the carbon atom at the 2-, 3- or 5-position of the piperazine ring, and when n is 2, any two of the 2-, 3- and 5-positions may be occupied by two X's; m represents 4-n; R² and R³ are in pairs linked to the same carbon atom, m pairs of R² and R³ may be the same or different, and R² and R³ individually represent a hydrogen atom, an alkyl group, an aryl group or an alkyloxycarbonylalkyl group; or any pair of R² and R³ together with the common carbon atom may form a cycloalkyl ring; A represents a hydrogen atom, or an unsubstituted or substituted alkyl, alkenyl, alkadienyl, cycloalkyl, aryl, acyl, aralkyl, acyloxyalkyl, alkyloxycarbonyl, alkylsulfonyl, carbamoyl or acylcarbamoyl group; Y represents an oxygen or sulfur atom; and >Z represents



where R⁴ represents a hydrogen atom, an azido group, or an alkoxy, aryloxy, aralkyloxy, acyloxy, alkylthio, arylthio, aralkylthio, acylthio, oxazolylthio, thiazolylthio, isoxazolylthio, isothiazolylthio, imidazolylthio, pyrazolylthio, pyridylthio, pyrazinylthio, pyrimidinylthio, pyridazinylthio, quinolylthio,

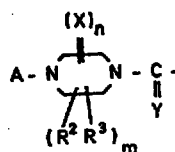
isoquinolylthio, quinazolylthio, indolylthio, indazolylthio, oxadiazolylthio, thiadiazolylthio, triazolylthio, tetrazolylthio, triazinylthio, benzimidazolylthio, benzoxazolylthio, benzothiazolylthio, triazolopyridylthio, or purinylthio group which may be substituted by groups selected from a halogen atom, an alkyl group, an alkoxy group, an alkylthio group, a nitro group, a cyano group, or an acyl group.

In one aspect, it is an object of this invention to provide valuable penicillins and cephalosporins, which have a broad anti-bacterial spectrum against Gram-positive and Gram-negative bacteria, and which are quite effective as therapeutic drugs for human and animal infectious diseases.

In another aspect, it is also an object to provide semi-synthetic penicillins and cephalosporins having an effective anti-bacterial activity against Gram-negative bacteria, particularly *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Proteus* species, and high resistance to β -lactamase produced from bacteria, as it is significant at present from the clinical standpoint.

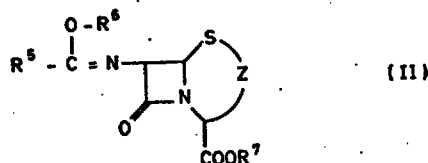
Furthermore, it is another object to provide a process for producing the compound having the property as mentioned above.

On the other hand, as a result of our research, it was found that the novel compound of the general formula (I) which is prepared by bonding the moiety,

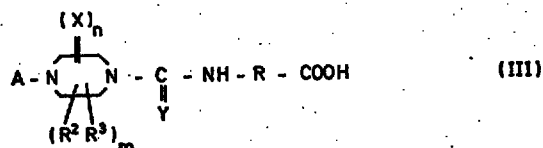


wherein A, X, Y, R^2 , R^3 , m and n are as mentioned above, to the amino group in the acyl group of 6-(aminoacyl-amino)penicillanic acid or 7-(aminoacylamino)cephalosporanic acids, can sufficiently satisfy the above-mentioned aim and have extremely valuable therapeutic effects (Belgium Patent No. 828692).

This invention provides a process for producing penicillins and cephalosporins represented by the general formula (I), which comprises (a) reacting a compound represented by the general formula (II),

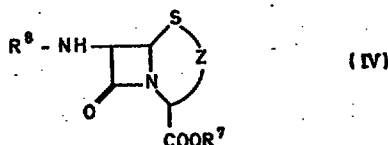


wherein R^5 represents a residue of an acyl group devoid of carbonyl group; R^6 represents an alkyl, aralkyl, or alkoxyalkyl group; R^7 represents a carboxyl-protecting group; and $>Z$ is the same as above, with a reactive derivative, with respect to the carboxyl group of a compound of formula (III),



wherein R, R^2 , R^3 , A, X, Y, m and n are the same as above, and (b) hydrolyzing the compound obtained in step (a), and, if desired, treating the hydrolyzation product thus obtained by a conventional method to remove the carboxyl-protecting group R^7 .

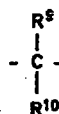
This invention also provides a process for producing the compound of formula (I), which comprises (a) converting a compound of formula (IV),



wherein R^8 represents an acyl group; and R^7 and $>Z$ are the same as above, by iminohalogenation reaction to the corresponding imino halide compound, (b) converting the imino halide compound obtained in step (a) by iminoetherification reaction to the corresponding imino ether compound, (c) reacting the imino ether compound obtained in step (b) with a reactive derivative, with respect to the carboxyl group of the compound of formula (III), and then (d) hydrolyzing the compound obtained in step (c), and, if desired, treating the hydrolyzation product thus obtained by a conventional method to remove the carboxyl-protecting group R^7 .

Hereinafter, the invention will be further explained in detail.

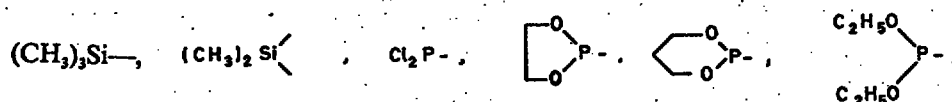
That is to say, in the general formulae (I) and (III), R represents an amino acid residue. Examples of such amino acid residues include residues of amino acids derived from various aliphatic, araliphatic, aromatic, alicyclic and heterocyclic compounds, which amino acids may have the amino group at a 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 R^9 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, pyrazyl, pyrimidyl, pyridazyl, quinolyl, isoquinolyl, indolyl, indazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-thiadiazolyl or 1,2,4-thiadiazolyl. Each group represented by said R^9 may be substituted by halogen atoms or various groups, for example, hydroxyl, nitro, alkyl, alkoxy, alkylthio, acyl, or alkylsulfonylamino; R^{10} represents a hydrogen atom; and R^9 and R^{10} together with the common carbon atom may form a cycloalkyl ring such as cyclohexyl or cycloheptyl; a cycloalkenyl ring such as cyclopentenyl or cyclohexenyl; or a cycloalkadienyl ring such as cyclopentadienyl or cyclohexadienyl.

These amino acids include optically active compounds and racemic compounds.

In the general formulae (I), (II) and (IV), the carboxyl-protecting group represented by symbols R^1 and R^7 , respectively, may be any of those which have heretofore been used in the field of penicillin or cephalosporin type compounds. Concretely, the carboxyl-protecting group includes (1) ester-forming groups capable of being removed by catalytic reduction, chemical reduction or treatment under mild conditions, e.g. aralkyl groups such as benzyl, 4-nitrobenzyl, diphenylmethyl, trityl and 3,5-di(tert.-butyl)-4-hydroxybenzyl, alkyl groups such as tert.-butyl and trichloroethyl, phenylcarbonylalkyl groups such as 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 by enzymes in a living body, e.g. acyloxyalkyl groups such as pivaloyloxymethyl, and phthalidyl group; (3) silicon-, phosphorus- or tin-containing groups which are capable of being easily removed by treating with H_2O or an alcohol, such as



$(C_4H_9)_3Sn-$. The examples of the carboxyl-protecting 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 DOS 2,301,014; 2,253,287 and 2,337,105, and may be used in this invention.

In general formula (I), the salt-forming cation represented by symbol R^1 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 and potassium salt; alkaline earth metal salts such as calcium salt or magnesium salt. In addition to the above cations, there may be used cations capable of forming salts with other nitrogen-containing organic bases, such as trimethylamine, triethylamine, tributylamine, pyridine, dimethylaniline, N-methylpiperidine, N-methylmorpholine, diethylamine or dicyclohexylamine.

In the general formulae (I) and (III), R^2 and R^3 individually represent a hydrogen atom; an alkyl group such as methyl, ethyl, propyl, butyl, pentyl, hexyl or octyl; an aryl group such as phenyl, or naphthyl; an alkoxycarbonylalkyl group such as methoxycarbonylmethyl or ethoxycarbonylmethyl. Furthermore, R^2 and R^3 together with the common carbon atom may form a cycloalkyl ring such as cyclopentyl, cyclohexyl, or cycloheptyl.

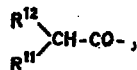
In the general formulae (I) and (III), A represents a hydrogen atom; an alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, heptyl, octyl or dodecyl; an alkenyl group such as vinyl, propenyl or butenyl; an alkadienyl group such as 1,3-butadienyl, 1,3-pentadienyl or 3,7-dimethyl-2,6-decadienyl; a cycloalkyl group such as cyclopentyl, cyclohexyl or cycloheptyl; an aryl group such as phenyl or naphthyl; an acyl group such as formyl, acetyl, propionyl, isovaleryl, caproyl, enanthoyl, carpryloyl, palmitoyl, stearoyl, acryloyl, cyclohexanecarbonyl, benzoyl, phenylglycyl, furoyl or thenoyl; an aralkyl group such as benzyl or phenethyl; an acyloxyalkyl group such as acetyloxyethyl, pivaloyloxymethyl or benzoyloxymethyl; an alkoxycarbonyl group such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl or butoxycarbonyl; an alkylsulfonyl group such as methanesulfonyl, ethanesulfonyl, propanesulfonyl or butanesulfonyl; a carbamoyl group such as carbamoyl, N-alkylaminocarbamoyl (e.g. N-methylaminocarbonyl), N-ethylaminocarbonyl, N-propylaminocarbonyl or N-butylaminocarbonyl, N-arylaminocarbonyl (e.g. N-phenylaminocarbonyl), N,N-dialkylaminocarbonyl (e.g. N,N-dimethylaminocarbonyl or N,N-diethylaminocarbonyl), cyclic aminocarbonyl (e.g. pyrrolidinocarbonyl, piperidinocarbonyl or morpholinocarbonyl); or an acylcarbamoyl group such as N-acetylcarbamoyl, N-propionylcarbamoyl, N-butyrylcarbamoyl, N-benzoylcarbamoyl, N-furoylcarbamoyl or N-thenoylcarbamoyl. 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, amino groups (e.g. dialkylamino or cyclic amino), carboxyl groups, acyl groups, etc.

Further, R^4 represents a hydrogen atom, an azide group, alkoxy groups such as methoxy, ethoxy or propoxy; aryloxy group such as phenoxy or naphthoxy; aralkyloxy groups such as benzyloxy or phenethyloxy; acyloxy groups such as acetyloxy, propionyloxy, butyryloxy, benzoyloxy, naphthoyloxy, cyclopentanecarbonyloxy, cyclohexanecarbonyloxy, furoyloxy or thenoyloxy; alkylthio groups such as methylthio, ethylthio or propylthio; arylthio groups such as phenylthio, or (1- or 2-)naphthylthio; aralkylthio groups such as benzylthio or phenethylthio; acylthio groups such as acetylthio, propionylthio, butyrylthio, benzoylthio, (1- or 2-)naphthoylthio, cyclopentanecarbonylthio, cyclohexanecarbonylthio, furoylthio, thenoylthio, isothiazolecarbonylthio, isoxazolecarbonylthio, thiadiazolecarbonylthio or triazolecarbonylthio; an oxazolylthio group, or a group selected from thiazoylthio, isoxazolylthio, isothiazoylthio, imidazolylthio, pyrazolylthio, pyridylthio, pyrazinylthio, pyrimidinylthio, pyridiazinylthio, quinolylthio, isoquinolylthio, quinazolylthio, indolylthio, indazolylthio, oxadiazolylthio, thiadiazolylthio, triazolylthio, tetrazolylthio, triazinylthio, benzimidazolylthio, benzoxazolylthio, benzothiazolylthio, triazolopyridylthio or purinylthio.

