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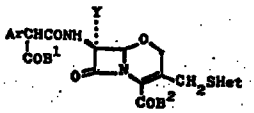
(72) Inventors MASAYUKI NARISADA and WATARU NAGATA

(54) ARYLMALONAMIDO-1-OXADETHIACEPHALOSPORINS

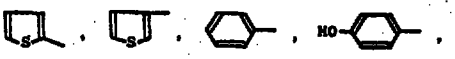
(71) We, SHIONOGI & CO. LTD., a Japanese Body Corporate, of 12, 3-chome, Dosho-machi, Higashi-ku, Osaka, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

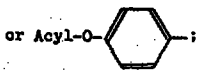
This invention relates to certain 1 - oxadethia - cephalosporins.

The invention provides a compound of the formula:

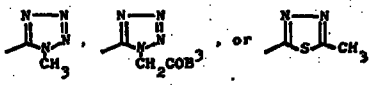


(I)

wherein Ar is 

or Acyl-O- ;

COB^1 and COB^2 are each independently carboxy or protected carboxy;
Het is



COB^3 being carboxy or protected carboxy; and
Y is hydrogen or methoxy;
provided that when Y is methoxy, Het is



The invention includes salts, e.g. pharmaceutically acceptable salts, of the above compounds (I).

Cephalosporin analogs having oxygen in place of a sulfur atom in the nucleus have been described in the Journal of Heterocyclic Chemistry, Volume 5, page 779 (1968) by J. C. Sheehan and M. Dadic; German Patent Application (OLS) No. 2,219,601 (1972); the Canadian Journal of Chemistry, Volume 52, page 3996 (1974) by Saul Wolfe et al.; and the Journal of American Chemical Society, Volume 96, page 7582 (1974) by B. G. Christensen et al.

In contrast to the reports of B. G. Christensen et al. suggesting that their racemic 1-oxacephalosporins showed about half the potency of (1-thia)cephalosporins, the

optically active products prepared by the present inventors were about 4 to 8 times as antibacterially active as the corresponding (1-thia)cephalosporins. However, the β-lactam ring of the 1-oxadethiacephalosporins tends to be less stable with respect to their possible utility as clinical drugs than that of (1-thia)cephalosporins.

Compounds (I) (defined above) selected from the optically active compounds prepared by the present inventors overcome the above-mentioned deficiency of 1-oxadethiacephalosporins.

Furthermore, compounds (I) show the following characteristics:

1) more potent antibacterial activity against gram negative bacteria;

2) higher stability of the β-lactam ring;

3) closer minimal inhibitory concentration values between the bacteria producing and non-producing β-lactamase;

4) less dependency on inoculum size;

5) higher effectiveness against bacteria resistant to certain other cephalosporins (e.g. Enterobacteria, Serratia or indole positive Proteus);

6) higher contribution of bactericidal character; and

7) higher blood level.

Additionally, compounds (I) wherein Y is methoxy have the following properties:

a) broader antibacterial spectra [e.g. 3.6 γ/ml of more against Pseudomonas sp., an aerobic bacteria (Bacteroid fragilis)];

b) higher potency against bacteria producing β-lactamase;

c) higher stability in blood; and

d) lower binding with serum proteins.

In formula (I), preferred groups Ar are 3-thienyl, p-hydroxyphenyl, and p-acyloxyphenyl, in which the acyl moiety is 1—5C alkanoyl, carbamoyl, 2—6C N-alkylcarbamoyl or ureidocarbonyl.

The group Acyl in the definition of Ar can be acyl containing up to 8 carbon atoms, especially 1—5C alkanoyl, 8—12C aralkanoyl, 7—9C aroyl, 2—5C alkoxycarbonyl, 8—20C aralkoxycarbonyl, carbamoyl, 2—6C N-alkylcarbamoyl or ureidocarbonyl.

Specific examples of groups Acyl include formyl, acetyl, propionyl, butyryl, isobutyryl, enanthoyl, phenylacetyl, phenylpropionyl, benzoyl, toluoyl, carbethoxycarbonyl, benzyloxycarbonyl, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N-isobutyl carbamoyl, N,N-dimethylcarbamoyl, carbamoylcarbamoyl or N^{α}-methylureidocarbonyl.

Groups COB^1, COB^2 and COB^3 can be carboxy groups or protected carboxy groups conventional in the chemistry of penicillins and cephalosporins (usually containing up to 15 carbon atoms). Protective groups can be the same or different for each carboxy group in the molecule. Usually, such protective groups are removed to give free carboxy compounds or salts thereof at any stage of synthesis of compounds (I). The structure of the carboxy-protective group(s) can vary widely and generally has no special significance other than protection, deprotection, and, when included, salt formation.

Specific examples of the above-mentioned protective groups are esters (including optionally substituted alkyl esters, e.g. t-butyl, mono-hydroxy-t-butyl, 2,2,2-trichloroethyl and acyloxymethyl esters; aralkyl esters, e.g. benzyl, p-tolylmethyl, p-nitrobenzyl, p-methoxybenzyl, phthalidyl, diphenylmethyl, trityl and phenacyl esters; metal esters, e.g. trimethylsilyl, dimethylmethoxysilyl and trimethylstannyl esters; and other easily removable aliphatic esters; and aromatic esters, e.g. phenyl tolyl, 3,4-dimethylphenyl and 5-indanyl esters) and pharmaceutically acceptable salts (including alkali metal salts, e.g. sodium and potassium salts; alkaline earth metal salts, e.g. magnesium, calcium and acyloxycalcium salts; and salts with organic bases, e.g. procaine, triethylamine and dicyclohexylamine). Each carboxy group in the molecule can be free or protected by the same or different groups.

Preferably COB^1, COB^2 and COB^3 are each, independently, free carboxy or pharmaceutically acceptable salts. Other preferred groups COB^1 are 5-indanyloxycarbonyl, phenoxycarbonyl and dimethylphenoxycarbonyl.

Some carboxy protective groups are useful for changing the character of the products as drugs. Thus, some groups are known for use with drugs which are known in the art. These groups include the following pharmaceutically acceptable groups: phthalidyl, acyloxymethyl, indanyl, phenyl, tolyl, dimethylphenyl, and carbethoxymethyl esters.

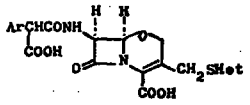
Preferably Y is methoxy, although compounds (I) wherein Y is hydrogen are also important.

Usually, compounds (I) are employed as salts for administration to human or

veterinary subjects. Most preferred salts are sodium or potassium salts, and salts with certain organic bases. Salts are selected from the viewpoints of safety, solubility, stability, etc.

Compounds of particular interest within the scope of formula (I) are:

(a) compounds of the formula:



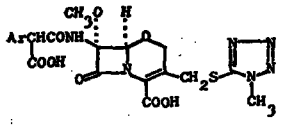
(IX)

wherein

Ar is phenyl, p-hydroxyphenyl, 2-thienyl, or 3-thienyl;

Het is 1-methyltetrazol-5-yl, 1-carboxymethyltetrazol-5-yl, or 2-methyl-1,3,4-thiadiazol-5-yl, and derivatives thereof at the carboxy.

(b) compounds of the formula:



(XIII)

wherein

Ar is phenyl, p-hydroxyphenyl, p-acyloxyphenyl, 2-thienyl, or 3-thienyl, and derivatives thereof at the carboxy.

Specific examples of compounds (I) include the following:

7β - [α - (2 - thienyl) - α - carboxyacetamido] - 3 - (1 - methyltetrazol - 5-yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid,

7β - [α - (2 - thienyl) - α - carboxyacetamido] - 3 - (1 - carboxymethyltetrazol-5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid,

7β - [α - (2 - thienyl) - α - carboxyacetamido] - 3 - (2 - methyl - 1,3,4 - thiadiazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid,

7β - [α - (3 - thienyl) - α - carboxyacetamido] - 3 - (1 - methyltetrazol - 5-yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid,

7β - [α - (3 - thienyl) - α - carboxyacetamido] - 3 - (1 - carboxymethyltetrazol-5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid,

7β - [α - (3 - thienyl) - α - carboxyacetamido] - 3 - (2 - methyl - 1,3,4 - thiadiazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid,

7β - (α - phenyl - α - carboxyacetamido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid,

7β - (α - phenyl - α - carboxyacetamido) - 3 - (1 - carboxymethyltetrazol - 5-yl)thiomethyl - 1 - oxadethia - 3 - cephem - 3 - carboxylic acid,

7β - (α - phenyl - α - carboxyacetamido) - 3 - (2 - methyl - 1,3,4 - thiadiazol-5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid,

7β - (α - p - hydroxyphenyl - α - carboxyacetamido) - 3 - (1 - methyltetrazol-5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid,

7β - (α - p - hydroxyphenyl - α - carboxyacetamido) - 3 - (1 - carboxymethyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid,

7β - (α - p - hydroxyphenyl - α - carboxyacetamido) - 3 - (2 - methyl - 1,3,4-thiadiazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid,

7β - (α - p - acetoxyphenyl - α - carboxyacetamido) - 3 - (1 - methyltetrazol - 5-yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid,

7β - (α - p - acetoxyphenyl - α - carboxyacetamido) - 3 - (1 - carboxymethyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid,

7β - (α - p - acetoxyphenyl - α - carboxyacetamido) - 3 - (2 - methyl - 1,3,4-thiadiazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid,

7β - (α - p - propionyloxyphenyl - α - carboxyacetamido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid,

7β - (α - p- pentanoyloxyphenyl - α - carboxyacetamido) - 3 - (2 - methyl-

1,3,4 - thiadiazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid,

7β - (α - p - carbamoyloxyphenyl - α - carboxyacetamido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid,

7β - (α - p - carbamoyloxyphenyl - α - carboxyacetamido) - 3 - (2 - methyl-1,3,4 - thiadiazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4-carboxylic acid,

7β - (α - p - N - methylcarbamoyloxyphenyl - α - carboxyacetamido) - 3 - (1-methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid,

7β - (α - p - N - pentylcarbamoyloxyphenyl - α - carboxyacetamido) - 3 - (2-methyl - 1,3,4 - thiadiazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylic acid,

7β - (α - p - ureidocarbonyloxyphenyl - α - carboxyacetamido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid,

7β - [α - (2 - thienyl) - α - carboxyacetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid,

7β - [α - (3 - thienyl) - α - carboxyacetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid,

7β - (α - phenyl - α - carboxyacetamido) - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid,

7β - (α - p - hydroxyphenyl - α - carboxyacetamido) - 7α - methoxy - 3 - (1-methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid,

7β - (α - p - acetoxyphenyl - α - carboxyacetamido) - 7α - methoxy - 3 - (1-methyltetrazol 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid,

7β - (α - p - propionyloxyphenyl - α - carboxyacetamdo) - 7α - methoxy - 3-(1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4-carboxylic acid,

7β - (α - p- - benzoyloxyphenyl - α - carboxyacetamido) - 7α - methoxy - 3-(1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4-carboxylic acid,

7β - (α - p - carbamoyloxyphenyl - α - carboxyacetamido) - 7α - methoxy - 3-(1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4-carboxylic acid,

7β - (α - p - N - mehylcarbamoyloxyphenyl - α - carboxyacetamido) - 7α-methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3-cephem - 4 - carboxylic acid,

7β - (α - p - N - propylcarbamoyloxyphenyl - α - carboxyacetamido) - 7α-methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3-cephem - 4 - carboxylic acid,

7β - (α - p - ureidocarbonyloxyphenyl - α - carboxyacetamido) - 7α - methoxy-3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylic acid, and

7β - (α - p - N^{α} - methylureidocarbonyloxyphenyl - α - carboxyacetamido) - 7α-methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3-cephem - 4 - carboxylic acid; and

derivatives thereof protected at the carboxy group with pharmaceutically acceptable groups or conventional protective groups e.g. the derivatives being salts (e.g. salts with inorganic or organic bases e.g. sodium, potassium, magnesium, calcium, and other alkali metal or alkaline earth metal salts, or triethylamine, dicyclohexylamine, morpholine, or N-methylmorpholine salts), and esters (e.g. t-butyl, t-amyl-, 2,2,2-trichloroethyl, acyloxymethyl, phthalidyl, diphenylmethyl, trityl, benzyl, p-nitrobenzyl, p-methoxybenzyl, phenacyl, phenyl or indanyl esters).

Compounds (I) having a 1-methyltetrazol-5-ylthiomethyl group at position 3 are the strongest antibacterial drugs against gram negative bacterial accompanied with a smaller drop in activity at higher inoculum sizes.

Compounds (I) having a 1-carboxymethyltetrazol-5-ylthiomethyl group at position

3 show stronger antiinfection effects in vivo than would be expected from in vitro data. This is due to their ability in achieving high blood levels.

Compounds (I) having a phenylmalonamido, (2-thienyl)malonamido or (3-thienyl)-malonamido group at position 7 show potent antibacterial activity, particularly against gram negative bacteria.