Each of the groups except for the hydrogen atom and the azido group mentioned above for R^4 may be substituted by groups selected from halogen atoms, alkyl groups, alkoxy groups, alkylthio groups, nitro groups, cyano groups, or acyl groups.

In the general formula (IV), R^5 is an acyl group represented by R^5-CO- wherein R^5 is a residue of the acyl group devoid of carbonyl group. The acyl group is the acyl group which has heretofore been known in the field of penicillin or

cephalosporin type compounds. Examples of the acyl group include acyl groups derived from various aliphatic, aromatic, araliphatic, alicyclic and heterocyclic compounds. Preferable as said acyl group is an acyl group represented by the formula



wherein R^{11} is an alkyl group such as methyl, ethyl, propyl or butyl; an aryl group such as phenyl or naphthyl; an aralkyl group such as benzyl or phenethyl; an aryloxy group such as phenoxy or naphthoxy; or a γ -N-protected-amino- γ -protected carboxypropyl group such as γ -N-ethoxycarbonylamino- γ -benzhydryloxy-carbonylpropyl, γ -N-ethoxycarbonylamino- γ -trimethylsilyloxy-carbonylpropyl, γ -N-phenylcarbamoylamino- γ -benzhydryloxy-carbonylpropyl or γ -N-phenylcarbamoylamino- γ -trimethylsilyloxy-carbonylpropyl; and R^{12} represents a hydrogen atom; a hydroxyl group; a halogen atom such as chlorine or bromine; an alkyl group such as methyl, ethyl or propyl. Each of the groups mentioned above for said R^{11} and R^{12} may be substituted by any of such substituents as, for example, halogen atoms, hydroxyl groups, nitro groups, alkyl groups, alkoxy groups, alkylthio groups, or acyl groups.

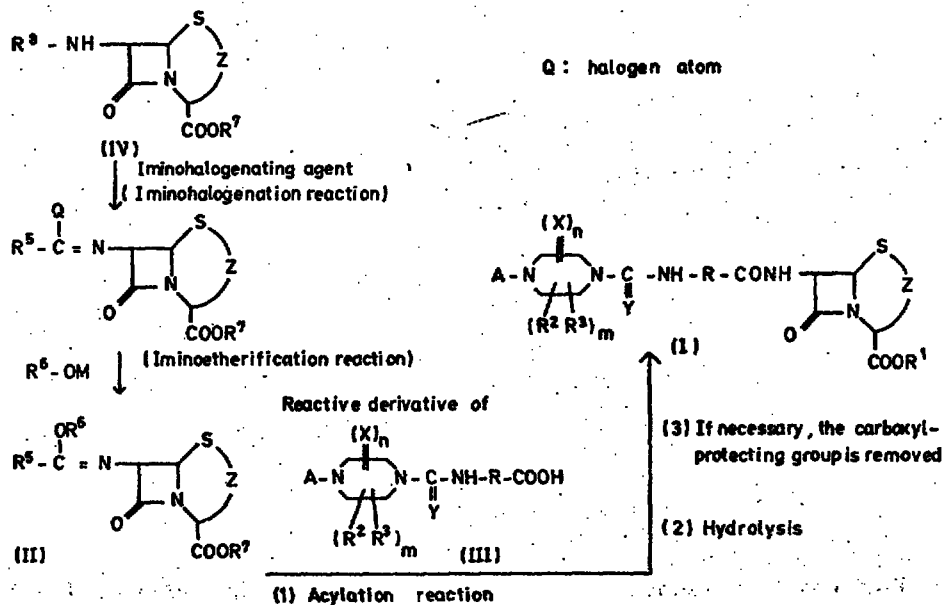
The compound of formula (III) can be prepared according to the method disclosed in Belgian Patent No. 828692.

The reactive derivative in the carboxyl group of the compound of formula (III) is, for example, an acid halide, an acid anhydride, a mixed acid anhydride with an organic or inorganic acid, an active acid amide, or an active ester. Concretely, the reactive derivatives are, for example, an acid chloride; an acid azide; an acid cyanide; a mixed acid anhydride with an aliphatic carboxylic, aromatic carboxylic, alkyl carbonic, aralkyl carbonic, dialkylphosphoric, diphenylphosphoric, methanesulfonic, or p-toluenesulfonic acid; an acid amide with an imidazole, 4-substituted-imidazole, dimethylpyrazole, triazole, tetrazole or saccharin; a cyanomethyl ester; a substituted-phenyl ester; and a substituted-phenyl thioester.

Furthermore, as the reactive derivative with respect to the carboxyl group of the compound of formula (III), there may be used a reactive derivative produced by reacting the compound of formula (III) with an activating agent, such as N,N'-dicyclohexyl carbodiimide, N-cyclohexyl-N'-morpholinoethyl carbodiimide, N,N'-diethyl carbodiimide, N,N'-carbonyl di(2-methylimidazole), dimethylchloroformiminium chloride, dimethylethoxyformiminium chloride, trialkyl ester of phosphorous acid, phosphorus oxychloride, phosphorus trichloride, thionyl chloride or oxalyl chloride.

Next, the modes of practice of the process are explained below.

According to the following reaction scheme, the objective compound of the general formula (I) can be prepared.



12
14
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The iminohalogenation reaction, which is a reaction of the compound of formula (IV) with an iminohalogenating agent, is carried out to form the corresponding imino halide compound. As the iminohalogenating agents, there are frequently used, for example, phosphorus trichloride, phosphorus pentachloride, phosphorus tribromide, phosphorus pentabromide, phosphorus oxychloride, thionyl chloride, and phosgene. This reaction is carried out in a solvent or solvents. As the solvents, there are frequently used, for example, methylene chloride, chloroform, benzene, dichloroethane, trichloroethane, and tetrachloroethane. Furthermore, there may be used other inert solvents such as tetrahydrofuran, dioxane or dimethoxyethane. The iminohalogenation reaction conditions are not particularly limited, though the reaction is ordinarily conducted while the reaction medium is cooled.

The thus obtained imino halide compound is allowed to react with an iminoetherificating agent to form the corresponding imino ether compound (iminoetherification reaction). The iminoetherificating agent is a compound represented by the formula, R^6-OM , wherein R^6 represents an alkyl, aralkyl or alkoxyalkyl group, and M represents a hydrogen atom, or an alkali metal atom. More particularly, the iminoetherificating agent include, for example, alcohols such as methyl alcohol, ethyl alcohol, propyl alcohol, isopropyl alcohol, butyl alcohol, isobutyl alcohol, tert.-butyl alcohol, benzyl alcohol or methoxymethyl alcohol, and alcoholates of such alcohols with alkali metals. The iminoetherification reaction conditions are not particularly limited, though the reaction is ordinarily conducted while the reaction medium is cooled or heated. The iminoetherification reaction mixture may be concentrated by evaporation under reduced pressure to remove the iminohalogenating agent and the iminoetherificating agent, or the reaction mixture may be allowed to proceed to the next reaction as it is.

The acylation reaction, which is a reaction of the compound of formula (II) with the reactive derivative in the carboxyl group of the compound of formula (III), is ordinarily conducted while the reaction medium is cooled or heated. When the acylation reaction is conducted in the presence of an additional solvent such as dimethylformamide, satisfactory results may be obtained. However the acylation reaction conditions are not particularly limited.

Each of the iminohalogenation reaction, the iminoetherification reaction and the acylation reaction can be conducted, as it is known, in the presence of an organic base or bases such as *N,N*-dimethylaniline, pyridine, quinoline, picoline, lutidine, trialkylamine, or dialkylbenzylamine.

The thus obtained reaction product is hydrolyzed to remove the acyl group R^5 . In this case, the hydrolysis proceeds sufficiently by pouring the preceding reaction mixture into water. The carboxyl-protecting group R^7 may also be hydrolyzed simultaneously depending upon the kind of the carboxyl-protecting group, and converted into a hydrogen atom. Furthermore, the remaining carboxyl-protecting group which has not been hydrolyzed can be removed, if desired. The reaction to remove the carboxyl-protecting group is varied depending upon the kind of carboxyl-protecting group, and the reaction is conducted by an ordinary known procedure such as catalytic reduction, chemical reduction, or treatment under mild conditions. Particularly, when R^7 is a phenacyl or benzyhydril group the carboxyl-protecting group can be easily removed by treating with sodium benzenethiolate in dimethylformamide or tetrahydrofuran, or with trifluoroacetic acid in anisole.

The thus obtained penicillin or cephalosporin is isolated according to the ordinary procedure.

The compound of the general formula (I) wherein R^1 is a non-toxic salt-forming cation is easily obtained in the usual procedure from the compound of the general formula (I) wherein R^1 is a hydrogen atom or a carboxyl-protecting group.

The thus obtained objective compounds of the general formula (I) have not only a broad anti-bacterial spectrum against Gram-positive and Gram-negative bacteria, but also supremely high anti-bacterial activity against *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Proteus* species. Furthermore, these compounds are quite effective as therapeutic drugs for human and animal infectious diseases.

According to this invention, the objective compound of the general formula (I) can effectively be prepared in a series of reactions from the compound of the general formula (II) which is easily obtainable.

Procedures for producing the compounds of the present invention are shown

below with reference to the examples, wherein the compound prepared using the reactive derivative of D(—) isomer of the compound of formula III is shown as D(—) or as D(—) isomer.

EXAMPLE 1.

2.9 g of a triphenylmethyl ester of 6-(phenylacetamido)penicillanic acid and 2.06 ml of N,N-dimethylaniline were dissolved in 30 ml of methylene chloride, and 1.15 g of phosphorus pentachloride was added to this solution at -25°C . The mixture was allowed to react at -30° to -20°C for 1.5 hours, followed by adding dropwise 20 ml of methyl alcohol while keeping the temperature at -30° to -20°C . The reaction mixture was further allowed to react at the same temperature for 2.5 hours, followed by addition of 3.43 ml of N,N-dimethylaniline.

On the other hand, 1.76 g of D(—)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)phenylacetic acid and 0.76 ml of N,N-dimethylaniline were dissolved in a mixed solvent consisting of 8 ml of methylene chloride and 4 ml of dimethylformamide. The solution was cooled to -10° to -5°C , followed by adding dropwise 0.65 g of ethyl chlorocarbonate, and stirred at the same temperature for 30 minutes. After the reaction mixture was cooled to -25°C , it was added to the preceding reaction mixture.