Compounds (I) having a p-hydroxyphenylmalonamido, p-acetoxyphenylmalonamido, p-carbamoyloxyphenylmalonamido, p-N-methylcarbamoyloxyphenylmalonamido or p-ureidocarbonyloxyphenylmalonamido group at position 7 are potent antibacterials showing less deactivation in living animals because of their lower protein binding and higher blood levels than are exhibited by the corresponding unsubstituted arylmalonamido compounds. They also show highly intensified activity against Pseudomonas strains, including those strains resistant to carbenicillin.

Compounds (I) having a methoxy group for Y at position 7α are more stable against β-lactamase, more broadly effective (e.g. have improved activity against Pseudomonas bacteria and other gram negative bacteria), and are more potent than those having hydrogen for Y.

All compounds (I) are novel substances which show potent antibacterial activity and are useful medicines, veterinary drugs and disinfectants. For example, the compounds (I) may be administered orally or parenterally to humans or other animals at daily doses of e.g. from 0.05 to 50 mg/kg body weight.

The compounds (I) are usually used as vials containing sterilized microcrystals or lyophilizate and administered as solutions made up before use. Furthermore, an effective amount of a compound (I) may be administered orally or parenterally with one or more pharmaceutically acceptable carriers, additives, diluents or stabilizers, in various preparation forms, e.g. vials, injections, salves, solutions, tablets, powders and capsules.

Thus, the invention provides a pharmaceutical or veterinary formulation which comprises a compound of the invention or a salt of the invention.

The invention further provides a pharmaceutical or veterinary composition which comprises a compound of the invention or a salt of the invention together with a pharmaceutically acceptable or veterinarily acceptable, respectively, diluent, carrier or excipient. The above compositions or formulations may be in unit dosage form.

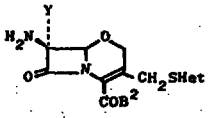
The salts of compounds (I), including alkali metal salts, are used mainly for parenteral administration. The acyloxymethyl, indanyl, phenyl, phthalidyl, and like esters are also suitable for oral application.

Compounds (I) are also useful intermediates for preparing useful compounds within or beyond the scope of the formula (I).

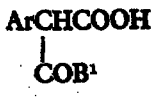
Also included within the scope of the invention is a method for inhibiting the growth of bacteria in an environment, which method comprises administering to the environment an effective amount of a compound of the invention or a salt of the invention, or a formulation of the invention, or of a composition of the invention.

Such a method can be employed in the prevention or cure of disease in a non-human animal, in the prevention of decay in a perishable substance or material, or in disinfecting a substance, material, article or building structure.

Compounds (I) can, for example, be prepared by treating an amine of formula (II) with an arylmalonic acid of formula (III) or reactive derivatives thereof.



(II)



(III)

wherein Ar, COB^1, COB^2, Het and Y are as defined above.

The amino group at position 7 of amine (II) may be activated by a silyl or stannyl group, or protected or activated by a group chosen from 1-haloalkylidine, 1-alkoxyalkylidene, alkylene, carbonyl, readily removable acyl, and like groups, for the acylation. Removal of these groups gives the objective compounds (I).

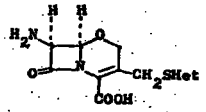
When the arylmalonic acid (III) is used as the free acid, the acylation is preferably carried out in a solvent (particularly nitriles, ethers, amides, halohydrocarbons, or mixtures thereof) and in the presence of a condensing reagent [e.g. N,N' - dialkylcarbodiimides (e.g. N,N' - dicyclohexylcarbodiimide); carbonyl compounds (e.g. carbonyldiimidazole); acylamines (e.g. 2 - ethoxy - 1 - ethoxycarbonyl - 1,2 - dihydroquinoline); isoxazolinium salts (e.g. N - ethyl - 5 - phenylisoxazolinium - 3-

sulfonate or N - t - butyl - 5 - methylisoxazolinium perchlorate); and other condensing reagents] at −10°C to 70°C.

When the arylmalonic acid (III) is used in the form of a reactive derivative, it can, for example, be an anhydride [e.g. a mixed anhydride with an alkylcarbonic acid, an aralkylcarbonic acid, a hydrohalogenic acid (an acid halide), hydrogen azide (acid azide), phosphoric acid, phosphorous acid, sulfuric acid, sulfurous acid, hydrogen cyanide (acid cyanide); a symmetrical intermolecular anhydride; a mixed anhydride with an aliphatic or aromatic sulfonic or carboxylic acid; or a special intramolecular anhydride such as ketene, isocyanate and like reactive anhydrides]; a reactive ester [e.g. an enol ester; an aryl ester (e.g. a pentachlorophenyl, p-nitrophenyl, 2,4-dinitrophenyl or benzotriazole ester)]; a diacylimino ester; a reactive amide [e.g. amides with imidazole or triazole; or reactive amides, e.g. 2 - ethoxy - 1,2 - dihydroquinolin-1 - amide] or a formimino derivative (e.g. a N,N - dialkyliminomethyl ester or a N,N-diacylaniline).

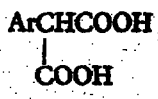
If required, the above-mentioned acylating reagents can be used in the presence of an acid receptor [e.g. an inorganic base (e.g. a hydroxide, carbonate or bicarbonates of an alkali metal or alkaline earth metal), an organic base (e.g. a tertiary amine or an aromatic base), an alkylene oxide (e.g. ethylene oxide or propylene oxide), an amide (e.g. N,N-dimethylformamide or hexamethylphosphorotriamde) and other acid receptors] or a molecular sieve, preferably in a solvent (particularly a ketone, an ester, an ether, a nitrile, an amide, a halohydrocarbon, or a mixture thereof).

Similarly, compounds of formula (IX) can be prepared by reacting an amine of the formula:



(X)

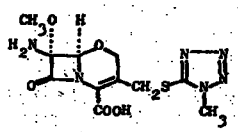
wherein Het is as defined above in connection with formula (IX), or a derivative thereof at the carboxy with a malonic acid derivative of the formula:



(XI)

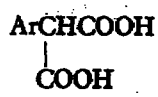
wherein Ar is as defined above in connection with formula (IX), or with a reactive derivative thereof in which one of the carboxy groups may be protected.

Similarly, compounds of formula (XIII) can be prepared by reacting an amine of the formula:



(XIV)

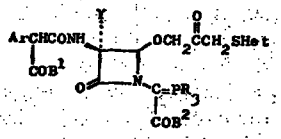
or a derivative thereof at the carboxy with a malonic acid derivative of the formula:



(XV)

wherein Ar is as defined above in connection with formula (XIII), or with a reactive derivative thereof in which one of the carboxy groups may be protected.

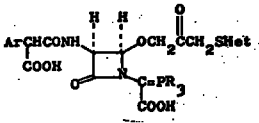
Alternatively, compounds (I) can be prepared from the corresponding non-fused ring azetidinones by cyclization, e.g. by a Wittig reaction. Thus, for example, an azetidinone of formula (IV) may be heated in an inert solvent (e.g. an ether, an aromatic hydrocarbon, a halohydrocarbon, an amide, a sulfoxide, or an anhydride to give a compound (I) in high yield.



(IV)

wherein Ar, COB^1, COB^2, Het and Y are as defined above; and each of the three groups R is the same or different being optionally substituted alkyl or aryl.

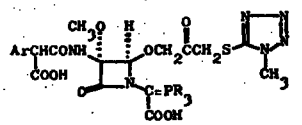
Similarly, compounds of formula (IX) can be prepared by heating an azetidinone of the formula:



(XII)

wherein Ar and Het are each as defined above in connection with formula (IX), and each of the three groups R is the same or different and is optionally substituted alkyl or aryl, or a derivative thereof at the carboxy.

Similarly, compounds of formula (XIII) can be prepared by heating an azetidone of the formula:



(XVI)

wherein Ar is as defined above in connection with formula (XIII), and each of the three groups R is the same or different and is optionally substituted alkyl or aryl, or a derivative thereof at the carboxy.

When Ar is p-hydroxyphenyl, compounds (I) can be treated with an acylating reagent to give compounds (I) wherein Ar is acyloxyphenyl. The acylating reagent and reaction conditions employed are conventional in the art.

When Ar is p-hydroxyphenyl, the compounds can at first be protected at the hydroxy group with an easily removable protective group and afterwards deprotected to give the desired hydroxyphenyl compounds. Representative protective groups include those which form esters [including C_1—C_6, α-haloalkanoyl (e.g. trifluoroacetyl or trichloroacetyl), C_1—C_6 alkanoyl (e.g. acetyl or formyl), C_4—C_8 β-ketocarboxylic acyl (e.g. acetoaceyl), C_2—C_{12} alkoxycarbonyl (e.g. t-butoxycarbonyl, cyclopropylmethoxycarbonyl, norbornyloxycarbonyl or 2,2,2-trichloroethoxycarbonyl), C_8—C_{15} aralkoxycarbonyl (e.g. benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitro- or p-methylbenzyloxycarbonyl or diphenylmethoxycarbonyl), and like acyls] and ethers [including C_1—C_6 alkyl (e.g. methyl, t-butyl, cyclopropylmethyl, isobornyl, tetrahydropyranyl or methoxymethyl), C_7—C_{15} aralkyl (benzyl, p-methoxy, p-methyl- or p-nitrobenzyl or diphenylmethyl, trityl), and like groups]. The protective group is preferably introduced at the stage of use of the arylmalonic acid (III) or reactive derivatives thereof. The deprotection may, for example, be carried out by 1) cleavage of acylates or ethers with an acid (e.g. a mineral acid, a Lewis acid, a strong carboxylic acid or a sulfonic acid) or a base (e.g. sodium or potassium carbonate, hydroxide or an organic base) at room temperature or, if required, at elevated temperature in the presence of a cation scavenger, or 2) hydrogenation of p-nitrobenzyloxycarbonyl or benzyl-oxycarbonyl with hydrogen and platinum or palladium in a conventional manner.

When the carboxy group at position 4, or in the side chain at position 7 and/or in group Het is protected, the protective group(s) may be removed to give the desired compound (I) by conventional methods for removing protective groups. Thus, for example: 1) highly reactive esters, amides and anhydrides are readily hydrolyzed with an acid or a base; 2) 2-haloethyl, benzyl, methylbenzyl, nitrobenzyl and diarylmethyl esters are cleaved by mild reduction (e.g. with tin, zinc or divalent chromium salts in the presence of an acid; with sodium dithionite; or with catalytic hydrogenation with hydrogen over a catalyst, e.g. platinum, palladium or nickel); 3) benzyl, methoxybenzyl, methylbenzyl, dimethoxybenzyl, t-alkyl, trityl, diarylmethyl and cyclopropylmethyl esters are cleaved by the action of an acid or by solvolysis (e.g. with a mineral acid e.g. hydrochloric acid, a Lewis acid e.g. aluminum chloride, a sulfonic acid e.g. toluene-p-sulfonic acid, a strongly acidic carboxylic acid e.g. trifluoroacetic acid or formic acid, if necessary in the presence of a cation acceptor e.g. anisole); 4) phenacyl, ethynyl or p-hydroxy-3,5-di-t-butylbenzyl esters are cleaved by the action of a base (e.g. an alkali metal thiophenoxide, an inorganic base or a basic salt), and like methods.

Compounds (I) having one or more free carboxy groups can be converted into corresponding derivatives by introducing protective groups or substituents into the carboxy group(s) by conventional methods (e.g. for esters, by the action of the corresponding alcohols with said condensing reagents, diazo compounds or haloformates; for salts, the action of alkali metal hydroxides, carbonates or alkanoate salts, or the action of organic bases or ion-exchange resins).

The following detailed examples are provided to further illustrate and describe

the invention. The elemental analyses and physical constants of the products in each Examples are consistent with the given structures.

In the Examples, the products usually contain almost equal amounts of the isomers at the α-asymmetric carbon atom in the amide side chain. Both of the isomers are, of course, included in the scope of this invention, and, if necessary, such isomers are separable by chromatographic techniques or by other conventional methods. The nomenclature adopted is in accordance with that used in a Japanese Patent Application (open to Public Inspection No. 49—133594) filed by Merck Inc., U.S.A.

Preparation 1 (Preparation of 7α - amino compounds)

(1) To a solution of diphenylmethyl 7β - phenylacetamido - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (955 mg) in methylene chloride (24 ml) are added phosphorus pentachloride (666 mg) and pyridine (0.258 ml) in nitrogen gas at −20°C. After stirring at −20°C for 30 minutes and at room temperature for 30 minutes, the mixture is mixed with methanol (12 ml) at −20°C and stirred at room temperature for 30 minutes. The reaction mixture is diluted with water (6 ml), stirred for 30 minutes and concentrated under reduced pressure. The residue is dissolved in 5% aqueous solution of sodium hydrogen carbonate under ice cooling, and extracted with ethyl acetate. The extract is washed with water, dried on sodium sulfate, and concentrated under reduced pressure. The separated crystals are collected by filtration and washed with ether to yield diphenylmethyl 7β - amino - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3-cephem - 4 - carboxylate (661 mg). mp. 151—156°C. Yield: 86.5%.

IR: $\nu_{max}^{CHCl_3}$ 3420, 3345, 1790, 1718, 1630 cm^{-1}.

NMR: δ^{CDCl_3} 1.75brs2H, 3.81s3H, 4.28brs2H, 4.50d(4Hz)1H, 4.64brs2H, 4.98d(4Hz)1H, 6.90s1H, 7.20—7.70m10H.

UV: $\lambda_{max}^{(CH_3)_2SO}$ 286 nm (ε=8695). $[\alpha]_D^{22.5}$ −232.8±7.6° (c=0.360, $(CH_3)_2SO$).

(2) In a procedure similar to that of above (1), diphenylmethyl 7β - phenylacetamido - 3 - (2 - methyl - 1,3,4 - thiadiazol - 5 - yl) - thiomethyl - 1 - oxadethia - 3-cephem - 4 - carboxylate (381.5 mg) in methylene chloride (8 ml) is treated with phosphorus pentachloride (259 mg) and pyridine (0.1 ml) at −20°C, with methanol (8 ml), and with water (4 ml) to give diphenylmethyl 7β - amino - 3 - (2 - methyl-1,3,4 - thiadiazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (273.3 mg). Yield: 88.8%.

IR: $\nu_{max}^{CHCl_3}$ 3420, 3350, 1794, 1723 cm^{-1}.

NMR: δ^{CDCl_3} 1.88s2H, 2.67s3H, 4.25+4.55ABq(14Hz)2H, 4.52d(4Hz)1H, 4.68s2H, 5.00d(4Hz)1H, 7.07s1H.

(3) In a procedure similar to that of above (1), diphenylmethyl 7β - phenylacetamido - 3 - (1 - t - butoxycarbonylmethyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia-3 - cephem - 4 - carboxylate (300 mg) in methylene chloride (10 ml) is treated with phosphorus pentachloride (180 mg) and pyridine (0.07 ml) at −20°C, with methanol (4 ml), and with water (4 ml) to give diphenylmethyl 7β - amino - 3 - (1 - t - butoxycarbonylmethyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (189 mg). Yield: 76%.

IR: $\nu_{max}^{CHCl_3}$ 1795, 1753, 1722 cm^{-1}.

NMR: δ^{CDCl_3} 1.45s9H, 1.60—2.00m2H, 4.30s2H, 4.40—4.60m1H, 4.65brs2H, 4.86s2H, 5.00d(4Hz)1H, 6.95s1H.

Preparation 2 (Introduction of 7α - methoxy)

(1) A solution of diphenylmethyl 7β - amino - 3 - (1 - methyltetrazol - 5 - yl)-thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (600 mg) and 3,5 - di - t-butyl - 4 - hydroxybenzaldehyde (353 mg) in a mixture of benzene (15 ml) and methylene chloride (5 ml) is refluxed for 1 hour while removing water by means of molecular sieve in a Dean Stark water-separator. The resulting solution of diphenylmethyl 7β - (3,5 - di - t- butyl - 4 - hydroxybenzal)amino - 3 - (1 - methyltetrazol-5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate is cooled at −10°C to −15°C, mixed with anhydrous magnesium sulfate (1 g) and then nickel peroxide (0.69 g) with stirring, and stirred at −10°C to −15°C for 30 minutes and at room

temperature for 15 minutes. The reaction mixture is filtered, and the solid is washed with benzene. To the resulting solution of diphenylmethyl 7 - (3,5 - di - t - butyl-4 - oxo - 2,5 - cyclohexadienylidenemethyl) - imino - 3 - (1 - methyltetrazol - 5 - yl)-thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate is added methanol (10 ml), and the solution is allowed to stand at room temperature for 1 hour, and concentrated to dryness under reduced pressure. The residue is chromatographed on silica gel (30 g) containing 10% water and eluted with a mixture of benzene and ethyl acetate (4:1) to give diphenylmethyl 7β - (3,5 - di - t - butyl - 4 - hydroxybenzal)amino-7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylate (906 mg) as practically pure yellow foam. Yield: 99.7%.

(2) To a solution of the above product in a mixture of methanol (10 ml) and tetrahydrofuran (5 ml) is added Girard T reagent (315 mg), and the mixture is stirred for 1 hour at room temperature, diluted with water, and extracted with methylene chloride. The extract is washed with water, dried on sodium sulfate, and evaporated to dryness under reduced pressure. The residue is purified by chromatography on silica gel (30 g) containing 10% water and eluted with a mixture of ethyl acetate: benzene: methylene chloride (1:1:1) to give diphenylmethyl 7β - amino - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4-carboxylate (469 mg). Over-all yield throughout this example: 73.6%. m.p. 160—162°C (decomposition).

IR: $\nu_{max}^{CHCl_3}$ 3425, 3350, 1792, 1724 cm^{-1}.

NMR: δ^{CDCl_3} 2.00brs2H, 3.38s3H, 3.87s3H, 4.32s2H, 4.73s2H, 4.92s1H, 7.00s1H.

As is apparent from above preparation, nickel peroxide is found to be one of the best oxidizing reagents of the phenolic intermediate to introduce a methoxy at position 7α of 1-oxa and also 1-thia cephem rings.

I. Ring Formation

Example I-1

A solution of diphenylmethyl α - [4β - (1 - methyltetrazol - 5 - yl)thioacetonyl-oxy - 3β - (α - phenyl - α - diphenylmethoxycarbonyloxyacetamido) - 2 - oxoazetidin-1 - yl] - α - triphenylphosphoranylideneacetate (650 mg) in dioxane (5 ml) is refluxed in nitrogen atmosphere for 16 hours. The reaction mixture is concentrated under reduced pressure. The residue is purified by chromatography on silica gel (20 g) containing 10% water, and eluted with a mixture of benzene and ethyl acetate (4:1) to give diphenylmethyl 7β - (α - phenyl - α - diphenylmethoxycarbonylacetamido)-3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (432 mg). mp 107—109°C. Yield: 80%.

IR: ν_{max}^{KBr} 3410, 1793, 1719, 1694, 1630, 1600 cm^{-1}.

Example I-2

In a procedure similar to that described in Example I-1, diphenylmethyl α-[4β - (1 - methyltetrazol - 5 - yl)thioacetonyloxy - 3β - (α - phenyl - α - diphenyl-methoxycarbonylacetamido) - 3α - methoxy - 2 - oxoazetidin - 1 - yl] - α - triphenyl-phosphoranylideneacetate (543 mg) is refluxed in dioxane (5 ml) for 15 hours in nitrogen gas, and purified by chromatography on silica gel (15 g) to give diphenyl-methyl 7β - (α - diphenylmethoxycarbonyl - α - phenylacetamido) - 7α - methoxy-3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carb-oxylate (540 mg). Yield: 67%.

Example I-3

In a procedure similar to that of Example I-2, diphenylmethyl α - [3β - (α - p-benzyloxyphenyl - α - diphenylmethoxycarbonylacetamido) - 3α - methoxy - 4β - {3-(1 - methyltetrazol - 5 - yl)thiomethyl - 2 - oxopropoxy} - 2 - oxoazetidin - 1 - yl]-α-triphenylphosphoranilideneacetate is refluxed in dioxane for 10 hours under nitrogen and purified by chromatography on silica gel to give diphenylmethyl 7β - (α - di-phenylmethoxycarbonyl - α - p - benzyloxyphenylacetamido) - 7α - methoxy - 3 - (1-methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate.

The starting material of this process is prepared from diphenylmethyl - α - (3β-benzamido - 4β - allyloxy - 2 - oxoazetidin - 1 - yl) - α - isopropylideneacetate by the alignment of reactions comprising with 1) peracid, 2) t-butyl hypochlorite, 3) lithium methoxide, 4) lithium 1 - methyltetrazol - 5 - ylmercaptide, and 5) chromium trioxide

to give diphenylmethyl α - [3β - benzamido - 3α - methoxy - 4β - [3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 2 - oxopropoxy] - 2 - oxoazetidin - 1 - yl] - α - isopropylideneacetate, which is treated with 6) phosphorus pentachloride, 7) methanol, and 8) triethylamine to give diphenylmethyl α - [3β - amino - 3α - methoxy - 4β - {3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 2 - oxopropoxy} - 2 - oxoazetidin - 1 - yl] - α - isopropylideneacetate, which is treated with 9) α - p - benzyloxyphenyl - α - benzyloxycarbonylacetyl chloride and triethylamine, 10) ozone, 11) zinc and acetic acid, 12) thionyl chloride and pyridine, and 13) triphenylphosphine.

II. Amide formation

Example II-1

To a stirred solution of diphenylmethyl 7β - amino - 3 - (1 - methyltetrazol - 5-yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (192 mg) in tetrahydrofuran (2 ml) and acetone (1 ml) are added mono-diphenylmethyl phenylmalonate (208 mg) and N - ethoxycarbonyl - 2 - ethoxy - 1,2 - dihydroquinoline (148 mg) at 0°C, and then the mixture is allowed to stand at room temperature overnight. The reaction mixture is diluted with ethyl acetate, washed with 2N-hydrochloric acid, water, 5% aqueous solution of sodium hydrogencarbonate, and then water, dried on sodium sulfate, and evaporated to dryness. The residue is purified by chromatography on silica gel (20 g) containing 10% water and eluted with a mixture of benzene and ethyl acetate (4:1). The crystals obtained from the fraction are washed with a mixture of ether and n-pentane to give diphenylmethyl 7β - (α - phenyl - α - diphenylmethoxycarbonylacetamido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3-cephem - 4 - carboxylate, m.p. 100—105°C. Yield: 40%.

IR: $\nu_{max}^{CHCl_3}$ 1800, 1720, 1680 cm^{-1}.

NMR: δ^{CDCl_3} 7.00s1H, 6.95s1H, 5.80dd(4.9Hz)1H, 5.06d(4Hz)1H, 4.75s1H, 4.65brs2H, 4.33s2H, 3.86s3H.

By using α - (diphenylmethoxycarbonyl - α - phenyl)acetyl chloride, triethylamine hydrochloride, and pyridine instead of mono-diphenylmethyl phenylmalonate and N - ethoxycarbonyl - 2 - ethoxy - 1,2 - dihydroquinoline, the reaction is analogously carried out for 25 minutes to give the same product as mentioned above in 99% yield. m.p. 107—109°C.

IR: ν_{max}^{KBr} 3410, 1793, 1719, 1694, 1630, 1600 cm^{-1}.

UV: $\lambda_{max}^{(CH_3)_2SO}$ 281 nm (ε=10136).

NMR: $\delta^{(CD_3)_2SO}$ 3.84s3H, 4.30brs2H, 4.58brs2H, 4.69s1H/2, 4.71s1H/2, 5.02d(4Hz)1H, 5.76dd(4;9Hz)1H, 6.86brs1H, 6.90brs1H, 7.0 — 7.5m20H, 7.76d(9Hz)1H,

$[\alpha]_D^{25}$ −144.2±8.1° (c=0.226, $(CH_3)_2SO$).

Example II-2

To a stirred solution of diphenylmethyl 7β - amino - 3 - (1 - methyltetrazol - 5-yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (500 mg) in methylene chloride (20 ml) are added pyridine (0.1 ml) and a solution of α - (p - nitrobenzyloxycarbonyl) - α -phenylacetyl chloride (510 mg) in methylene chloride (2 ml) under ice—cooling in nitrogen atmosphere, and the mixture is stirred for 25 minutes. The reaction mixture is poured into water, and extracted with methylene chloride. The extract is dried on sodium sulfate and evaporated to dryness to yield residue (1.04 g) which is chromatographed on silica gel (40 g) containing 10% water, eluted with a mixture of benzene and ethyl acetate (4:1), and crystalized from a mixture of ethyl acetate and ether to give diphenylmethyl 7β - (α - p - nitrobenzyloxycarbonyl - α-phenylacetamido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3-cephem - 4 - carboxylate (670 mg),
mp. 122—125°C. Yield: 83%.

UV: $\lambda_{max}^{(CH_3)_2SO}$ 278 nm (ε=18490).

IR: ν_{max}^{KBr} 3400, 3340, 1792, 1742, 1718, 1680, 1631, 1604, 1520, 1345 cm^{-1}.

NMR: $\delta^{(CH_3)_2SO}$ 3.88s3H/2, 3.89s3H/2, 4.24brs2H, 4.65brs2H, 5.05s1H, 5.20d(4Hz)1H, 5.32brs2H, 5.75m1H, 6.86s1H, 7.20—7.70m15H, 7.50—8.0$A_2X_2$4H.

$[\alpha]_D^{22.5}$ −150.6±5.4° (c=0.350, $(CH_3)_2SO$).

Example II-3

To a stirred solution of diphenylmethyl 7β - amino - 3 - (1 - methyltetrazol - 5-yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxlyate (100 mg) in methylene chloride (11 ml) are added pyridine (21 mg) and a solution of α - (indan - 5 - yl)-oxycarbonyl - α - phenylacetyl chloride (prepared from the corresponding acid (77 mg)) in methylene chloride (2 ml) under ice cooling, and the mixture is stirred for 30 minutes. The reaction mixture is poured into a mixture of ethyl acetate and water, and the organic layer is taken up. This is washed with diluted hydrochloric acid, aqueous solution of sodium hydrogen-carbonate, water, and aqueous solution of sodium chloride, dried on magnesium sulfate, and evaporated to dryness. The residue is purified by chromatography on silica gel (5.5 g) containing 10% water, and eluted with a mixture of benzene and ethyl acetate (4:1) to give diphenylmethyl 7β - [α-(5 - indenyl(oxycarbonyl - α - phenylacetamido] - 3 - (1 - methyltetrazol - 5 - yl)-thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (144 mg) as pale yellow foam. Yield: 95.4%.