The resulting mixture was allowed to react at -25°C for 2 hours, and then freed of the solvent by evaporation under reduced pressure. The residue was dissolved in a mixed solvent consisting of 30 ml of water and 50 ml of ethyl acetate. The solution was adjusted to a pH of 1.0 by addition of dilute hydrochloric acid with ice-cooling, and stirred for 15 minutes. The organic layer was separated from the aqueous layer, followed by addition of 20 ml of water, and adjusted to a pH of 7.0 by addition of sodium hydrogencarbonate with ice-cooling. The resulting aqueous layer was separated from the organic layer, followed by addition of 20 ml of ethyl acetate, and then adjusted to a pH of 2.0 by addition of dilute hydrochloric acid with stirring. The mixture was further stirred at 15° to 20°C for 3 hours to deposit crystals, which were collected by filtration to obtain 1.2 g of a monohydrate of 6-/D(—)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)-phenylacetamido/penicillanic acid, m.p. (decomp.) 154° — 156°C , yield 45%.

IR(KBr) cm^{-1} :

$\nu_{\text{C=O}}$ 1775 (lactam), 1735 ($-\text{COOH}$), 1705, 1680, 1665 ($-\text{CON}-$)

NMR($(\text{CD}_3)_2\text{SO}$)

τ values: 0.20 (1H, d), 0.76 (1H, d), 2.69 (5H, s), 4.32 (1H, d), 4.53 (1H, q), 4.64 (1H, d), 5.00 (3H, br), 5.83 (1H, s), 6.13 (2H, bs), 6.49 (2H, bs), 6.62 (2H, q), 8.44 (3H, s), 8.58 (3H, s), 8.91 (3H, t)

In the same manner as above, the objective compounds of the general formula (I) shown in Table 1 were obtained.

TABLE I

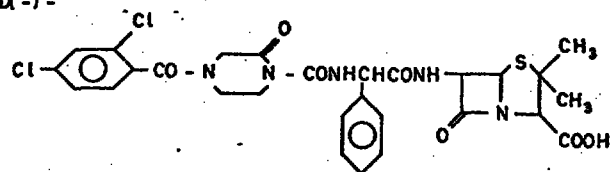
Objective compound of the general formula (I)	
D(-)- <chem>CCCCCCCC(=O)N1CCN(C1)C(=O)Nc2ccccc2C(=O)N3[C@H](C)[C@@H](C(=O)O)[C@@H](S3)c4ccccc4</chem> m.p. (decomp.) 151°-153°C	
D(-)- <chem>ClCC(=O)N1CCN(C1)C(=O)Nc2ccccc2C(=O)N3[C@H](C)[C@@H](C(=O)O)[C@@H](S3)c4ccccc4</chem> m.p. (decomp.) 215°C	
D(-)- <chem>c1ccc(cc1)C(=O)N1CCN(C1)C(=O)Nc2ccccc2C(=O)N3[C@H](C)[C@@H](C(=O)O)[C@@H](S3)c4ccccc4</chem> m.p. (decomp.) 120°-124°C	
D(-)- <chem>CC(=O)Nc1ccc(cc1)C(=O)N2CCN(C2)C(=O)Nc3ccccc3C(=O)N4[C@H](C)[C@@H](C(=O)O)[C@@H](S4)c5ccccc5</chem> m.p. (decomp.) 172°-176°C	
D(-)- <chem>COc1cc(OC)c(OC)cc1C(=O)N1CCN(C1)C(=O)Nc2ccccc2C(=O)N3[C@H](C)[C@@H](C(=O)O)[C@@H](S3)c4ccccc4</chem> m.p. (decomp.) 120°-124°C	

— cont'd —

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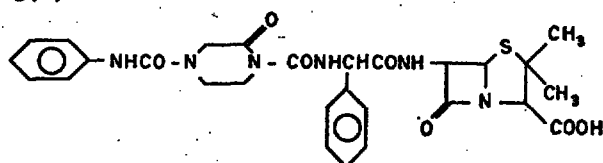
Table 1 (Cont'd)

D(-) -



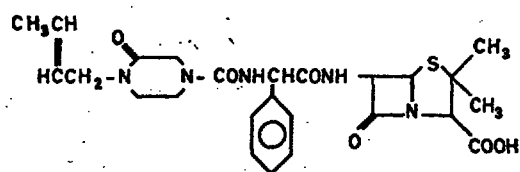
m.p. (decomp.) 130° - 133° C.

D(-) -



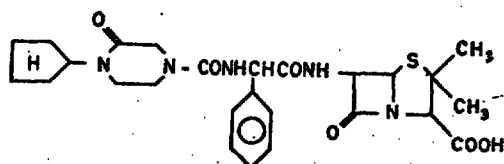
m.p. (decomp.) 168° - 170° C

D(-) -



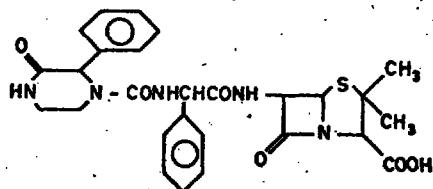
m.p. (decomp.) 95° C

D(-) -



m.p. (decomp.) 134° C

D(-) -



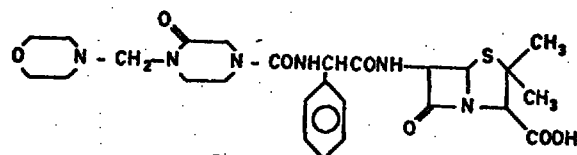
m.p. (decomp.) 125° - 128° C

cont'd —

— cont'd —

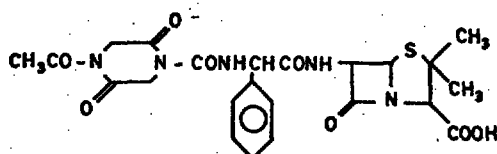
Table 1 (Cont'd)

D(-)-



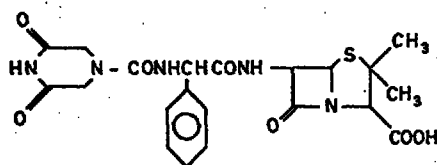
m.p. (decomp.) 85°C

D(-)-



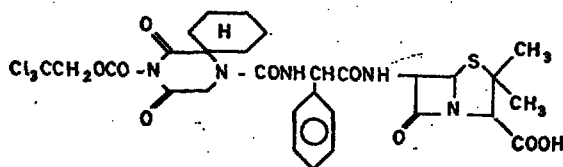
m.p. (decomp.) 162°-164°C

D(-)-



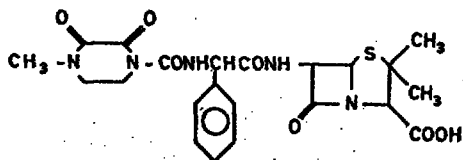
m.p. (decomp.) 176°-181°C

D(-)-



m.p. (decomp.) 120°-125°C

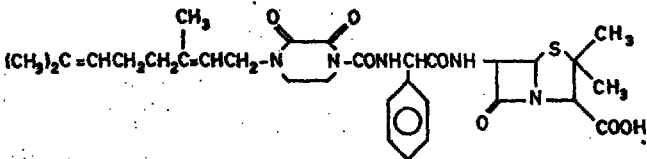
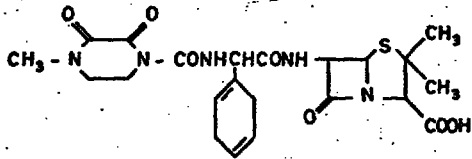
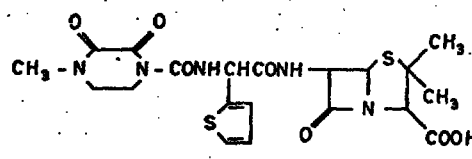
D(-)-



m.p. (decomp.) 156°-157°C

— cont'd —

Table 1 (Cont'd)

D(-) -  m.p. (decomp.) 93° - 94° C
D(-) -  m.p. (decomp.) 84° - 87° C
D(-) -  m.p. (decomp.) 185° C

EXAMPLE 2.

(1) 2.26 g of a phenacyl ester of 6-(phenyl-acetamido)penicillanic acid and 2.06 ml of N,N-dimethyl-aniline were dissolved in 30 ml of methylene chloride, and 1.15 g of phosphorus pentachloride was added to this solution at -25°C. The mixture was allowed to react at -30° to -20°C for 1.5 hours, followed by adding dropwise 20 ml of methyl alcohol while keeping the temperature at -30° to -20°C. The reaction mixture was further allowed to react at the same temperature for 3 hours, followed by addition of 3.43 ml of N,N-dimethylaniline.

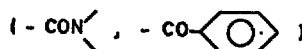
On the other hand, 1.76 g of D(-)-α-(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)phenylacetic acid and 0.76 ml of N,N-dimethylaniline were dissolved in a mixed solvent consisting of 8 ml of methylene chloride and 4 ml of dimethylformamide. The solution was cooled to -15° to -10°C, followed by adding dropwise 0.65 g of ethyl chlorocarbonate, and stirred at the same temperature for 40 minutes. After the reaction mixture was cooled to -25°C, it was added to the preceding reaction mixture.

The resulting mixture was allowed to react at -25°C for 3 hours, and then freed of the solvent by evaporation under reduced pressure. The residue was dissolved in a mixed solvent consisting of 20 ml of water and 40 ml of ethyl acetate. The organic layer was separated from the aqueous layer, washed with a saturated aqueous sodium chloride solution, dilute hydrochloric acid, and a 5% aqueous sodium hydrogen-carbonate solution, and then dried over anhydrous magnesium sulfate. The ethyl acetate was removed by evaporation under reduced pressure, and the residue was solidified by addition of 50 ml of diethyl ether. The thus

obtained white powder was filtered and washed with diethyl ether to obtain 2.29 g of a phenacyl ester of 6-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonyl-amino)phenylacetamidolpenicillanic acid, yield 72%.

IR(KBr) cm^{-1} :

$\nu_{\text{C=O}}$ 1775 (lactam), 1760 (ester), 1710—1665



(2) 2g of the above-obtained phenacyl ester of 6-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonyl-amino)phenylacetamidolpenicillanic acid was dissolved in 30 ml of tetrahydrofuran, and 0.42 g of sodium benzenethiolate was added to this solution at 15° to 20°C. The mixture was stirred for 1 hour to deposit crystals, which were collected by filtration, and the filtrate was concentrated by evaporation under reduced pressure to result in the second crop of crystals. The first crystals and the second crystals were combined, and dissolved in 10 ml of water. To the solution was added 15 ml of ethyl acetate, and the mixture was then adjusted to a pH of 2.0 by addition of dilute hydrochloric acid while stirring at 18° to 20°C. The solution was further stirred at 18° to 20°C for 5 hours to deposit crystals, which were collected by filtration to obtain 1.47 g of a monohydrate of 6-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)phenylacetamidolpenicillanic acid, yield 87%. This agreed with the compound obtained in Example 1, in the analytical data of IR, NMR and melting point.

The above-mentioned operation steps (1) and (2) were repeated, except that the phenacyl ester of 6-(phenylacetamido)penicillanic acid used in step (1) was replaced by a phenacyl ester of 6-(butyramido)-penicillanic acid, to obtain a monohydrate of 6-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazine-carbonylamino)-phenylacetamidolpenicillanic acid, yield 65%.

(3) 1.0 g of the above-obtained monohydrate of 6-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazine-carbonylamino)phenylacetamidolpenicillanic acid was dissolved in 20 ml of acetone. To the solution was added 5 ml of an acetone solution containing 0.33 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 1.02 g of a sodium salt of 6-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)phenylacetamidolpenicillanic acid, m.p. 183°—185°C (decomp.), yield 98%.