IR: $\nu_{max}^{CHCl_3}$ 1800, 1735, 1685 cm^{-1}.

Example II-4

To a solution of diphenylmethyl 7β - amino - 3 - (1 - methyltetrazol - 5 - yl)-thiomethyl-1-oxadethia-3-cephem-4-carboxylate (144 mg) in methylene chloride (4 ml) are added pyridine (0.048 ml) and a solution of phenylmalonyl hemichloride in methylene chloride (2 ml) (prepared by reacting phenylmalonic acid (108 mg) with thionyl chloride (0.048 ml) in a mixture of ether (1 ml) and dimethylformamide (2 drops) at room temperature for 20 hours) and the mixture is kept at 0°C for 20 minutes. The reaction mixture is diluted with ethyl acetate, washed with dilute hydrochloric acid and water, dried on sodium sulfate, and concentrated. The residue is purified by chromatography on silica gel containing 10% water, and eluted with a mixture of ethyl acetate and benzene (1:1 to 1:0) to give diphenylmethyl 7β 1 (α - carboxy - α - phenylacetamido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1-oxadethia - 3 - cephem - 4 - carboxylate (107 mg). Yield: 61%.

Example II-5

To a solution of 7β - amino - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1-oxadethia - 3 - cephem - 4 - carboxylic acid (78 mg) and triethylamine (0.036 ml) in methylene chloride (1 ml) is added a solution of phenylmalonyl monochloride monobenzhydryl ester in methylene chloride (2 ml) [prepared by reacting monobenz-hydryl phenylmalonate (60 mg) with thionyl chloride (0.04 ml) in a mixture of ether (1 ml) and dimethylformamide (1 drop) at room temperature for 10 hours] and the mixture is kept at 0°C for 1 hour. The reaction mixture is diluted with a mixture of ethyl acetate and acetic acid (9:1) to give 7β - (α - diphenylmethoxycarbonyl - α-phenylacetamido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3-cephem - 4 - carboxylic acid (60 mg).

Example II-6

To a solution of 7β - amino - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1-oxadethia - 3 - cephem - 4 - carboxylic acid (78 mg) and triethylamine (0.036 ml) in methylene chloride (1 ml) is added a solution of phenylchloroformylketene (45 mg) in methylene chloride (0.5 ml), and the mixture is kept at 0°C for 2 hours. The reaction mixture is washed with water, dried, and evaporated. The residue is dissolved in ethyl acetate, purified by chromatography on silica gel (10 g) containing 10% water, and eluted with a mixture of ethyl acetate and acetic acid (9:1) to yield 7β 1 (α-phenyl - α - carboxyacetamido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxa-dethia - 3 - cephem - 4 - carboxylic acid (88 mg). Yield: 74%.

Example II-7

A solution of diphenylmethyl 7β - amino - 3 - (1 - methyltetrazol - 5 - yl)thio-methyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (96 mg) in methylene chloride (3 ml) is added to a solution of a mixed anhydride [prepared by reacting mono-t-butyl p-hydroxyphenylmalonate (76 mg) with i-butyl chloroformate (0.037 ml) in the presence of triethylamine (0.0416 ml) in methylene chloride (4 ml) at −30°C for 30 minutes and at 0°C for 10 minutes], and the mixture is stirred at −30°C for 30 minutes, at 0°C for 2 hours, and at room temperature for 30 minutes. The reaction mixture is concentrated under reduced pressure. The residue is dissolved in a mixture (2 ml) of pyridine and water (7:3), and stirred at room temperature for 1 hour. The

reaction mixture is poured into ice-water, and extracted with ethyl acetate. The extract is washed wtih water, 2N-hydrochloric acid, water, 5% aqueous solution of sodium hydrogen carbonate, and water, dried on sodium sulfate, and concentrated under reduced pressure. The residue (148 mg) is purified by chromatography on silica gel (15 g) containing 10% water and eluted with a mixture of benzene and ethyl acetate (4:1). The eluate is triturated in a mixture of ether and pentane to give diphenylmethyl 7β - (α - p - hydroxyphenyl - α - t- butoxycarbonylacetamido) - 3-(1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (66 mg). mp. 124—126°C. Yield: 46%.

IR: $\nu_{max}^{CHCl_3}$ 3410, 3320, 1800, 1717, 1679, 1510 cm^{-1}.

NMR: δ^{CDCl_3} 1.40s9H, 3.80s3H, 4.27brs2H, 4.38s1H/2, 4.42s1H/2, 4.62brs2H, 5.04d(4Hz)1H, 5.70dd(4;10Hz)1H, 6.46—8.31m17H.

Example II-8

To a suspension of α - p - hydroxyphenylmalonic acid monobenzhydryl ester (507 mg) in methylene chloride (3 ml) are added triethylamine (139 μl) and oxalyl chloride (85 μl) at 0°C. After stirring for 45 minutes at 0°C, the mixture is added to a solution of diphenylmethyl 7β - amino - 3 - (1 - methyltetrazol - 5 - yl) - thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (191 mg) in methylene chloride (3 ml) and pyridine (80 μl) at 0°C. After stirring for 30 minutes at 0°C, the reaction mixture is diluted with ethyl acetate, washed with 2N-hydrochloric acid, water, 5% sodium hydrogencarbonate aqueous solution, and water, dried on sodium sulfate, and concentrated under reduced pressure. The residue is chromatographed on silica gel (15 g) containing 10% water, and eluted with a mixture of benzene and ethyl acetate (9:1) to give diphenylmethyl 7β - [α - p - hydroxyphenyl - α - diphenylmethoxycarbonylacetamido] - 3 - (1 - methyltetrazol - 5 - yl) - thiomethyl - 1 - oxadethia-3 - cephem - 4 - carboxylate as colorless foam (137 mg). Yield: 41.6%.

IR: $\nu_{max}^{CHCl_3}$ 3325, 1798, 1722, 1679 cm^{-1}.

NMR: δ^{CDCl_3} 3.73s3H, 4.20brs2H, 4.53brs2H, (4.60s+4.63s)1H, 4.93brd(4Hz)1H, 5.47—5.77m1H.

Example II-9

To a solution of diphenylmethyl 7β -amino - 3 - (1 - methyltetrazol - 5 - yl)-thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (96 mg) in a mixture of tetrahydrofuran (1 ml) and acetone (0.5 ml) are added mono-t-butyl α-(2-thienyl)-malonate (129 mg) and 1-ethoxy-carbonyl-2-ethoxy-1,2-dihydroquinoline (132 mg) in four equal portions at 1 hour intervals with stirring at room temperature in nitrogen gas, and the mixture is stirred for 1 hour. The reaction mixture is diluted with ethyl ethyl acetate, washed with 2N-hydrochloric acid, water, 5% aqueous sodium hydrogencarbonate, and water, dried on sodium sulfate, and concentrated under reduced pressure. The residue (251 mg) is purified by chromatography on silica gel (10 g) containing 10% water, and eluted with a mixture of benzene and ethyl acetate (4:1). The eluate is triturated with a mixture of ether and pentane to give diphenylmethyl 7β-[a - (2 - thienyl) - α - t - butoxycarbonylacetamido] - 3 - (1 - methyltetrazol - 5-yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate as amorphous powder (49 mg). mp. 97—99°C. Yield: 34.8%.

IR: $\nu_{max}^{CHCl_3}$ 3400, 1800, 1720, 1690, 1511 cm^{-1}.

NMR: δ^{CDCl_3} 1.47s9H, 3.93s3H, 4.32s2H, 4.69brs2H, 4.80brs1H, 5.09d(4Hz)1H, 5.75dd(10;4Hz)1H, 6.90—7.73m15H.

Example II-10

To a solution of diphenylmethyl 7β - amino - 3 - (1 - methyltetrazol - 5 - yl) - thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (96 mg) in a mixture of tetrahydrofuran (1 ml) and acetone (0.5 ml) are added mono-t-butyl α-(3-thienyl)-malonate (132 mg) and 1-ethoxy-carbonyl-2-ethoxy-1,2-dihydroquinoline (132 mg) under ice-cooling, and the mixture is stirred at room temperature for 4 hours. The reaction mixture is diluted with ethyl acetate, washed with water, 1N-hydrochloric acid, water, 5% aqueous solution of sodium hydrogen carbonate, and saturated solution of sodium chloride, dried on magnesium sulfate, and concentrated. The residue (198 mg) is purified by chromatography on silica gel (10 g) containing 10% water,

and eluted with a mixture of benzene and ethyl acetate (1:1) to yield diphenylmethyl 7β - [α - (3 - thienyl) - α - t - butoxycarbonylacetamido] - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (56 mg) as colorless powder. mp. 85—90°C. Yield: 39.7%.

IR: $\nu_{max}^{CHCl_3}$ 1798, 1720, 1685, 1630 cm^{-1}.

NMR: δ^{CDCl_3} 1.45s9H, 3.85s3H, 4.32s2H, 4.67m3H, 5.06d(4Hz)1H, 5.86dd(10;4Hz)1H, 7.00s1H, 7.1—7.65m14H.

Example II-11

To a solution of diphenylmethyl 7β - amino - 3 - (1 - t - butoxycarboxylmethyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (102 mg) in a mixture of tetrahydrofuran (2 ml) and acetone (1 ml) are added monobenzhydryl α-phenylmalonate (186 mg) and N-ethoxycarbonyl - 2 - ethoxy - 1,2 - dihydroquinoline (88 mg) in two portions, and the mixture is stirred at room temperature for 3.5 hours. The reaction mixture is mixed with ethyl acetate, washed with 2N-hydrochloric acid, water, 5% sodium hydrogencarbonate aqueous solution and water, dried on sodium sulfate, and concentrated under reduced pressure. The residue is chromatographed on silica gel (10 g) containing 10% water, eluted with a mixture of benzene and ethyl acetate (9:1), and concentrated to give diphenylmethyl 7β - (α - diphenylmethoxycarbonyl - α - phenylacetamido) - 3 - (1 - t - butoxycarbonylmethyltetrazol-5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (63 mg) as colorless foam. Yield: 39%.

IR: $\nu_{max}^{CHCl_3}$ 1800, 1750, 1725, 1680 cm^{-1}.

NMR: δ^{CDCl_3} 6.96s1H, 6.93s1H, 5.75dd(4;9Hz)1H, 5.03d(4Hz)1H, 4.90s2H, 4.73s1H/2, 4.71s1H/2, 4.60brs2H, 4.30s2H, 1.40s9H.

Example II-12

To a solution of diphenylmethyl 7β - amino - 3 - (1 - t - butoxycarbonylmethyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (87 mg) in acetonitrile (2 ml) are added N - [α - t- butoxycarbonyl - α - (2 - thienyl)acetoxy]-succinimide (76 mg) and N-methylmorpholine (0.016 ml) in nitrogen atmosphere, and the mixture is stirred for 90 minutes. The reaction mixture is mixed with ethyl acetate, washed with dilute hydrochloric acid, water, 5% sodium hydrogencarbonate aqueous solution, and water, dried on sodium sulfate, and concentrated. The residue is chromatographed on silica gel (10 g) containing 10% water, and eluted with a mixture of benzene and ethyl acetate (9:1) to give diphenylmethyl 7β - [α - t- butoxycarbonyl - α - (2 - thienyl) - acetamido] - 3 - (1 - t- butoxycarbonylmethyltetrazol-5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem 4 - carboxylate (96 mg) as colorless foam. Yield: 80%.

IR: $\nu_{max}^{CHCl_3}$ 1802, 1750, 1722, 1690 cm^{-1}.

NMR: δ^{CDCl_3} 6.93s1H, 5.72dd(4;9Hz)1H, 5.06d(4Hz)1H, 4.83s2H 4.75brs1H, 4.60brs2H, 4.30s2H, 1.45s18H.

Example II-13

To a solution of diphenylmethyl 7β - amino - 3 - (2 - methyl - 1,3,4 - thiadiazol-5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (215 mg) in a mixture of tetrahydrofuran (4 ml) and acetone (2 ml) are added three lost of hemidiphenylmethyl α-phenylmalonate (131 mg×3) and 1 - ethoxycarbonyl - 2 - ethoxy-1,2 - dihydroquinoline (107 mg×3) at room temperature in 1.5 hours interval. After 2 hours, the reaction mixture is diluted with ethyl acetate, washed with water, diluted hydrochloric acid, water, aqueous sodium hydrogencarbonate, and water, dried on sodium sulfate, and concentrated. The residue is purified by chromatography on silica gel (30 g) containing 10% water, eluted with a mixture of benzene and ethyl acetate (4:1), and the eluate is triturated with a mixture of ether and n-pentane to give diphenylmethyl 7β - (α - phenyl - α - diphenylmethoxycarbonylacetamido) - 3 - (2-methyl - 1,3,4 - thiadiazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (170 mg) as colorless foam. Yield: 47.5%.

IR: $\nu_{max}^{CHCl_3}$ 3350, 1799, 1715, 1690sh cm^{-1}.

NMR: δ^{CDCl_3} 2.67s3H, 4.22+4.53ABq(14Hz)2H, 4.57s2H, 4.75s1H, 5.00d(4Hz)1H, 5.73dd(4;9.5Hz)1H, 6.92s1H, 6.97s1H.

Example II-14

To a solution of α - diphenylmethoxycarbonyl - α - phenylacetic acid (103.9 mg) in methylene chloride (2 ml) cooled at 0°C are added triethylamine (0.042 ml) and oxalyl chloride (0.0256 ml). After stirring for 10 minutes at 0°C, the mixture is poured into a solution of diphenylmethyl 7β - amino - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (101.7 mg) and pyridine (0.0594 ml) in methylene chloride (5 ml) at 0°C, stirred for 1 hour at 0°C, diluted with ethyl acetate, washed with dilute hydrochloric acid, water, aqueous sodium hydrogencarbonate, and water, dried on sodium sulfate, and concentrated under reduced pressure. The obtained residue is chromatographed on silica gel (20 g) containing 10% water, and eluted with a mixture of benzene and ethyl acetate (4:1) to give diphenylmethyl 7β - (α - diphenylmethoxycarbonyl - α - phenylacetamido)-7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylate (121.2 mg) as colorless foam. Yield: 72.4%.

IR: $\nu_{max}^{CHCl_3}$ 3320, 1792, 1725, 1700 cm^{-1}.

NMR: δ^{CDCl_3} (3.40s+3.42s)3H, 3.69s3H, 4.22s2H, 4.45s2H, 4.75s1H, 5.00s1H, 6.92s2H, 7.85s1H.

Example II-15

A mixture of α - (indan - 5 - yl)oxycarbonyl - α -phenylacetic acid (148 mg) and thionyl chloride (0.25 ml) is heated at 70°C for 1 hour, and evaporated under reduced pressure. The residue is dissolved in benzene (2 ml) and evaporated again to dryness. The residue is dissolved in methylene chloride (2 ml), and poured into a solution of diphenylmethyl 7β - amino - 7α methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (101.7 mg) and pyridine (0.016 ml) in methylene chloride (4 ml) at 0°C. After stirring for 30 minutes at 0°C, the mixture is diluted with ethyl acetate, washed with aqueous sodium hydrogencarbonate, water, diluted hydrochloric acid, and water, dried on sodium sulfate, and evaporated under reduced pressure. The residue is chromatographed on silica gel (20 g) containing 10% water to give diphenylmethyl 7β - [α - (indan - 5 - yl)oxycarbonyl - α-phenylacetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1-oxadethia - 3 - cephem - 4 - carboxylate (116.1 mg) as colorless foam. Yield: 73.8%.

IR: $\nu_{max}^{CHCl_3}$ 3390, 3320, 1780, 1727, 1700 cm^{-1}.

NMR: δ^{CDCl_3} 2.05quintet(7Hz)2H, 2.87t(7Hz)4H, 3.48s3H, 3.77s3H, 4.23s2H, 4.53s2H, 4.87s1H, 5.02s1H.

Example II-16

To a solution of α - diphenylmethoxycarbonyl - α - p - acetoxyphenylacetic acid (142 mg) in methylene chloride (2 ml) cooled at 0°C are added triethylamine (0.0416 ml) and oxalyl chloride (0.0256 ml). After stirring for 15 minutes at 0°C, the mixture is mixed gradually with a solution of diphenylmethyl 7β - amino - 7α - methoxy-3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (101.7 mg) and pyridine (0.024 ml) in methylene chloride (4 ml) at 0°C, stirred for 15 minutes, diluted with ethyl acetate, washed with aqueous sodium hydrogencarbonate, water, diluted hydrochloric acid, and water, dried on sodium sulfate, and concentrated under reduced pressure. The obtained residue is chromatographed on silica gel (20 g) containing 10% water to give diphenylmethyl 7β - (α-diphenylmethoxycarbonyl - α - p - acetoxyphenylacetamido) - 7α - methoxy - 3 - (1-methyltetrazol - 5 - yl) - thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (133.4 mg) as colorless foam from fractions eluted with a mixture of benzene and ethyl acetate (2:1). Yield: 74.5%.

IR: $\nu_{max}^{CHCl_3}$ 3325, 1792, 1730, 1700sh cm^{-1}.

NMR: δ^{CDCl_3} 2.40s3H, 3.40s3H, 3.67s3H, 4.17s2H, 4.42s2H, 4.73s1H, 4.98s1H.

Example II-17

To a solution of α - diphenylmethoxycarbonyl - α - p - hydroxyphenylacetic acid (254 mg) in methylene chloride (3 ml) are added triethylamine (0.083 ml) and oxalyl chloride (0.051 ml) at 0°C. After stirring for 15 minutes, the mixture is added to a solution of diphenylmethyl 7β - amino - 7α - methoxy - 3 - (1 - methyltetrazol - 5-yl) - thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (101.7 mg) and pyridine (0.048 ml) in methylene chloride (4 ml) at 0°C. After stirring for 30 minutes

at 0°C, the mixture is diluted with ethyl acetate, washed with aqueous sodium hydrogencarbonate, water, hydrochloric acid, and water, dried on sodium sulfate, and evaporated under reduced pressure. The obtained residue is chromatographed on silica gel (20 g) containing 10% water and eluted with a mixture of benzene and ethyl acetate (2:1) to give diphenylmethyl 7β - (α - diphenylmethoxycarbonyl - α - p-hydroxyphenylacetamido) - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl-1 - oxadethia - 3 - cephem - 4 - carboxylate (86.4 mg) as colorless foam. Yield: 49.6%.

IR: $\nu_{max}^{CHCl_3}$ 3585, 3315, 1790, 1722, 1700sh cm^{-1}.

NMR: δ^{CDCl_3} (3.45s+3.48s)3H, (3.72s+3.75s)3H, 4.18s2H, 4.45s2H, (4.67s+4.70s)1H, 5.02s1H.

Example II-18

To a suspension of α - (5 - indanyl)oxycarbonyl - α - p - hydroxyphenylacetic acid (370 mg) in methylene chloride (4 ml) are added triethylamine (139 μl) and oxalyl chloride (85 μl) at 0°C in nitrogen to give clear solution. After stirring for 20 minutes at 0°C, the mixture is added to a solution of diphenylmethyl 7β - amino-7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl) - thiomethyl - 1 - oxadethia - 3-cephem - 4 - carboxylate (203 mg) in methylene chloride (5 ml) and pyridine (80 μl), and the mixture is stirred for 10 minutes. The reaction mixture is diluted with ethyl acetate, washed with 2N-hydrochloric acid, water, 5% sodium hydrogencarbonate aqueous solution, and water, dried over sodium sulfate, and concentrated under reduced pressure to give pale yellow foam, which is chromatographed on silica gel (50 g) containing 10% water, and eluted with a mixture of benzene and acetic acid (1:1) to give diphenylmethyl 7β - [α - p - hydroxyphenyl - α - (5 - indanyl) - oxycarbonylacetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl) - thiomethyl-1 - oxadethia - 3 - cephem - 4 - carboxylate as crystalline residue (230 mg); Yield: 71.6%) which is recrystallized from a mixture of chloroform and ether to give pure crystals melting at 114—116°C.

UV: $\nu_{max}^{CH_3OH}$ 272 (ε=9500), 284 (ε=9260) nm.

NMR: $\delta^{CD_3COCD_3}$ 2.1m2H, 2.87t(7Hz)4H, 3.43s3H, 3.91s3H, 4.31s2H, 4.65s2H, 5.07s1H, 5.13s1H, 6.92brs3H.

IR: $\nu_{max}^{CHCl_3}$ 3590, 3335, 1789, 1736, 1722, 1700, 1601 cm^{-1}.

Example II-19

To a solution of α - t - butoxycarbonyl - α - (3 - thienyl)acetic acid (97 mg) in methylene chloride (1 ml) are added triethylamine (0.042 ml) and oxalyl chloride (0.026 ml) at 0°C in nitrogen atmosphere. After stirring for 30 minutes at 0°C, the mixture is poured into a solution of diphenylmethyl 7β -amino - 7α - methoxy - 3-(1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (101 mg) and pyridine (0.024 ml) in methylene chloride (3 ml) at 0°C in nitrogen atmosphere. After stirring at 0°C for 90 minutes, the mixture is diluted with methylene chloride, washed with 5% sodium hydrogencarbonate in water, 2N-hydrochloric acid, and water, dried on sodium sulfate, concentrated under reduced pressure, chromatographed on silica gel (5 g) containing 10% water, and eluted with a mixture of benzene and ethyl acetate (2:1) to give diphenylmethyl 7β - [α - t - butoxycarbonyl - α - (3 - thienyl)acetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5-yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (144 mg) as colorless foam. Yield: quantitative.

IR: $\nu_{max}^{CHCl_3}$ 1795, 1720, ca. 1700 cm^{-1}.

NMR: δ^{CDCl_3} 6.96s1H, (5.07s+5.05s)1H, 4.60brs3H, 4.30brs2H, 3.83s3H, (3.53s+3.50s)3H, 1.41s9H.

Example II-20

To a solution of 3-thienylmalonic acid indanyl ester (120 mg) in methylene chloride (1.5 ml) are added triethylamine (42 μl) and oxalyl chloride (26 μl) under ice cooling. After stirring for 15 minutes, the mixture is added to a solution of diphenylmethyl 7β - amino - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl) - thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (116 mg) in methylene chloride

(3 ml) and pyridine (24 μl), and the mixture is stirred at 0°C for 1 hour. The reaction mixture is poured into ethyl acetate, washed with 2N-hydrochloric acid, water, 5% sodium hydrogencarbonate aqueous solution, and water, dried over magnesium sulfate, and concentrated. The residue is chromatographed on silica gel (10 g) containing 10% water, and eluted with a mixture of benzene and ethyl acetate (10:1) to give diphenylmethyl 7β - [α - (3 - thienyl) - α - (indan - 5 - yl)oxycarbonylacetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia-3 - cephem - 4 - carboxylate (140 mg). Yield: 78%.

IR: $\nu_{max}^{CHCl_3}$ 3400, 3327, 1789, 1736, 1712 cm^{-1}.

NMR: δ^{CDCl_3} 2.07m2H, 2.87br-t(7Hz)4H, 3.50s3H, 3.77s3H, 4.24s2H, 4.56s2H, 4.97s1H, (5.02s+5.04s)1H, 6.88brs3H.

$[\alpha]_D^{22.5}$ −68.2±1.1° (c=1.023, $CHCl_3$).

Example II-21

To a solution of 3-thienylmalonic acid monobenzhydryl ester (710 mg) in methylene chloride (5 ml) are added triethylamine (210 μl) and oxalyl chloride (130 μl) under ice cooling. After stirring for 15 minutes at the same temperature, the mixture is added to a solution of diphenylmethyl 7β - amino - 7α - methoxy - 3 - (1-methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (510 mg) in methylene chloride (15 ml) and pyridine (120 μl) under ice cooling. After stirring for 30 minutes, the mixture is poured into ethyl acetate, washed with 2N-hydrochloric acid, water, 5% sodium hydrogencarbonate and water, dried on magnesium sulfate, and concentrated. The residue is chromatographed on silica gel (100 g) containing 10% water, and eluted with a mixture of benzene and ethyl acetate (10:1—4:1) to give diphenylmethyl 7β - [α - (3 - thienyl) - α - diphenylmethoxycarbonylacetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate as colorless foam (834 mg).

IR: $\nu_{max}^{CHCl_3}$ 1790, 1728, 1710sh cm^{-1}.

NMR: δ^{CDCl_3} 3.30s3H, 3.60s3H, 4.09s2H, 4.37s2H, 4.79s1H, 4.90s1H, 6.87s2H.

Example II-22 (phenyl ester)

To a suspension of 3-thienylmalonic acid monophenyl ester (105 mg) in methylene chloride (1.5 ml) are added triethylamine (42 μl) and oxalyl chloride (26 μl) under ice cooling.

After stirring for 15 mnutes, the mixture is added to a solution of diphenylmethyl 7β - amino - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1-oxadethia - 3 - cephem - 4 - carboxylate (116 mg) in methylene chloride (3 ml) and pyridine (24 μl) at 0°C, and the mixture is stirred at 0°C for 1 hour. The reaction mixture is poured into ethyl acetate, washed wth 2N-hydrochloric acid, water, 5% sodium hydrogencarbonate aqueous solution, and water, dried over magnesium sulfate, and concentrated. The residue is chromatographed on silica gel (10 g) containing 10% water, and eluted with a mixture of benzene and ethyl acetate (8:1) to give diphenylmethyl 7β - [α - (3 - thienyl) - α - phenoxycarbonylacetamido] - 7α - methoxy-3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate as colorless foam (125 mg). Yield: 76%.

IR: $\nu_{max}^{CHCl_3}$ 3406, 3341, 1789, 1740, 1711 cm^{-1}.