IR(KBr) cm^{-1} :

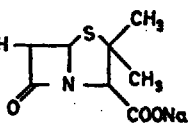
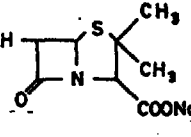
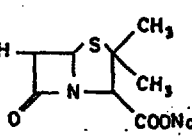
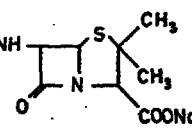
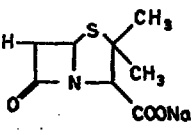
$\nu_{\text{C=O}}$ 1765 (lactam), 1720—1670

NMR($(\text{CD}_3)_2\text{SO} + \text{D}_2\text{O}$)

(—CON<), 1600 (—COO—)
 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)

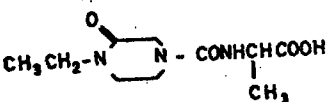
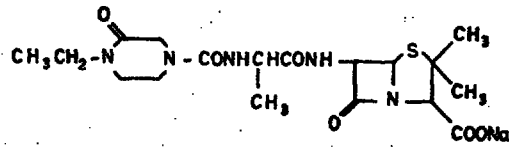
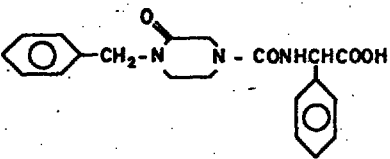
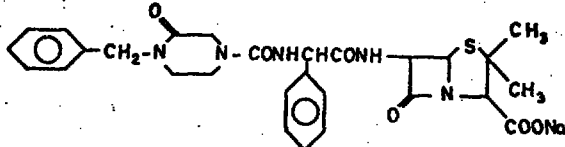
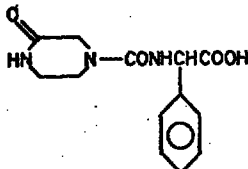
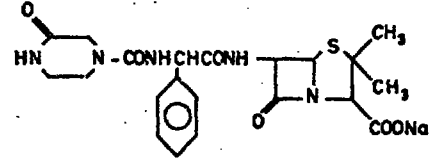
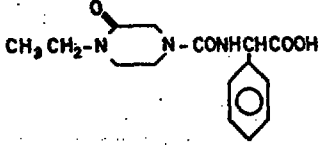
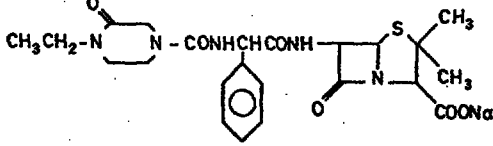
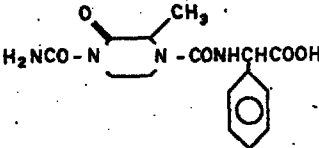
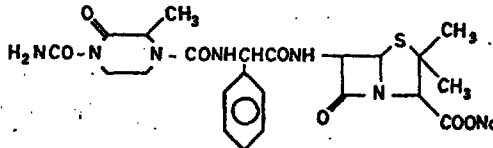
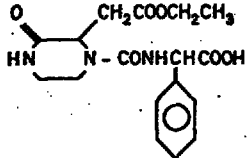
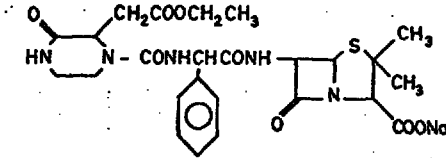
Using the phenacyl ester of 6-(phenylacetamido)-penicillanic acid and the compound of formula (III) as shown in Table 2, the above-mentioned operation steps (1), (2) and (3) were repeated to obtain the respective objective compounds as shown in Table 2. The structure of each objective compound was confirmed by IR and NMR. All the objective compounds were D(-) isomers.

Table 2

The compound of formula (III)	Objective compound
$\text{CH}_3\text{CO}-\text{N} \begin{array}{c} \diagup \text{O} \diagdown \\ \text{---} \end{array} \text{N}-\text{CONHCHCOOH}$ 	$\text{CH}_3\text{CO}-\text{N} \begin{array}{c} \diagup \text{O} \diagdown \\ \text{---} \end{array} \text{N}-\text{CONHCHCONH}$   m.p. (decomp.) 205°C, yield 62%
$\text{CH}_3\text{SO}_2-\text{N} \begin{array}{c} \diagup \text{O} \diagdown \\ \text{---} \end{array} \text{N}-\text{CONHCHCOOH}$ 	$\text{CH}_3\text{SO}_2-\text{N} \begin{array}{c} \diagup \text{O} \diagdown \\ \text{---} \end{array} \text{N}-\text{CONHCHCONH}$   m.p. (decomp.) 199°C, yield 59%
$\text{CH}_3(\text{CH}_2)_2\text{CH}_2-\text{N} \begin{array}{c} \diagup \text{O} \diagdown \\ \text{---} \end{array} \text{N}-\text{CONHCHCOOH}$ 	$\text{CH}_3(\text{CH}_2)_2\text{CH}_2-\text{N} \begin{array}{c} \diagup \text{O} \diagdown \\ \text{---} \end{array} \text{N}-\text{CONHCHCONH}$   m.p. (decomp.) 158°-161°C, yield 53%
$\text{H}-\text{CO}-\text{N} \begin{array}{c} \diagup \text{O} \diagdown \\ \text{---} \end{array} \text{N}-\text{CONHCHCOOH}$ 	$\text{H}-\text{CO}-\text{N} \begin{array}{c} \diagup \text{O} \diagdown \\ \text{---} \end{array} \text{N}-\text{CONHCHCONH}$   m.p. (decomp.) 203°-205°C, yield 60%
$(\text{CH}_3)_3\text{CCOOCH}_2-\text{N} \begin{array}{c} \diagup \text{O} \diagdown \\ \text{---} \end{array} \text{N}-\text{CONHCHCOOH}$ 	$(\text{CH}_3)_3\text{CCOOCH}_2-\text{N} \begin{array}{c} \diagup \text{O} \diagdown \\ \text{---} \end{array} \text{N}-\text{CONHCHCONH}$   m.p. (decomp.) 218°C, yield 52%

— cont'd —

Table 2 (Cont'd)

	 m.p. (decomp.) 195°C, yield 55%
	 m.p. (decomp.) 205° - 208° C, yield 62%
	 m.p. (decomp.) 213°C, yield 67%
	 m.p. (decomp.) 207°C, yield 68%
	 m.p. (decomp.) 215°C, yield 46%
	 m.p. (decomp.) 200°C, yield 63%

— cont'd —

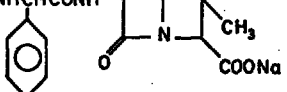
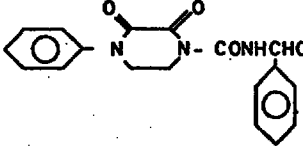
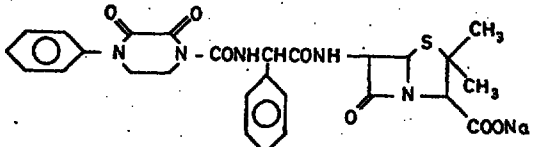
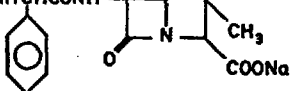
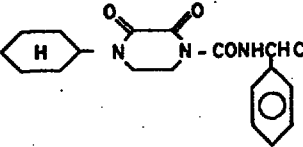
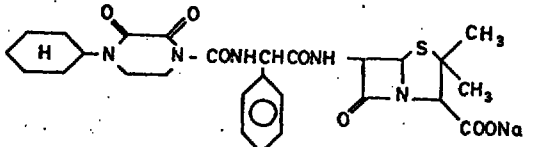
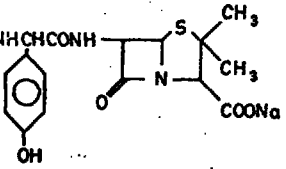
Table 2 (Cont'd)

<chem>CC(C)C(=O)O[Na]</chem>	<chem>CCCCN1C(=O)N(C1c2ccccc2)C(=O)O</chem>	<chem>CCCCN1C(=O)N(C1c2ccccc2)C(=O)Nc3c[nH]c4c3C(C)C(=O)O[Na]</chem>	m.p. (decomp.) 171°C, yield 61%
<chem>CC(C)C(=O)O[Na]</chem>	<chem>CC(=O)OCCN1C(=O)N(C1c2ccccc2)C(=O)O</chem>	<chem>CC(=O)OCCN1C(=O)N(C1c2ccccc2)C(=O)Nc3c[nH]c4c3C(C)C(=O)O[Na]</chem>	m.p. (decomp.) 175°C, yield 60%
<chem>CC(C)C(=O)O[Na]</chem>	<chem>CC(C)C(=O)N1C(=O)N(C1c2ccccc2)C(=O)O</chem>	<chem>CC(C)C(=O)N1C(=O)N(C1c2ccccc2)C(=O)Nc3c[nH]c4c3C(C)C(=O)O[Na]</chem>	m.p. (decomp.) 186°C, yield 60%
<chem>CC(C)C(=O)O[Na]</chem>	<chem>CCCCCN1C(=O)N(C1c2ccccc2)C(=O)O</chem>	<chem>CCCCCN1C(=O)N(C1c2ccccc2)C(=O)Nc3c[nH]c4c3C(C)C(=O)O[Na]</chem>	m.p. (decomp.) 177°C, yield 54%
<chem>CC(C)C(=O)O[Na]</chem>	<chem>CCCCCNC1C(=O)N(C1c2ccccc2)C(=O)O</chem>	<chem>CCCCCNC1C(=O)N(C1c2ccccc2)C(=O)Nc3c[nH]c4c3C(C)C(=O)O[Na]</chem>	m.p. (decomp.) 180°C, yield 56%
<chem>CC(C)C(=O)O[Na]</chem>	<chem>CCCCCCN1C(=O)N(C1c2ccccc2)C(=O)O</chem>	<chem>CCCCCCN1C(=O)N(C1c2ccccc2)C(=O)Nc3c[nH]c4c3C(C)C(=O)O[Na]</chem>	m.p. (decomp.) 185°C, yield 56%

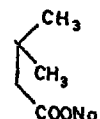
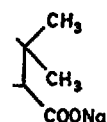
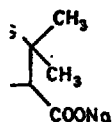
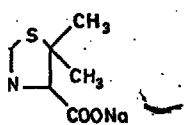
— cont'd —

— cont'd —

Table 2 (Cont'd)

$\text{CH}_2=\text{CHCH}_2\text{-N} \begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{N} \quad \text{N} \end{array} \text{-CONHCHCOOH}$ 	$\text{CH}_2=\text{CHCH}_2\text{-N} \begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{N} \quad \text{N} \end{array} \text{-CONHCHCONH}$  m.p. (decomp.) 198° - 200° C, yield 48%
	 m.p. (decomp.) 185° - 187° C, yield 71 %
$\text{ClCH}_2\text{CH}_2\text{-N} \begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{N} \quad \text{N} \end{array} \text{-CONHCHCOOH}$ 	$\text{ClCH}_2\text{CH}_2\text{-N} \begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{N} \quad \text{N} \end{array} \text{-CONHCHCONH}$  m.p. (decomp.) 210° C, yield 64%
	 m.p. (decomp.) 166° - 167° C, yield 65 %
$\text{CH}_3\text{-N} \begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{N} \quad \text{N} \end{array} \text{-CONHCHCOOH}$ 	$\text{CH}_3\text{-N} \begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{N} \quad \text{N} \end{array} \text{-CONHCHCONH}$  m.p. (decomp.) 170° - 172° C, yield 70%

— cont'd —



— cont'd —

Table 2 (Cont'd)

	m.p. (decomp.) 175°C, yield 65%
	m.p. (decomp.) 175°-177°C, yield 66%

EXAMPLE 3.