NMR: δ^{CDCl_3} 3.49s3H, 3.78s3H, 4.24s2H, 4.55s2H, 4.97s1H, 5.03s1H, 6.88s1H.

$[\alpha]_D^{22.5}$ −74.8±1.1° (c=1.005 $CHCl_3$).

Example II-23

To a solution of 3-thienylacetic acid mono-3,4-dimethylphenyl ester (120 mg) in methylene chloride (1.5 ml) are added triethylamine (42 μl) and oxalyl chloride (26 μl) under ice cooling. After stirring for 15 minutes, the mixture is added to a solution of diphenylmethyl 7β - amino - 7α - methoxy - 3 - (1 - methyltetrazol - 5-yl) - thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (116 mg) in methylene chloride (3 ml) and pyridine (24 μl), and the mixture is stirred at 0°C for 1 hour. The reaction mixture is poured into ethyl acetate, washed with 2N-hydrochloric acid, water, 5% sodium hydrogencarbonate aqueous solution, and water, dried over magnesium sulfate, and concentrated. The residue is chromatographed over silica gel (10 g)

containing 10% water, and eluted with a mixture of benzene and ethyl acetate (10:1) to give diphenylmethyl 7β - [α - (3 - thienyl) - α - (3,4 - dimethylphenyl)oxycarbonylacetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate(128 mg). Yield: 72%.

IR: $\nu_{max}^{CHCl_3}$ 3405, 3340, 1790, 1737, 1712 cm^{-1}.

NMR: δ^{CDCl_3} 2.22s6H, 3.50s3H, 3.76s3H, 4.24s2H, 4.56s2H, 4.95s1H, (5.00s+5.02s)1H, 6.86s2H, 6.90s1H.

$[\alpha]_D^{22.5}$ −68.1±1.1° (c=1.002, $CHCl_3$).

Example II-24

To a solution of α - diphenylmethoxycarbonyl - α - (2 - thienyl) - acetic acid (176 mg) in methylene chloride (1 ml) are added triethylamine (0.055 ml) and oxalyl chloride (0.034 ml) at 0°C, under nitrogen. After stirring for 15 minutes at 0°C, the mixture is added to a solution of diphenylmethyl 7β - amino - 7α - methoxy - 3-(1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (101 mg) and pyridine in methylene chloride (3 ml) at 0°C. The mixture is stirred for 30 minutes, diluted with ethyl acetate, washed with 5% sodium hydrogencarbonate aqueous solution, water, 2N-hydrochloric acid, and water, dried on sodium sulfate, and concentrated under reduced pressure. The obtained residue is chromatographed on silica gel (10 g) containing 10% water, and eluted with a mixture of benzene and ethyl acetate (4:1) to give diphenylmethyl 7β - [α - diphenylmethoxycarbonyl - α-(2 - thienyl)acetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl) - thiomethyl-1 - oxadethia - 3 - cephem - 4 - carboxylate (140 mg) as colorless foam. Yield: 85%.

IR: $\nu_{max}^{CHCl_3}$ 1785, 1720, ca. 1700 cm^{-1}.

NMR: δ^{CDCl_3} 6.93s2H, 5.00s2H, 4.50brs2H, 4.15brs2H, 3.80s3H, 3.40brs3H.

Example II-25

To a solution of α - (p - benzyloxyphenyl)malonic acid monobenzyl ester (376 mg) in methylene chloride (4 ml) are added triethylamine (105 μl) and oxalyl chloride (65 μl) under ice cooling. After stirring for 15 minutes under ice-cooling, the mixture is added to a solution of diphenylmethyl 7β - amino - 7α - methoxy - 3-(1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (254 mg) and pyridine (60 μl) in methylene chloride (7 ml) under ice cooling. After stirring for 30 minutes at the same temperature, the mixture is poured into ethyl acetate, washed with 2N-hydrochloric acid, water, 5% sodium hydrogencarbonate aqueous solution, and water, dried over magnesium sulfate, and evaporated. The residue is chromatographed on silica gel (20 g) containing 10% water, and eluted with a mixture of benzene and ethyl acetate (10:1) to give diphenylmethyl 7β - [α - (p-benzyloxyphenyl) - α - benzyloxycarbonylacetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate as colorless foam (390 mg).
5.09s2H, 6.82d(9Hz)2H, 6.84s1H.

NMR: δ^{CDCl_3} 3.38s3H, 3.62s3H, 4.13s2H, 4.45s2H, 4.56s1H, 4.96s3H,

IR: $\nu_{max}^{CHCl_3}$ 3411, 3326, 1789, 1722, 1700sh cm^{-1}.

$[\alpha]_D^{23}$ −72.0±2° (c=0.553, $CHCl_3$).

Example II-26

To a solution of α - diphenylmethoxycarbonyl - p - (p - methoxybenzyl)oxyphenylacetic acid (193 mg) in methylene chloride (2 ml) are added triethylamine (0.0416 ml) and oxalyl chloride (0.0256 ml) at 0°C, and the mixture is stirred for 30 minutes. The resulting solution is added to a solution of diphenylmethyl 7β - amino-7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3-cephem - 4 - carboxylate (101.7 mg) and pyridine (0.024 ml) in methylene chloride (4 ml) at 0°C. After stirring for 30 minutes at 0°C, the mixture is diluted with ethyl acetate, washed with water, dried on sodium sulfate, and concentrated. The residue is chromatographed on silica gel (20 g) containing 10% water, and eluted with a mixture of benzene and ethyl acetate (4:1) to give diphenylmethyl 7β - [α - p - (p)-methoxybenzyl)oxyphenyl - α - diphenylmethoxycarbonylacetamido] - 7α - methoxy-3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (190.7 mg) as colorless foam. Yield: 98%.

IR: $\nu_{max}^{CHCl_3}$ 3420, 3325, 1792, 1730, 1700sh cm^{-1}.

NMR: δ^{CDCl_3} (3.38s+3.40s)3H, 3.70s3H, 3.77s3H, 4.20s2H, 4.47s2H 4.68s1H, 4.95s2H, 5.00s1H.

Example II-27

In a procedure similar to that of Example II-26, diphenylmethyl 7β - amino - 7α-methoxy - 3 - (1 - methyltetrazol - 5 - yl) - thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylate (800 mg) is treated with α - p - (p - methoxybenzyl)oxyphenyl - α-p - methoxybenzyloxycarbonylacetyl chloride prepared from the corresponding free acid (1370 mg) and oxalyl chloride in the presence of pyridine (190 mg) and triethylamine (0.33 ml) in methylene chloride (42 ml) to give diphenylmethyl 7β - [α-p - (p - methoxybenzyl)oxyphenyl - α - p - methoxybenzyloxycarbonylacetamido] - 7α-methoxy - 3 - (1 - methyltetrazol - 5 - yl) - thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylate (1.45 g). Yield: nearly quantitative.

IR: $\nu_{max}^{CHCl_3}$ 1792, 1725, 1700sh cm^{-1}.

NMR: δ^{CDCl_3} 3.45s3H/2, 3.48s3H/2, 3.78s6H, 3.82s3H, 4.27brs2H, 4.57brs3H, 4.98s2H, 5.03s1H, 5.13s2H.

Example II-28

To a stirred suspension of p - (p - methoxybenzyloxy)phenylmalonic acid (125 mg) in methylene chloride (3 ml) are added triethylamine (55 μl) and oxalyl chloride (26 μl) at −15°C, and the suspension is stirred for 40 minutes at 0°C. The mixture is added to a solution of diphenylmethyl 7β - amino - 7α 1 methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (100 mg) in methylene chloride (3 ml) and pyridine (63 μl), and the mixture is stirred for 30 minutes at 0°C. The reaction mixture is diluted with ethyl acetate, washed with aqueous 2N-hydrochloric acid and water, dried over sodium sulfate, and concentrated to give crude product (212 mg), which is chromatographed on silica gel (20 g) and eluted with a mixture of ethyl acetate and acetic acid (99:1) to give diphenylmethyl 7β - [α - p - (p - methoxybenzyloxy)phenyl - α - carboxyacetamido] - 7α - methoxy-3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadetha - 3 - cephem - 4 - carboxylate as foam (71 mg). Yield: 45%.

IR: $\nu_{max}^{CHCl_3}$ 3385, 3300—2400br, 1790, 1762, 1714, 1612 cm^{-1}.

NMR: δ^{CDCl_3} 3.43s3H/2, 3.46s3H/2, 3.74s3H, 3.78s6H, 4.22brs2H, 4.56brs3H, 4.96s2H, 5.05s1H.

The product obtained above (40 mg) gives 7β - (α - p - hydroxyphenyl - α carboxyacetamido) - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl) - thiomethyl - 1-oxadethia - 3 - cephem - 4 - carboxylic acid by the action of trifluoroacetic acid (0.2 ml) and anisole (0.4 ml) at 0°C for 20 minutes.

III. Deprotection

Example III-1

To a solution of diphenylmethyl 7β - (α - phenyl - α - diphenylmethoxycarbonylacetamido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylate (120 mg) in methylene chloride (3 ml) are added anisole (0.3 ml) and trifluoroacetic acid (0.3 ml) in nitrogen atmosphere at 0°C, and the mixture is stirred for 1.5 hours. The reaction mixture is concentrated under reduced pressure. The residue is purified by chromatography on silica gel (10 g) containing 10% water, and eluted with a mixture of ethyl acetate and acetic acid (9:1) to give 7β - (α - phenyl-α - carboxyacetamido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia-3 - cephem - 4 - carboxylic acid (57 mg) as powder. mp. 157—159°C (decomposition). Yield: 81%.

IR: ν_{max}^{Nujol} 1778, 1670, 1606 cm^{-1}.

IR: ν_{max}^{KBr} 3420, 2520br, 1775, 1674, 1606, 1528.5, 1376 cm^{-1}.

UV: $\lambda_{max}^{1\%\ NaHCO_3}$ 265.5 nm (ε=9442).

NMR: δ (1% $NaHCO_3$ in D_2O) 4.02s3H, 4.05+4.32ABq(13.5Hz)2H, 4.55brs2H, 5.16d(4Hz)1H/2, 5.21d(4Hz)1H/2, 5.48d(4Hz)1H, 7.37s5H, 5.08brs1H (the last peak gradually dminished).

$[\alpha]_D^{23}$ $-90.3 \pm 4.2°$ (c=0.310, 1% $NaHCO_3$).

CD: $\lambda(\theta)$ (0.155% $NaHCO_3$) 305(0), 285(−2500), 276.5(0), 258(+11700), 249.5(0), 232(−59100), 210(−3500).

Example III-2

To a solution of diphenylmethyl 7β - [α - (5 - indanyl)oxycarbonyl - α - phenylacetamido] - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (144 mg) in methylene chloride (3 ml) are added anisole (0.2 ml) and trifluoroacetic acid (0.4 ml) under ice cooling, and the mixture is stirred for 2 hours. The reaction mixture is diluted with ethyl acetate, washed with water and aqueous sodium hydrogencarbonate, dried, and evaporated. To the residue is triturated with ether, and the resulting powder is collected by filtration to give sodium 7β - [α-(5 - indanyl)oxycarbonyl - α - phenylacetamido] - 3 - (1 - methyltetrazol - 5 - yl)-thoimethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (60 mg).

IR: ν_{max}^{Nujol} 1760, 1690sh, 1670 cm^{-1}.

Example III-3

To a solution of diphenylmethyl 7β - (α - carboxy - α - phenylacetamido) - 3-(1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (576 mg) in methylene chloride (10 ml) are added anisole (1 ml) and trifluoroacetic acid (1 ml) in nitrogen atmosphere under ice cooling, and the mixture is stirred for 70 minutes. The reaction mixture is concentrated under reduced pressure to give 7β-(α - phenyl - α - carboxyacetamido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1-oxadethia - 3 - cephem - 4 - carboxylic acid. Yield: nearly quantitative. Crude product.

IR: ν_{max}^{Nujol} 1778, 1670, 1604 cm^{-1}.

Example III-4

To a solution of 7β - (α - diphenylmethoxycarbonyl - α - phenylacetamido) - 3-(1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid (72 mg) in methylene chloride (2 ml) are added anisole (0.2 ml) and trifluoroacetic acid (0.2 ml) at 0°C. After 50 minutes under ice-cooling, the reaction mixture is concentrated under reduced pressure. The residue is purified by chromatography on silica gel (5 g) containing 10% water, and eluted with a mixture of acetic acid and ethyl acetate (1:9) to give 7β - (α - carboxy - α - phenylacetamido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid (41 mg). mp. 165—170°C (decomposition). Yield: 75%.

IR: ν_{max}^{Nujol} 1778, 1670, 1605 cm^{-1}.