3.72 g of a potassium salt of 6-(phenylacetamido)penicillanic acid was suspended in 30 ml of methylene chloride, and 0.25 ml of N,N-dimethylaniline was added to this suspension. To the mixture was added 1.52 ml of trimethylsilyl chloride at 10° to 15°C, and the mixture was allowed to react for 30 minutes. After the reaction mixture was cooled -50°C, 4.12 ml of N,N-dimethylaniline and 2.3 g of phosphorus pentachloride were added. The resulting mixture was allowed to react at -45° to -40°C for 1.5 hours, followed by addition of 13.7 ml of isobutyl alcohol. The reaction mixture was further allowed to react at -45° to -40°C for 3 hours, followed by addition of 6.86 ml of N,N-dimethylaniline.

On the other hand, 3.52 g of D(-)-α-(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)phenylacetic acid and 1.21 g of triethylamine were dissolved in a mixed solvent consisting of 20 ml of methylene chloride and 10 ml of dimethylformamide. To the solution was added dropwise 1.3 g of ethyl chlorocarbonate at -15° to -10°C, and the mixture was stirred at the same temperature for 30 minutes. After the reaction mixture was cooled to -40°C, it was added to the preceding reaction mixture.

The resulting mixture was allowed to react at -40° to -30°C for 2 hours, and at -15°C overnight, and then freed of the solvent by evaporation under reduced pressure. The residue was treated in the same manner as in Example 1, to obtain 1.72 g of a monohydrate of 6-[D(-)-α-(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)phenylacetamido]penicillanic acid, yield 32%. This agreed with the compound obtained in Example 1, in the analytical data of IR, NMR and melting point.

The above-mentioned operation was repeated, except that the 1.52 ml of trimethylsilyl chloride was replaced by 0.82 ml of phosphorus trichloride, to obtain 2.1 g of monohydrate of 6-[D(-)-α-(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)phenylacetamido]penicillanic acid, yield 39%.

EXAMPLE 4.

Using (4-methyl-2,3-dioxo-1-piperazino-carbonylamino)phenylacetic acid and the compound of formula (IV) shown in Table 3, the same operation as in Example 2-(1) was repeated to obtain the respective objective compounds as shown in Table 3. The structure of each objective compound was confirmed by IR and NMR.

Table 3

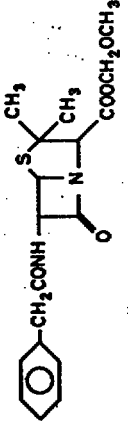
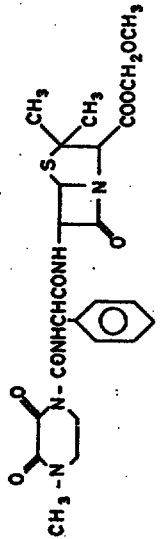
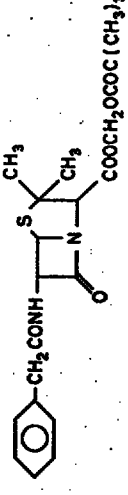
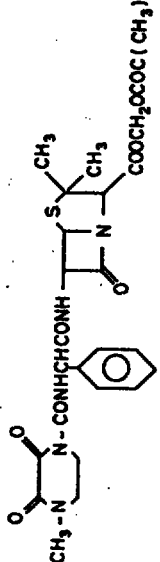
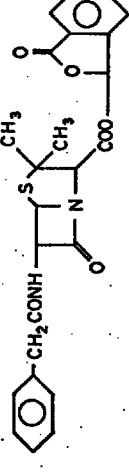
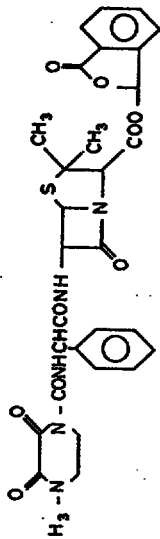
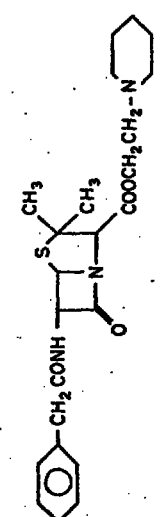
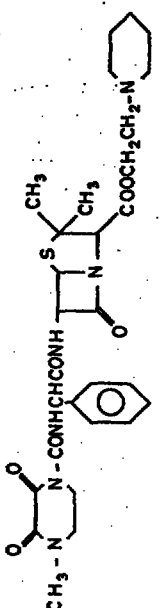
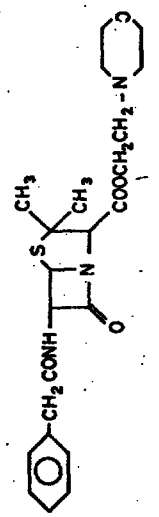
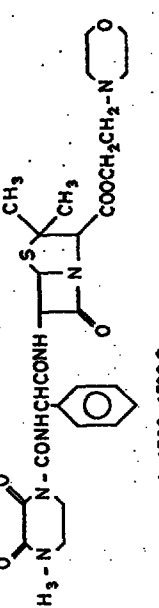
The compound of formula (IV)	Objective compound
	D(-) -  m.p. (decomp.) 111° - 115° C
	D(-) -  m.p. (decomp.) 108° - 111° C
	D(-) -  m.p. (decomp.) 157° - 160° C

Table 3 (Cont'd)

	DI(-) -  m.p. (decomp.) 166° - 169° C
	DI(-) -  m.p. (decomp.) 150° - 153° C

EXAMPLE 5.

1.95 g of 7-phenylacetamido-3-acetoxymethyl- Δ^3 -cephem-4-carboxylic acid was suspended in 20 ml of methylene chloride, and 0.72 ml of triethylamine and 0.48 ml of phosphorus trichloride were successively added to this suspension at 15° to 20°C. The mixture was stirred at 15° to 20°C for 1 hour, followed by addition of 2.06 ml of N,N-dimethylaniline and 1.15 g of phosphorus pentachloride while keeping the temperature at -20° to -15°C. Then the reaction mixture was further allowed to react for 3 hours at the same temperature, followed by adding dropwise 6.85 ml of isobutyl alcohol at the same temperature, and stirred at -15°C for 7 hours. After the solvent was removed by evaporation under reduced pressure, the residue was dissolved in 20 ml of methylene chloride, followed by addition of 3.43 ml of N,N-dimethylaniline, and cooled to -25°C.

On the other hand, 1.68 g of D(-)- α -(4-methyl-2,3-dioxo-1-piperazino-carbonylamino)phenylacetic acid and 0.84 ml of triethylamine were dissolved in 20 ml of methylene chloride, followed by adding dropwise 0.65 g of ethyl chlorocarbonate at -20° to -15°C, and stirred at the same temperature for 1.5

5

10

15

hours. After the reaction mixture was cooled to -25°C , it was added to the preceding reaction mixture.

The resulting mixture was allowed to react at -20° to -15°C for 2 hours, and then at -10° to -5°C for 1 hour. The solvent was removed by evaporation under reduced pressure, and the residue was dissolved in a mixed solvent consisting of 30 ml of ethyl acetate, 3 ml of acetone and 10 ml of water. The solution was adjusted to a pH of 2.0 by addition of dilute hydrochloric acid, and separated into an organic layer and an aqueous layer. The aqueous layer was extracted with 10 ml of ethyl acetate. The organic layer and the ethyl acetate extract were combined, followed by addition of 10 ml of water, and adjusted to a pH of 7.0 by addition of sodium hydrogencarbonate with ice-cooling. The resulting aqueous layer was separated from the organic layer, washed with 20 ml of diethyl ether, and then adjusted to a pH of 2.0 by addition of dilute hydrochloric acid to deposit crystals, which were collected by filtration to obtain 1.62 g of 7-[D(-)- α -(4-methyl-2,3-dioxo-1-piperazino-carbonylamino)phenylacetamido]-3-acetoxymethyl- Δ^3 -cephem-4-carboxylic acid, m.p. 175°C , yield 58%.

IR(KBr) cm^{-1} :

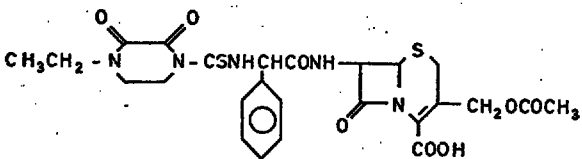
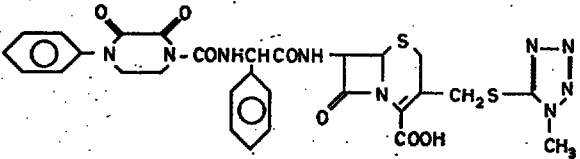
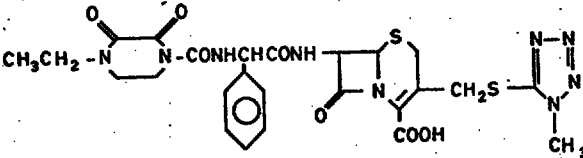
$\nu_{\text{C=O}}$ 1770 (lactam), 1720—1650
(—CON—, —COOH)

NMR($(\text{CD}_3)_2\text{SO}$)

τ values: 0.23 (1H, s), 0.63 (1H, d), 2.66 (5H, s), 4.32 (1H, q), 4.43 (1H, d), 5.05 (1H, d), 5.21 (2H, q), 6.15 (2H, bs), 6.40 (2H, bs), 6.57 (2H, bs), 7.0 (3H, s), 8.0 (3H, s)

In the same manner as above, the compounds as shown in Table 4 were obtained. The structure of each compound was confirmed by IR and NMR.

Table 4

Objective compound of the general formula (I)	
D(-) -	 m.p. (decomp.) 112°C
D(-) -	 m.p. (decomp.) 163°C
D(-) -	 m.p. (decomp.) $163^{\circ}\text{--}165^{\circ}\text{C}$

— cont'd —

Table 4 (Cont'd)

d to

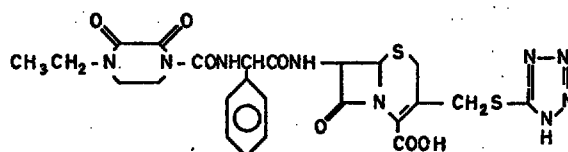
ours, and
on under
ing of 30
adjusted
into an
10 ml of
combined,
dition of
ayer was
and then
crystals,
ethyl-2,3-
yl- Δ^3 -

1, s)
2, 4 were
NMR.

ont'd —

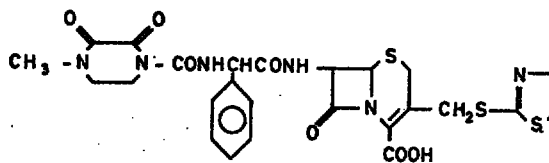
— cont'd —

D(-) -



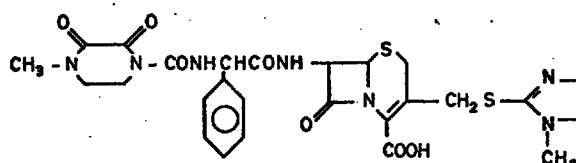
m.p. (decomp.) 159° -160°C

D(-) -



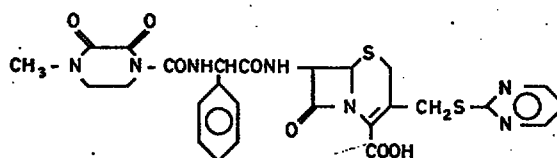
m.p. (decomp.) 180° - 182°C

D(-) -



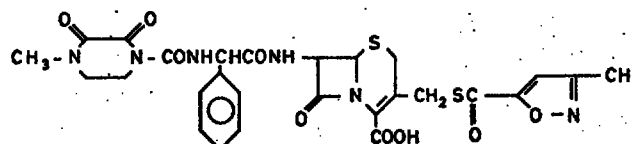
m.p. (decomp.) 182°.-184° C

D(-) -



m.p. (decomp.) 192°-194° C

D(-) -



m.p. (de comp.) 183° C

Table 4 (Cont'd)

D(-)- m.p. (decomp) 162° - 166° C
D(-)- m.p. (decomp) 177° - 180° C
D(-)- m.p. (decomp.) 171° - 175° C
D(-) - m. p. (decomp) 183° - 185° C
D(-) - m.p. (decomp.) 170° - 173° C

— cont'd —

Table 4 (Cont'd)

ClCCN1C(=O)N(C1)C(=O)NCC(=O)Nc2ccc(O)cc2C3C(=O)NC(S3)CCSC4=NC5=NC(=N4)N(C)N5

m.p. (decomp.) 193° - 195° C

[illegible]

m.p. (decomp.) 183°-185°C

O=C1NC(=O)N1CONHC2=CC=CC=C2C(=O)N3C(=O)NC(=S3)C4=CC(=C(C=C4)C(=O)O)CS5N6N=NN=C6N5C

mp (decomp) 153°-157°C

CCCC(=O)N1CCC(=O)N1C(=O)Nc2ccccc2C(=O)N3C(=O)NC(S3)C(=C(C(=O)O)CS4C=CC(=C4)N5C=CC=N5)S4

m.p. (decomp.) 175°-178° C

CC(=O)N1C(=O)N(C(=O)Nc2ccccc2C(=O)N3C(=O)c4ccccc4N3C(=O)CSCc5nc6c(cc5)C(=O)N(C)N(C)C6=O)c6=O

m.p. (decomp.) 95°-98°C

CCCC1=NC(=O)N(C1)C(=O)Nc2ccccc2C(=O)N3C(=O)NC4=CC=C(S4)C(=O)N5C(=O)N(CS5)C6=NC=NC=C6N

m.p. (decomp) 147°C

ont'd —

EXAMPLE 6.

(1) 1.58 g of a benzhydryl ester of 7-phenyl-acetamido-3-[2-(5-methyl-1,3,4-thiadiazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid and 1.03 ml of N,N-dimethylaniline were dissolved in 20 ml of methylene chloride, and 0.63 g of phosphorus pentachloride was added to this solution at -30° to -20°C . The mixture was allowed to react at -30° to -20°C for 2 hours, and at -20° to -15°C for 3 hours, and cooled to -30° to -20°C , followed by addition of 3.5 ml of isobutyl alcohol. Then the reaction mixture was further allowed to react at -30° to -20°C for 3 hours, followed by addition of 2.2 ml of N,N-dimethylaniline.

On the other hand, 0.84 g of D(-)- α -(4-methyl-2,3-dioxo-1-piperazino-carbonylamino)phenylacetic acid and 0.38 ml of N,N-dimethylaniline were dissolved in a mixed solvent consisting of 6 ml of methylene chloride and 3 ml of dimethylformamide, and 0.33 g of ethyl chlorocarbonate was added dropwise to this solution at -10° to -5°C . After the mixture was stirred at the same temperature for 30 minutes, it was cooled to -30° to -20°C , and added to the preceding reaction mixture.

The resulting mixture was allowed to react at -30° to -20°C for 2 hours, and then at -15°C overnight. After the reaction, the solvent was removed by evaporation under reduced pressure, and the residue was dissolved in a mixed solvent consisting of 30 ml of ethyl acetate and 10 ml of water. The organic layer was separated from the aqueous layer, washed with a saturated aqueous sodium chloride solution, dilute hydrochloric acid and 5% aqueous sodium hydrogen-carbonate solution, successively, and then dried over anhydrous magnesium sulfate. The ethyl acetate was removed by evaporation under reduced pressure, and the residue was crystallized by addition of 30 ml of diethyl ether, to obtain 1.33 g of a benzhydryl ester of 7-[D(-)- α -(4-methyl-2,3-dioxo-1-piperazino-carbonylamino)phenylacetamido]-3-[2-(5-methyl-1,3,4-thiadiazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid, m.p. (decomp.) 148° — 150°C , yield 68%.

IR(KBr) cm^{-1} : $\nu_{\text{C=O}}$ 1775 (lactam), 1730 (ester), 1710—1660 (—CON<)

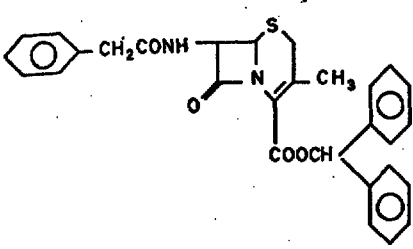
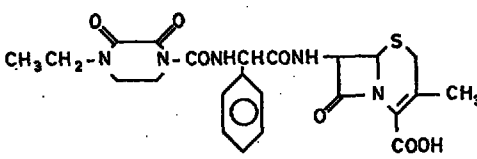
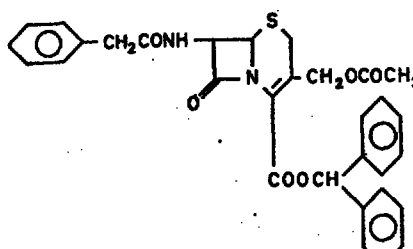
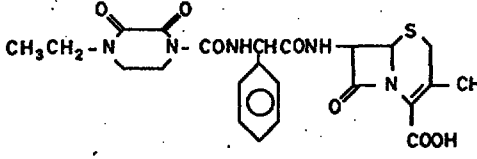
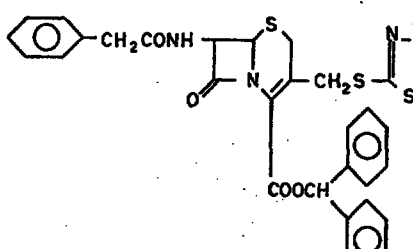
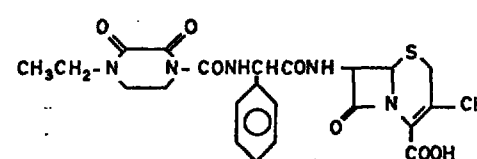
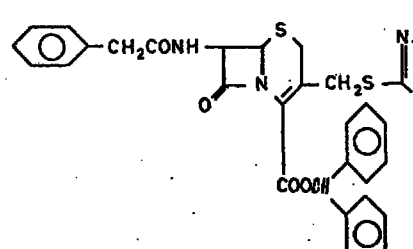
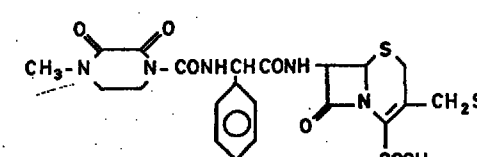
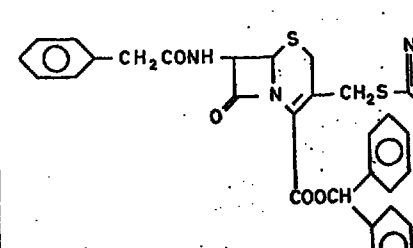
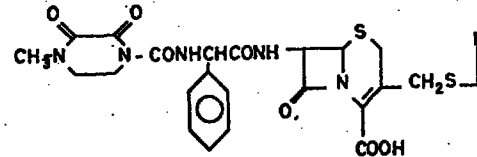
(2) 1.0 g of the above-obtained benzhydryl ester of 7-[D(-)- α -(4-methyl-2,3-dioxo-1-piperazino-carbonylamino)phenylacetamido]-3-[2-(5-methyl-1,3,4-thiadiazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid was dissolved in a mixture consisting of 10 ml of methylene chloride and 1 ml of anisole, and 0.5 ml of trifluoroacetic acid was added to this solution at 15° to 20°C . The mixture was allowed to react for 3 hours, and freed of the solvent by evaporation under reduced pressure. The residue was powdered by addition of 10 ml of ethyl acetate to obtain 0.69 g of 7-[D(-)- α -(4-methyl-2,3-dioxo-1-piperazino-carbonylamino)phenylacetamido]-3-[2-(5-methyl-1,3,4-thiadiazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid, m.p. (decomp.) 158° — 162°C , yield 88%.

IR(KBr) cm^{-1} : $\nu_{\text{C=O}}$ 1780 (lactam), 1650—1720 (—CON<, —COOH)

NMR($(\text{CD}_3)_2\text{SO}$) τ values: 0.2 (1H, d), 0.6 (1H, d), 2.60 (5H, d), 4.35 (1H, q), 4.40 (1H, d), 5.0 (1H, d), 5.70 (2H, q), 6.10 (2H, bs), 6.25—6.55 (4H, bs), 7.0 (3H, s), 7.30 (3H, s)

Using D(-)- α -(4-methyl-2,3-dioxo-1-piperazino-carbonylamino)phenylacetic acid, D(-)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)phenylacetic acid, or D(-)- α -(4-methyl-2,3-dioxo-1-piperazino-carbonylamino)-p-hydroxyphenylacetic acid and the compound of formula (IV) shown in Table 5, the above-mentioned operation steps (1) and (2) were repeated to obtain the respective objective compounds of the general formula (I) as shown in Table 5. All the objective compounds were D(-) isomers, and the structure of each objective compound was confirmed by IR and NMR.

Table 5

The compound of formula (IV)	Objective compound
	 m.p. (decomp.) 168° C, yield 63%
	 m.p. (decomp.) 165° C, yield 60%
	 m.p. (decomp.) 150° C, yield 55%
	 m.p. (decomp.) 168°-170° C, yield 57%
	 m.p. (decomp.) 158°-159° C, yield 50%

— cont'd —

ethyl-1,4-
of N,N-
0.63 g of
20°C. The
to -15°C
3.5 ml of
at -30° to
iline.
azino-car-
dissolved
3 ml of
opwise to
the same
led to the

hours, and
moved by
n a mixed
anic layer
us sodium
hydrogen-
magnesium
pressure,
obtain 1.33
-carbonyl-
ethyl]-Δ³-

hyl-2,3-di-
4-thiadia-
mixture
0.5 ml of
xture was
r reduced
to obtain
o)phenyl-
carboxylic

nylacetic
c acid, or
nylacetic
entioned
objective
objective
ound was

Table 5 (Cont'd)

	m.p. (decomp.) 175°-180° C, yield 55%
	m.p. (decomp.) 128°-129° C, yield 56%
	m.p. (decomp.) 170°-172° C, yield 52%
	m.p. (decomp.) 147°-149° C, yield 47%
	m.p. (decomp.) 175°-180° C, yield 56%

— cont'd —

Table 5 (Cont'd)

	m.p. (decomp.) 156° - 157° C, yield 53%
	m.p. (decomp.) 185° - 189° C, yield 58%
	m.p. (decomp.) 177° - 180° C

EXAMPLE 7.