Example III-5

A solution of diphenylmethyl 7β - (α - p - nitrobenzyloxycarbonyl - α - phenylacetamido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (715 mg) in a mixture of methanol (40 ml) and tetrahydrofuran (40 ml) is shaken in the presence of pre-reduced 5% palladium on carbon (700 mg) and 10% hydrochloric acid (2 ml) under hydrogen at 1 atm. and at room temperature for 70 minutes. The reaction mixture is filtered to remove the catalyst, diluted with water (120 ml) containing 10% hydrochloric acid (2 ml), concentrated to remove the organic solvent, and extracted with ethyl acetate. The extract is washed with water, dried on magnesium sulfate, and evaporated under reduced pressure to give diphenylmethyl 7β - (α - carboxy - α - phenylacetamido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl-1 - oxadethia - 3 - cephem - 4 - carboxylate (576 mg). Yield: 97.6% (crude).

Example III-6

A mixture of diphenylmethyl 7β - (α - p - hydroxyphenyl - α - t - butoxycarbonylacetamido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3-cephem - 4 - carboxylate (74 mg), thiophenol (0.075 ml), and trifluoroacetic acid (0.75 ml) is stirred for 1.5 hours under ice-cooling. The reaction mixture is evaporated under reduced pressure. The residue is purified by chromatography on silica gel

containing 10% water, and eluted with a mixture of acetic acid and ethyl acetate (1:9). The eluate is triturated with a mixture of ether and pentane to give 7β - (α-p - hydroxyphenyl - α - carboxyacetamido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid (30 mg). Yield: 58.9%.

mp. 130—142° (decomposition).

IR: ν_{max}^{KBr} 3400, 1787, 1720 cm^{-1}.

UV $\lambda_{max}^{CH_3OH}$ 273 nm (ε=7850).

Example III-7

To a solution of diphenylmethyl 7β - (α - p - hydroxyphenyl - α - diphenylmethoxycarbonylacetamido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (137 mg) in methylene chloride (3 ml) are added anisole (0.3 ml) and trifluoroacetic acid (0.3 ml) at 0°C under nitrogen. After stirring for 1 hour at 0°C, the mixture is concentrated under reduced pressure, triturated with ether, and washed with ether to give 7β - (α - p - hydroxyphenyl - α - carboxyacetamido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylic acid as colorless powder (81 mg) decomposing at 130—142°C. Yield: 59.6%.

IR: ν_{max}^{KBr} 3400, 1787, 1720 cm^{-1}.

UV: $\lambda_{max}^{CH_3OH}$ 273 nm (ε=7850).

Example III-8

To a solution of diphenylmethyl 7β - [α - (2 - thienyl) - α - t - butoxycarbonylacetamido] - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylate (49 mg) in methylene chloride (1 ml) are added anisole (0.4 ml) and trifluoroacetic acid (1 ml) at 0°C, and the mixture is stirred under ice-cooling for 4 hours and at room temperature for 40 minutes. The reaction mixture is concentrated under reduced pressure. The residue is purified by chromatography on silica gel (5 g) containing 10% water, and eluted with a mixture of ethyl acetate and acetic acid (9:1). The eluate is triturated in ether to give 7β - [α - (2 - thienyl) - α - carboxyacetamido] - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylic acid (23 mg) as amorphous powder.

mp. 156—160°C (decomposition with foaming). Yield: 33.5%.

IR: ν_{max}^{KBr} 3390, 1765, 1670, 1608, 1520 cm^{-1}.

$[\alpha]_D^{24}$ −62.0±3.7° (c=0.279, 1% $NaHCO_3$).

CD: λ(θ) (0.279, 1% $NaHCO_3$) 300(0), 282(−2600), 276(0), 259(+11100), 249(0), 231.5(−47400), 210(−9700).

Example III-9

A mixture of diphenylmethyl 7β - [α - (3 - thienyl) - α - t- butoxycarbonylacetamido] - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4-carboxylate (56 mg), anisole (0.35 ml), and trifluoroacetic acid (0.35 ml) is stirred at 0°C for 2 hours. The reaction mixture is evaporated under reduced pressure. The residue is purified by chromatography on silica gel (5 g) containing 10% water, eluted with a mixture of ethyl acetate and acetic acid (9:1) and triturated in a mixture of n-pentane and ether (2:1) to give 7β - [α - (3 - thienyl) - α - carboxyacetamido]-3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid (37 mg) as colorless powder. mp. 155—160°C. Yield: 96.8%.

IR: ν_{max}^{Nujol} 3400, 1770, 1692, 1610 cm^{-1}.

Example III-10

To a solution of diphenylmethyl 7β - (α - diphenylmethoxycarbonyl - α - phenylacetamido) - 3 - (1 - t - butoxycarbonylmethyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (60 mg) in anisole (0.5 ml) is added trifluoroacetic acid (1 ml) under ice-cooling in nitrogen, and the mixture is kept at 0°C overnight. The reaction mixture is concentrated under reduced pressure, and the residue is triturated with ethyl acetate to give crude 7β - (α - carboxy - α - phenylacetamido)-3 - (1 - carboxymethyltetrazol - 5 - yl) - thiomethyl - 1 - oxadethia - 3 - cephem - 4-carboxylic acid (22 mg) as powder. Yield: 64%.

IR: ν_{max}^{KBr} 1775, 1725 cm^{-1}.

Example III-11

To a solution of diphenylmethyl 7β - [α - t- butoxycarbonyl - α - (2 - thienyl) acetamido] - 3 - (1 - t - butoxycarbonylmethyltetrazol - 5 - yl) - thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (96 mg) in anisole (0.5 ml) is added trifluoroacetic acid (1.5 ml) in nitrogen atmosphere under ice-cooling, and the mixture is allowed to stand overnight under ice-cooling. The reaction mixture is concentrated under reduced pressure. The residue is triturated with a mixture of ether and ethyl acetate to give crude 7β - [α - (2 - thienyl) - α - carboxyacetamido] - 3 - (1 - carboxymethyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid (30 mg). mp. decomposition from 160°C. Yield: 48%.

IR: ν_{max}^{KBr} 1780, 1725 cm^{-1}.

Example III-12

To a solution of diphenylmethyl 7β - (α - phenyl - α - diphenylmethoxycarbonylacetamido) - 3 - (2 - methyl - 1,3,4 - thiadiazol - 5 - yl)thiomethyl - 1 - oxadethia-3 - cephem - 4 - carboxylate (170 mg) in methylene chloride (3 ml) are added anisole (0.2 ml) and trifluoroacetic acid (0.4 ml) at 0°C, and the mixture is stirred at 0°C for 1.5 hours. The reaction mixture is concentrated under reduced pressure. The residue is purified on silica gel (10 g) containing 10% water, eluted with a mixture of ethyl acetate and acetic acid (9:1), and triturated with a mixture of ethyl acetate and ether to give 7β - (α - phenyl - α - carboxyacetamido) - 3 - (2 - methyl - 1,3,4-thiadiazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid (45.8 mg) as colorless powder. Yield: 45.1%. mp. 130—132°C.

IR: ν_{max}^{KBr} 3410, 1772, 1600 cm^{-1}.

Example III-13

To a solution of diphenylmethyl 7β - (α - diphenylmethoxycarbonyl - α - phenylacetamido) - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl) - thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (121.2 mg) in methylene chloride (2 ml) are added anisole (0.2 ml) and trifluoroacetic acid (0.4 ml) at 0°C. After stirring at 0°C for 1 hour, the reaction mixture is concentrated under reduced pressure and triturated with ether to give 7β - (α - carboxy - α - phenylacetamido) - 7α - methoxy - 3 - (1-methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid (46.5 mg) as colorless powder.
Yield: 59.8%. mp. 110—116°C.

UV: $\lambda_{max}^{CH_3OH}$ 275.5 nm (ε=9400).

$[\alpha]_D^{25}$ −19.4±2.8° (c=0.211, CH_3OH).

IR: ν_{max}^{KBr} 1780, 1717, 1631 cm^{-1}.

NMR: $\delta^{D_2O+NaHCO_3}$ (3.46s+3.53s)3H, (3.99s+4.02s)3H, 4.0—4.2m2H, 4.48s2H, 4.53s1H, 5.13s1H, 7.38s5H.

Example III-14

To a solution of diphenylmethyl 7β - (α - diphenylmethoxycarbonyl - α - p-acetoxyphenylacetamido) - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl-1 - oxadethia - 3 - cephem - 4 - carboxylate (133.4 mg) in methylene chloride (2 ml) are added anisole (0.2 ml) and trifluoroacetic acid (0.4 ml) at 0°C. The mixture is stirred for 45 minutes, evaporated, and triturated with a mixture of ether and pentane, and ether to give 7β - (α - carboxy - α - p - acetoxyphenylacetamido) - 7α - methoxy-3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid (77 mg) as colorless foam.
mp. 110—115°C. Yield: 91.9%.

UV: $\lambda_{max}^{CH_3OH}$ 275 nm (ε=9300).

$[\alpha]_D^{25}$ −27.5±2.6° (c=0.258, CH_3OH).

IR: ν_{max}^{KBr} 1782, 1728, 1635 cm^{-1}.

NMR: $\delta^{D_2O+NaHCO_3}$ 2.33s3H, (3.47s+3.53s)3H, (3.99s+4.02s)3H, ca. 4.13brs2H, 4.46brs2H, 5.13s1H, 7.12+7.47ABq(8Hz)4H.

Example III-15

To a solution of diphenylmethyl 7β - (α - diphenylmethoxycarbonyl - α - p-hydroxyphenylacetamido) - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl-

1 - oxadethia - 3 - cephem - 4 - carboxylate (84.6 mg) in methylene chloride (2 ml) are added anisole (0.1 ml) and trifluoroacetic acid (0.3 ml) at 0°C. After stirring for 45 minutes at 0°C, the mixture is evaporated under reduced pressure and triturated with a mixture of ether and n-pentane, and ether to yield 7β - (α - carboxy - α - p - hydroxyphenylacetamido) - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid (46.4 mg) as colorless powder. Yield: 89.9%.

mp. 117—122°C (decomposition).

UV: $\lambda_{max}^{CH_3OH}$ 276 nm (ε=10200).

$[\alpha]_D^{25}$ −15.3±2.6° (c=0.216, CH_3OH).

IR: ν_{max}^{KBr} 1780, 1719, 1632 cm^{-1}.

NMR: $\delta^{D_2O+NaHCO_3}$ (3.45s+3.53s)3H, (4.00s+4.02s)3H, (4.08s+4.13m)2H, (4.45s+4.48s)2-3H, 5.12s1H, 6.87+7.28ABq(8Hz)4H.

Example III-16

To a solution of diphenylmethyl 7β - [α - p - hydroxyphenyl - α - (5 - indanyl)oxycarbonylacetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (150 mg) in methylene chloride (12 ml) are added anisole (0.4 ml) and trifluoroacetic acid (0.4 ml) at 0°C in nitrogen. After stirring for 20 minutes at 0°C, the reaction mixture is concentrated under reduced pressure, diluted with benzene, and concentrated.

The residue is triturated with ether to give 7β - [α - p - hydroxyphenyl - α - (5 - indanyl)oxycarbonylacetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid as powder (91 mg) melting at 123—126°C with decomposition. Yield: 76.5%.

IR: ν_{max}^{KBr} 3385, 1785, 1727, 1705, 1631, 1613, 1595 cm^{-1}.

UV: $\lambda_{max}^{CH_3OH}$ 271.5 (ε=12950), 276.5 (ε=12700) nm.

$[\alpha]_D^{22}$ +1.3±0.8°,

$[\alpha]_{486}^{22}$ −25.1±1.2°,

$[\alpha]_{546}^{22}$ −5.2±1.2° (c=0.541, CH_3OH).

Example III-17

To a solution of diphenylmethyl 7β - [α - (p - benzyloxyphenyl) - α - benzyloxycarbonylacetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (100 mg) in methylene chloride (2 ml) are added anisole (0.2 ml) and a solution of aluminum chloride (250 mg) in nitromethane (1.2 ml) under ice cooling. After stirring for 2 hours under ice cooling and for 1 hour at room temperature, the mixture is poured into a mixture of ethyl acetate and methanol (5:1), washed with 2N-hydrochloric acid and saturated saline, dried over sodium sulfate, and concentrated. The residue is washed with ether to give 7β - (α - p - hydroxyphenyl - α - carboxyacetamido) - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid (35 mg).

IR: ν_{max}^{KBr} 1780, 1719, 1632 cm^{-1}.

Example III-18

To a solution of diphenylmethyl 7β - [α - t - butoxycarbonyl - α - (3 - thienyl)acetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl) - thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (144 mg) in anisole (0.3 ml) is added trifluoroacetic acid (1.7 ml) at 0°C in nitrogen gas. After stirring for 3 hours, the mixture is concentrated to dryness under reduced pressure, triturated with ether, and washed with ethyl acetate and ether to give 7β - [α - carboxy - α - (3 - thienyl)acetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid (61 mg) as light yellow powder. Yield: 61%. mp. 118—125°C (decomposition) from acetone.

$[\alpha]_D^{25}$ −12.8±2.5° (c=0.211, CH_3OH).

UV: $\lambda_{max}^{CH_3OH}$ 276 nm (ε=10200).

IR: ν_{max}^{KBr} 1780, 1705 cm^{-1}.

NMR: $\delta^{D_2O+NaHCO_3}$ 4.03s3H, (4.11s+4.21m)2H, (4.51s+4.53s)2—H, 5.15s1H, 7.05—7.25m1H, 7.27—7.52m2H.