Using D(-)-α-(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)phenylacetic acid and ββ-trichloro-ethyl ester of 7-phenylacetamido-3-[5-(1-methyl-1,2,3,4-tetrazolyl-thiomethyl)]-Δ³-cephem-4-carboxylic acid, the same operation as in Example 6-(1) was repeated to obtain ββ-trichloroethyl ester of 7-[D(-)-α-(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)phenylacetamido]-3-[5-(1-methyl-1,2,3,4-tetrazolyl)thiomethyl]-Δ³-cephem-4-carboxylic acid, m.p. (decomp.) 125°-135°C.

EXAMPLE 8.

(1) 3.06 g of a benzhydryl ester of 7-phenyl-acetamido-3-acetoxymethyl-Δ³-cephem-4-carboxylic acid was dissolved in 45 ml of methylene chloride, and 2.73 g of N,N-dimethylaniline and 0.96 g of trimethylsilyl chloride were added to this solution. The mixture was allowed to react at room temperature for 1 hour, and cooled to -45°C, followed by addition of 1.49 g of phosphorus pentachloride. Then the reaction mixture was further allowed to react at -40° to -30°C for 1 hour, and at -30° to -20°C for 3 hours, and cooled to -45°C, followed by addition of 6 ml of absolute methanol over a period of 10 minutes. The resulting mixture was allowed to react at -40° to -30°C for 1 hour, and at -30° to -20°C for 2 hours, followed by addition of 3.60 g of dimethylaniline.

On the other hand, 2.21 g of D(-)-α-(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)-p-hydroxyphenylacetic acid was dissolved in a mixed solvent consisting of 18 ml of methylene chloride and 4.4 ml of dimethylformamide, and

— cont'd —

0.88 g of N,N-dimethylaniline was added to this solution. The mixture was cooled to -15°C , followed by adding dropwise 0.79 g of ethyl chlorocarbonate. After the reaction mixture was allowed to react at -15° to -10°C for 2 hours, and cooled to -25°C , it was added to the preceding reaction mixture.

The resulting mixture was allowed to react at -25° to -20°C for 1 hour, and at -20° to -10°C for 14 hours, and freed of the solvent by evaporation under reduced pressure, followed by addition of 150 ml of ethyl acetate and 50 ml of water to dissolve the residue. Then the organic layer was separated from the aqueous layer, washed with water, dilute hydrochloric acid, a 5% aqueous sodium hydrogencarbonate solution and a saturated aqueous sodium chloride solution, successively, and dried over anhydrous magnesium sulfate. The ethyl acetate was removed by evaporation under reduced pressure, and the residue was crystallized by addition of 30 ml of diethyl ether. The crystals were collected by filtration to obtain 4.0 g of a benzhydryl ester of 7-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)-p-hydroxyphenylacetamido]-3-acetoxymethyl- Δ^3 -cephem-4-carboxylic acid, m.p. (decomp.) 143° — 145°C , yield 96.4%.

IR(KBr) cm^{-1} : $\nu_{\text{C=O}}$ 1775 (β -lactam), 1710 ($-\text{COO}-$), 1680, 1670 ($-\text{CON}<$)

(2) 4.0 g of the above-obtained benzhydryl ester of 7-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)-p-hydroxyphenylacetamido]-3-acetoxymethyl- Δ^3 -cephem-4-carboxylic acid was added to the mixture consisting of 8 ml of anisole and 32 ml of trifluoro-acetic acid at 0 to 5°C . The mixture was allowed to react for 40 minutes, and freed of the solvent by evaporation under reduced pressure, followed by addition of 20 ml of diethyl ether to deposit crystals, which were collected by filtration to obtain 2.9 g of 7-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)-p-hydroxyphenylacetamido]-3-acetoxymethyl- Δ^3 -cephem-4-carboxylic acid, m.p. (decomp.) 168° — 174°C , yield 92%.

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

(3) 2.5 g of the above-obtained 7-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)-p-hydroxyphenylacetamido]-3-acetoxymethyl- Δ^3 -cephem-4-carboxylic acid was dissolved in a mixed solvent consisting of 18 ml of acetone and 7 ml of n-butyl alcohol, and 20 ml of a n-butyl alcohol solution containing 0.7 g of a sodium 2-ethylhexanoate was added to this solution. The mixture was stirred for 1 hour to deposit crystals, which were filtered, washed with acetone, and dried to obtain 2.36 g of a sodium salt of 7-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)-p-hydroxyphenylacetamido]-3-acetoxymethyl- Δ^3 -cephem-4-carboxylic acid, yield 91%.

EXAMPLE 9.

The same operation as in Example 8 was repeated, except that the benzhydryl ester of 7-phenylacetamido-3-acetoxymethyl- Δ^3 -cephem-4-carboxylic acid was replaced by a benzhydryl ester of 7-phenoxyacetamido-3-acetoxymethyl- Δ^3 -cephem-4-carboxylic acid, a dibenzhydryl ester of 7-(δ -N-ethoxycarbonylamino- δ -carboxyvaleramido)-3-acetoxymethyl- Δ^3 -cephem-4-carboxylic acid, or a dibenzhydryl ester of 7-(δ -N-phenylcarbonylamino- δ -carboxyvaleramido)-3-acetoxymethyl- Δ^3 -cephem-4-carboxylic acid, to obtain a sodium salt of 7-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)-p-hydroxyphenylacetamido]-3-acetoxymethyl- Δ^3 -cephem-4-carboxylic acid, yield 60—80%.

EXAMPLE 10.

(1) 3.06 g of a benzhydryl ester of 7-phenyl-acetamido-3-[5-(1-methyl-1,2,3,4-tetrazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid was dissolved in 45 ml of methylene chloride, and 2.5 g of N,N-dimethylaniline and 0.87 g of trimethylsilyl chloride were added to this solution. The mixture was allowed to react at room temperature for 1 hour, and cooled to -45°C , followed by addition of 2.08 g of phosphorus pentachloride. Then the reaction mixture was further allowed to react at -40° to -30°C for 1 hour, and at -30° to -20°C for 3 hours, and cooled to -45°C , followed by addition of 5.5 ml of absolute methyl alcohol over a period of 10 minutes. The resulting reaction mixture was allowed to react at -40° to -30°C for 1 hour, and at -30° to -20°C for 2 hours, followed by addition of 3.24 g of N,N-dimethylaniline.

On the other hand, 2 g of D(-)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonyl-

was cooled
After the
cool

our, and at
er reduced
f water to
ous layer,
s sodium
s solution,
etate was
rystallized
litation to
iperazino-
m-4-car-

hyl-2,3-di-
oxymethyl-
of anisole
o react for
pressure,
hich were
o-1-piper-
-cephem-

680,

azino-car-
m-4-car-
one and 7
0.7 g of a
irred for 1
d dried to
azino-car-
m-4-car-

benzhydryl
acid was
methyl- Δ^3 -
ylamino- δ -
d, or a
ramido)-3-
7-[D(-)- α -
tamido]-3-

yl-1,2,3,4-
45 ml of
methylsilyl
at room
f 2.08 g of
ed to react
cooled to
a period of
to -30°C
4 g of N,N-
-carbonyl-

amino)-p-hydroxyphenylacetic acid was dissolved in a mixed solvent consisting of 17 ml of methylene chloride and 4 ml of dimethylformamide, and 0.8 g of N,N-dimethylaniline was added to this solution. The mixture was cooled to -15°C, followed by adding dropwise 0.71 g of ethyl chlorocarbonate, and allowed to react at -15° to -10°C for 2 hours. After the reaction mixture was cooled to -25°C, it was added to the preceding reaction mixture.

The resulting mixture was allowed to react at -25° to -20°C for 1 hour, and at -20° to -10°C for 14 hours, and freed of the solvent by evaporation under reduced pressure, followed by addition of 150 ml of ethyl acetate and 50 ml of water. Then the organic layer was separated from the aqueous layer, washed with water, dilute hydrochloric acid, a 5% aqueous sodium hydrogencarbonate solution and a saturated aqueous sodium chloride solution, and then dried over anhydrous magnesium sulfate. The ethyl acetate was removed by evaporation under reduced pressure, and to the residue was added 30 ml of diethyl ether to deposit crystals, which were collected by filtration to obtain 3.58 g of a benzhydryl ester of 7-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)-p-hydroxyphenylacetamido]-3-[5-(1-methyl-1,2,3,4-tetrazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid, m.p. (decomp.) 148°—150°C, yield 88.5%.

IR(KBr) cm^{-1} : $\nu_{\text{C=O}}$ 1773 (lactam), 1710 (—COO—), 1680, 1670 (—CON<)

(2) 3.5 g of the above-obtained benzhydryl ester of 7-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)-p-hydroxyphenylacetamido]-3-[5-(1-methyl-1,2,3,4-tetrazolyl)-thiomethyl]- Δ^3 -cephem-4-carboxylic acid was added to a mixture consisting of 7 ml of anisole and 30 ml of trifluoroacetic acid at 0° to 5°C. The mixture was allowed to react for 40 minutes, and freed of the solvent by evaporation under reduced pressure, followed by addition of 20 ml of diethyl ether to deposit crystals, which were collected by filtration to obtain 2.53 g of 7-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)-p-hydroxyphenylacetamido]-3-[5-(1-methyl-1,2,3,4-tetrazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid, m.p. (decomp.) 170°—171°C, yield 91.0%.

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

(3) 2.5 g of the above-obtained 7-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)-p-hydroxyphenylacetamido]-3-[5-(1-methyl-1,2,3,4-tetrazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid was dissolved in a mixed solvent consisting of 20 ml of acetone and 5 ml of n-butyl alcohol, and 15 ml of an n-butyl alcohol solution containing 0.64 g of sodium 2-ethyl-hexanoate was added to this solution. The mixture was stirred for 1 hour to deposit crystals, which were filtered, washed with acetone, and dried to obtain 2.2 g of a sodium salt of 7-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)-p-hydroxyphenylacetamido]-3-[5-(1-methyl-1,2,3,4-tetrazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid, yield 84%.

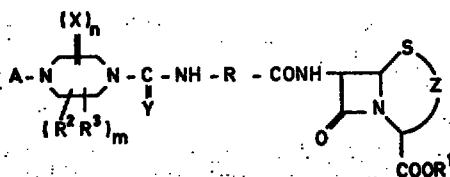
EXAMPLE 11.

The same operation as in Example 10-(1) and (2) were repeated, except that the benzhydryl ester of 7-phenylacetamido-3-[5-(1-methyl-1,2,3,4-tetrazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid was replaced by a benzhydryl ester of 7-phenylacetamido-3-[2-(5-methyl-1,3,4-thiadiazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid, to obtain 7-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)-p-hydroxyphenylacetamido]-3-[2-(5-methyl-1,3,4-thiadiazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid, m.p. (decomp.) 172°—177°C, yield 83.2%.

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

WHAT WE CLAIM IS:—

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



amino)-p-hydroxyphenylacetic acid was dissolved in a mixed solvent consisting of 17 ml of methylene chloride and 4 ml of dimethylformamide, and 0.8 g of N,N-dimethylaniline was added to this solution. The mixture was cooled to -15°C , followed by adding dropwise 0.71 g of ethyl chlorocarbonate, and allowed to react at -15° to -10°C for 2 hours. After the reaction mixture was cooled to -25°C , it was added to the preceding reaction mixture.

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IR(KBr) cm^{-1} : $\nu_{\text{C=O}}$ 1773 (lactam), 1710 ($-\text{COO}-$), 1680, 1670 ($-\text{CON}<$)

(2) 3.5 g of the above-obtained benzhydryl ester of 7-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)-p-hydroxyphenylacetamido]-3-[5-(1-methyl-1,2,3,4-tetrazolyl)-thiomethyl]- Δ^3 -cephem-4-carboxylic acid was added to a mixture consisting of 7 ml of anisole and 30 ml of trifluoroacetic acid at 0° to 5°C . The mixture was allowed to react for 40 minutes, and freed of the solvent by evaporation under reduced pressure, followed by addition of 20 ml of diethyl ether to deposit crystals, which were collected by filtration to obtain 2.53 g of 7-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)-p-hydroxyphenylacetamido]-3-[5-(1-methyl-1,2,3,4-tetrazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid, m.p. (decomp.) 170° — 171°C , yield 91.0%.

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

(3) 2.5 g of the above-obtained 7-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)-p-hydroxyphenylacetamido]-3-[5-(1-methyl-1,2,3,4-tetrazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid was dissolved in a mixed solvent consisting of 20 ml of acetone and 5 ml of n-butyl alcohol, and 15 ml of an n-butyl alcohol solution containing 0.64 g of sodium 2-ethyl-hexanoate was added to this solution. The mixture was stirred for 1 hour to deposit crystals, which were filtered, washed with acetone, and dried to obtain 2.2 g of a sodium salt of 7-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)-p-hydroxyphenylacetamido]-3-[5-(1-methyl-1,2,3,4-tetrazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid, yield 84%.

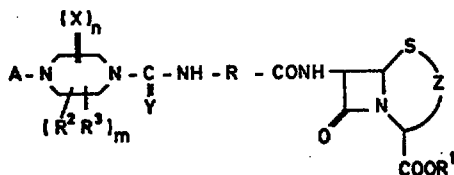
EXAMPLE 11.

The same operation as in Example 10-(1) and (2) were repeated, except that the benzhydryl ester of 7-phenylacetamido-3-[5-(1-methyl-1,2,3,4-tetrazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid was replaced by a benzhydryl ester of 7-phenylacetamido-3-[2-(5-methyl-1,3,4-thiadiazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid, to obtain 7-[D(-)- α -(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)-p-hydroxyphenylacetamido]-3-[2-(5-methyl-1,3,4-thiadiazolyl)thiomethyl]- Δ^3 -cephem-4-carboxylic acid, m.p. (decomp.) 172° — 177°C , yield 83.2%.

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

WHAT WE CLAIM IS:—

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

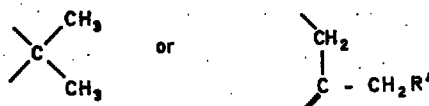


(I)



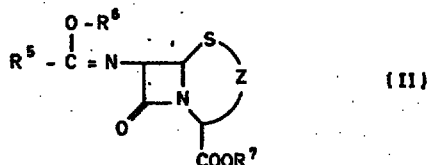
39 39 39

wherein R represents an amino acid residue; R¹ represents a hydrogen atom, a carboxyl-protecting group or a salt-forming cation; n represents 1 or 2; X represents an oxygen atom, and is linked to the carbon atom at the 2-, 3- or 5-position of the piperazine ring, and when n is 2, any two of the 2-, 3- and 5-positions may be occupied by the two X's; m represents 4-n; R² and R³ are in pairs linked to the same carbon atom, m pairs of R² and R³ may be the same or different, and R² and R³ individually represents a hydrogen atom, an alkyl group, an aryl group or an alkyloxycarbonylalkyl group; or any pair of R² and R³ together with the common carbon atom may form a cycloalkyl ring; A represents a hydrogen atom, or an unsubstituted or substituted alkyl, alkenyl, alkadienyl, cycloalkyl, aryl, acyl, aralkyl, acyloxyalkyl, alkyloxycarbonyl, alkylsulfonyl, carbamoyl or acylcarbamoyl group; Y represents an oxygen or sulfur atom; and >Z represents

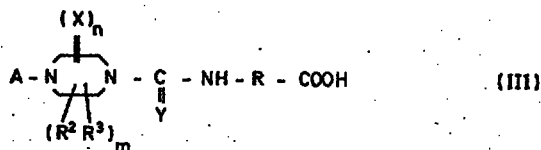


where R⁴ represents a hydrogen atom, an azido group, or an alkoxy, aryloxy, aralkyloxy, acyloxy, alkylthio, arylthio, aralkylthio, acylthio, oxazolylthio, thiazolylthio, isoxazolylthio, isothiazolylthio, imidazolylthio, pyrazolylthio, pyridylthio, pyrazinylthio, pyrimidinylthio, pyridazinylthio, quinolylthio, isoquinolylthio, quinazolylthio, indolylthio, indazolylthio, oxadiazolylthio, thiadiazolylthio, triazolylthio, tetrazolylthio, triazinylthio, benzimidazolylthio, benzoxazolylthio, benzothiazolylthio, triazolopyridylthio, or purinylthio group which may be substituted by groups selected from a halogen atom, an alkyl group, an alkoxy group, an alkylthio group a nitro group, a cyano group, or an acyl group. Which comprises:

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

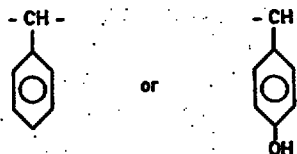


wherein R⁵ represents a residue of an acyl group devoid of carbonyl group; R⁶ represents an alkyl, aralkyl, or alkoxyalkyl group; R⁷ represents a carboxyl-protecting group; and >Z is the same as above with a reactive derivative, with respect to the carboxyl group of a compound of formula (III),



wherein R, R², R³, A, X, Y, m and n are the same as above, and (b) hydrolyzing the compound obtained in step (a), and, if desired, treating the hydrolyzation product obtained above by a conventional method to remove the carboxyl-protecting group R⁷.

2. The process according to Claim 1, wherein R is



R¹ is a hydrogen atom or a cation capable of forming a non-toxic salt; n is 2; two X's are linked to the carbon atoms at the 2- and 3-positions of the piperazine ring;



en atom, a
1 or X
2-, 3- or 5-
3- and 5-
are in pairs
or different,
up, an aryl
together with
a hydrogen
alkyl, aryl,
amoyl or
represents

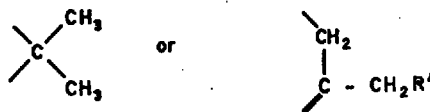
y, aryloxy,
azolythio,
azolythio,
inolythio,
azolythio,
azolythio,
thio group
alkyl group,
acyl group.

group; R⁶
carboxyl-
ative, with

eating the
move the

is 2; two
zine ring;

m is 2; R² and R³ are in pairs linked to the same carbon atom, 2 pairs of R² and R³ may be the same or different, and R² and R³ individually represent a hydrogen atom or a methyl group; A is a methyl or ethyl group; Y is an oxygen atom; and >Z is



in which R⁴ is an acetoxy, 2-(5-methyl-1,3,4-thiadiazolyl)thio, 2-(1,3,4-thiadiazolyl)thio, 2-(1-methyl-1,3,4-triazolyl)-thio, 5-(1-methyl-1,2,3,4-tetrazolyl)thio or 5-(1,2,3,4-tetrazolyl)thio group.

3. The process according to Claim 1, wherein R⁷ is selected from ester-forming groups capable of being removed by catalytic reduction, chemical reduction or treatment under mild conditions, and ester-forming groups capable of being easily removed owing to enzymes in a living body.

4. The process according to Claim 2, wherein the compound of the general formula (I) is 6-[D(-)-α-(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)phenylacetamidol]penicillanic acid or its non-toxic salt.

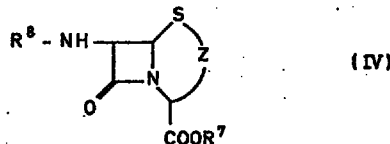
5. The process according to Claim 2, wherein the compound of the general formula (I) is 7-[D(-)-α-(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)-p-hydroxyphenylacetamidol]-3-acetoxymethyl-Δ³-cephem-4-carboxylic acid or its non-toxic salt.

6. The process according to Claim 2, wherein the compound of the general formula (I) is 7-[D(-)-α-(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)-p-hydroxyphenylacetamidol]-3-[2-(5-methyl-1,3,4-thiadiazolyl)-thiomethyl]-Δ³-cephem-4-carboxylic acid or its non-toxic salt.

7. The process according to Claim 2, wherein the compound of the general formula (I) is 7-[D(-)-α-(4-ethyl-2,3-dioxo-1-piperazino-carbonylamino)-p-hydroxyphenylacetamidol]-3-[5-(1-methyl-1,2,3,4-tetrazolyl)thiomethyl]-Δ³-cephem-4-carboxylic acid or its non-toxic salt.

8. A process for producing a compound represented by the general formula (I) as defined in Claim 1, which comprises:

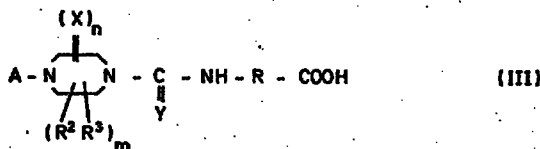
(a) converting a compound of formula (IV),



wherein R⁷ represents a carboxyl-protecting group; R⁸ represents an acyl group; and >Z is as defined in Claim 1, by imino halogenation reaction to the corresponding imino halide compound,

(b) converting the imino halide compound obtained in step (a) by imino-etherification reaction to the corresponding imino ether compound,

(c) reacting the imino ether compound obtained in step (b) with a reactive derivative with respect to the carboxyl group of the compound of formula (III),



wherein R, R², R³, A, X, Y, m and n are the same as defined in Claim 1 and then (d) hydrolyzing the compound obtained in step (c), and, if desired, treating the hydrolyzation product obtained above by a conventional method to remove the carboxyl-protecting group R⁷.



c1ccccc1C or Oc1ccc(C)cc1

$$\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{C} \\ \diagdown \\ \text{CH}_3 \end{array} \quad \text{or} \quad \begin{array}{c} \text{CH}_2 \\ | \\ \text{C} - \text{CH}_2\text{R}^4 \end{array}$$

16. Penicillins and cephalosporins of the general formula (I) whenever
35 produced by the process claimed, in any preceding claim or by an obvious chemical
equivalent thereof.

For the Applicants:
F. J. CLEVELAND & COMPANY,
Chartered Patent Agents,
40—43 Chancery Lane,
London, WC2A 1JQ.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1978.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.