Example III-19

To a solution of diphenylmethyl 7β - [α - (3 - thienyl) - α - diphenylmethoxycarbonylacetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1-oxadethia - 3 - cephem - 4 - carboxylate (830 mg) in methylane chloride (15 ml) are added anisole (2 ml) and trifluoroacetic acid (2 ml) under ice cooling. After stirring for 1 hour at the same temperature, the mixture is concentrated under reduced pressure. The residue is washed with ether to give 7β - [α - (3 - thienyl) - α - carboxyacetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid as powder (383 mg) melting at 110—114°C, identified with an authentic specimen by comparison of IR spectra in KBr disc and thin layer chromatograms.

Example III-20

To a solution of diphenylmethyl 7β - [α - (3 - thienyl) - α - phenoxycarbonylacetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl) - thiomethyl - 1-oxadethia - 3 - cephem - 4 - carboxylate (100 mg) in methylene chloride (2 ml) are added anisole (0.2 ml) and trifluoroacetic acid (0.2 ml) under ice cooling. After stirring for 1 hour, the mixture is concentrated, and triturated in ether to give 7β-[α - (3 - thienyl) - α - phenoxycarbonylacetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid as powder (38 mg) melting at 108—111°C. Yield: 50%.

IR: $\nu_{max}^{CHCl_3}$ 3400sh, 3325, 1788, 1745, 1705 cm^{-1}.

$[\alpha]_D^{23}$ −61.3±2.0° (c=0.517, $CHCl_3$).

Example III-21

To a solution of 7β - [α - (3 - thienyl) - α - (3,4 - diamethylphenyl)oxycarbonylacetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (105 mg) in methylene chloride (2 ml) are added anisole (0.2 ml) and trifluoroacetic acid (0.2 ml) under ice cooling. After stirring for 1 hour, the mixture is concentrated under reduced pressure, triturated with ether, and filtrated. The solid is washed with ether and dried to give 7β - [α - (3 - thienyl) - α-(3,4 - dimethylphenyl) - oxycarbonylacetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl) - thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid as powder (64 mg) melting at 110—113°C. Yield: 77%.

IR: $\nu_{max}^{CHCl_3}$ 3400sh, 3325, 1787, 1737, 1704 cm^{-1}.

$[\alpha]_D^{23}$ −53.4±1.9° (c=0.504, $CHCl_3$).

Example III-22

To a solution of diphenylmethyl 7β - [α - (3 - thienyl) - α - (indan - 5 - yl)-oxycarbonylacetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl-1 - oxadethia - 3 - cephem - 4 - carboxylate (97 mg) in methylene chloride (2 ml) are added anisole (0.3 ml) and trifluoroacetic acid (0.3 ml) under ice cooling. After stirring for 1 hour, the mixture is concentrated under reduced pressure and the residue is triturated with ether to give 7β - [α - (3 - thienyl) - α - (5 - indanyl)oxycarbonylacetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid as powder (34 mg) melting at 111—113°C. Yield: 45%.

IR: $\nu_{max}^{CHCl_3}$ 3406sh, 3335, 1789, 1744, 1704 cm^{-1}.

$[\alpha]_D^{23}$ −57.5±2.4° (c=0.402, $CHCl_3$).

Example III-23

To a solution of diphenylmethyl 7β - [α - diphenylmethoxycarbonyl - α - (2-thienyl)acetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1-oxadethia - 3 - cephem - 4 - carboxylate (140 mg) in methylene chloride are added anisole (0.2 ml) and trifluoroacetic acid (0.4 ml) at 0°C in nitrogen gas. After stirring for 1 hour at 0°C, the mixture is evaporated under reduced pressure, triturated with ether, and washed with ether to give 7β - [α - carboxy - α - (2 - thienyl)acetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl) - thiomethyl - 1 - oxade-

thia - 3 - cephem - 4 - carboxylic acid (60 mg) as colorless powder. Yield: 70%. mp. 104—109°C (decomposition).

UV: $\lambda_{max}^{CH_3OH}$ 275 nm (ε=8800).

$[\alpha]_D^{24}$ −15.0±1.5° (c=0.374, CH_3OH).

IR: ν_{max}^{KBr} 1785, 1715 cm^{-1}.

NMR: $\delta^{D_2O+NaHCO_3}$ 7.00—7.5m3H, 5.15s1H, 4.04s3H, (3.54s+3.48s)3H.

Example III-24

To a solution of diphenylmethyl 7β - [α - (5 - indanyl)oxycarbonyl - α - phenylacetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl) - thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (116.1 mg) in methylene chloride are added anisole (0.1 ml) and trifluoroacetic acid (0.2 ml). After stirring for 30 minutes at 0°C, the mixture is evaporated under reduced pressure, chromatographed on silica gel (10 g) containing 10% water, eluted with ethyl acetate containing 5% acetic acid, and crystallized from a mixture of ether and pentane to give 7β - [α - (indan - 5 - yl)-oxycarbonyl - α - phenylacetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)-thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid (74.5 mg) as colorless crystals. Yield: 81.4%. mp. 123—125°C (decomposition).

IR: ν_{max}^{KBr} 1770, 1702 cm^{-1}.

$[\alpha]_D^{25}$ −8.4±1.4° (c=0.286, CH_3OH).

NMR: δ^{CDCl_3} 2.07s2H, 2.85s4H, (3.32s+3.43s)3H, 3.79s3H, 4.25s2H, 4.50s2H, 4.69s1H, 4.97s1H.

Example III-25

To a solution of diphenylmethyl 7β - (α - p - carbamoyloxyphenyl - α - diphenylmethoxycarbonylacetamido) - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (170.1 mg) in methylene chloride (2 ml) are added anisole (0.4 ml) and trifluoroacetic acid (0.4 ml) at 0°C, and the mixture is stirred for 45 minutes, evaporated to dryness under reduced pressure, and triturated with ether to yield 7β - (α - p - carbamoyloxyphenyl - α - carboxyacetamido) - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl) - thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid (98.2 mg) as colorless powder. mp. 128—132°C.

IR: ν_{max}^{KBr} 1784, 1724(sh), 1710 cm^{-1}.

UV: $\lambda_{max}^{CH_3OH}$ 273 nm (ε=9500).

$[\alpha]_D^{25}$ −23.1±0.7° (c=0.900, CH_3OH).

Example III-26

In a procedure similar to that of Example III-25, diphenylmethyl 7β - (α - p-N - methylcarbomoyloxyphenyl - α - diphenylmethoxycarbonylacetamido) - 7α-methoxy - 3 - (1 - methyltetrazol - 5 - yl) - thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylate (100 mg) is treated with anisole (0.1 ml) and trifluoroacetic acid (0.1 ml) in methylene chloride (1 ml) at 0°C for 1 hour to give 7β - (α - p - N - methylcarbomoyloxyphenyl - α - carboxyacetamido) - 7α - methoxy - 3 - (1 - methyltetrazol-5 - yl) - thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid (52 mg) 49% yield. mp. 117—125°C.

IR: ν_{max}^{KBr} 3385, 1786, 1725 cm^{-1}.

UV: $\lambda_{max}^{CH_3OH}$ 271 nm (ε=9532).

Example III-27

In a procedure similar to that of Example III-25, diphenylmethyl 7β - (α - p-ureidocarbonyloxyphenyl - α - diphenylmethoxycarbonylacetamido) - 7α - methoxy-3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (213 mg) is treated with anisole (0.4 ml) and trifluoroacetic acid (0.4 ml) in methylene chloride (3 ml) for 1 hour at 0°C to give 7β - (α - p - ureidocarbonyloxyphenyl - α - carboxyacetamido) - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)-

thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid (125 mg) 91% yield. mp. 137—142°C.

IR: ν_{max}^{KBr} 3440, 3330, 1780, 1712 cm^{-1}.

NMR: $\delta^{(CD_3)_2SO}$ (3.25+3.41s)3H, (3.90s+3.93s)3H, 4.21brs2H, 4.98brs2H, 4.85brs1H, 5.05s1H, 7.20—7.15m2H, 7.13d(8Hz)2H, 7.42d(8Hz)2H, (9.15brs+9.27brs)1H, 10.25brs1H.

UV: $\lambda_{max}^{CH_3OH}$ 276 nm (ε=9105).

Example III-28

To a solution of diphenylmethyl 7β - [ν - p - (p - methoxybenzyl)oxyphenyl - α diphenylmethoxycarbonylacetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5-yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (170 mg) in methylene chloride (3.5 ml) are added anisole (0.35 ml) and trifluoroacetic acid (0.35 ml) at 0°C, and the mixture is stirred for 45 minutes at 0°C. After evaporation of the solvent, the product is triturated with ether to give 7β - (α - p - hydroxyphenyl - α-carboxyacetamido) - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1-oxadethia - 3 - cephem - 4 - carboxylic acid (91 mg) as colorless powder.

Yield: nearly quantitative. mp. 125—132°C (decomposition).

Example III-29

In a procedure similar to that of Example III-28, diphenylmethyl 7β - [α - p-(p - methoxybenzyl)oxyphenyl - α - p - methoxybenzyloxycarbonylacetamido] - 7α-methoxy - 3 - (1 - methyltetrazol - 5 - yl) - thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylate (1.45 g) is treated with anisole (4 ml) and trifluoroacetic acid (4 ml) in methylene chloride (8 ml) at 0°C for 40 minutes to give 7β - (α - p - hydroxyphenyl - α - carboxyacetamido) - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)-thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid. mp. 125—132°C (decomposition). Yield: quantitative.

Example III-30

1) To a solution of diphenylmethyl 7β - [α - p - (p - methoxybenzyl)oxyphenyl α - p - methoxybenzyloxycarbonyl - acetamido] - 7α - methoxy - 3 - (1-methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (1.20 g) in methylene chloride (24 ml) are added anisole (2.4 ml) and a solution of aluminum chloride (2.58 g) in nitromethane (12 ml) at 0°C under nitrogen. After stirring for 15 minutes at 0°C, the mixture is poured into cold 5% sodium hydrogencarbonate aqueous solution (100 ml) and filtered to remove the formed precipitate. The filtrate is washed twice with methylene chloride (2×100 ml), acidified with 2N-hydrochloric acid to pH 2.60, and poured in a column of high porous polymer HP-20 (60 ml) sold by Mitsubishi Chemical Industries Ltd. The column is washed with water (300 ml), and eluted with methanol. The eluate is concentrated under reduced pressure at room temperature. The residue is dissolved in methanol, treated with active carbon, and concentrated under reduced pressure to give 7β - (α - p - hydroxyphenyl - α - carboxyacetamido) - 7α - methoxy - 3 - (1-methyl - tetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid as powder (595 mg) decomposing at 125—132°C. Yield: 88.5%.

2) The same product can be prepared in a method similar to that of above 1), wherein

a) p-methoxy-benzyl ether is substituted by benzyl ether

b) p-methoxybenzyloxycarbonyl group is substituted by benzyloxycarbonyl group, and/or

c) diphenylmethyl ester is substituted by benzyl ester.

IV. O-Acylation

Example IV-1

To a solution of diphenylmethyl 7β - (α - p - hydroxyphenyl - α - diphenylmethoxycarbonylacetamido) - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (286 mg) in methylene chloride (2 ml) is added trichloroacetyl isocyanide (0.5 ml) while cooling at −78°C. After stirring at −78°C for 30 minutes and at 0°C for 1 hour, the mixture is diluted with benzene (20 ml) and ethyl acetate (20 ml), washed with water, dried, and concentrated. The obtained residue is chromatographed on silica gel (30 g) containing 10% water and eluted with a mixture of benzene and ethyl acetate (1:1) to give

diphenylmethyl 7β - (α - p - carbomoyloxyphenyl - α - diphenylmethoxycarbonylacetamido) - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (179.9 mg) as colorless foam. Yield: 59.5%.

IR: $\nu_{max}^{CHCl_3}$ 3530, 3425, 3325, 1790, 1750, 1728, 1700sh cm^{-1}.

NMR: δ^{CDCl_3} (3.42s+3.45s)3H, 3.73s3H, 4.22H, 4.42s2H, 4.80s1H, 5.03s1H, 5.33s2H.

Example IV-2

In a procedure similar to that described above in Example IV-1, diphenylmethyl 7β - (α - p - hydroxyphenyl - α - diphenylmethoxycarbonylacetamido) - 7α - methoxy-3 - (1 - methyltetrazol - 5 - yl) - thiomethyl - 1 - oxadethia - 3 - cephem - 4-carboxylate (100 mg) is treated with methyl isocyanate (0.2 ml) in tetrahydrofuran (1 ml) in the presence of 1,5 - diazabicyclo[3,5,0]undecene at 0°C for 4.5 hours to give diphenylmethyl 7β - (α - p - N - methylcarbomoyloxyphenyl - α - diphenylmethoxycarbonylacetamido) - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (52 mg). Yield: 49%.

IR: $\nu_{max}^{CHCl_3}$ 3460, 1785, 1725, 1700 cm^{-1}.

NMR: δ^{CDCl_3} 2.87d(5Hz)3H, 3.45brs3H, 3.80s3H, 4.23brs2H, 4.47brs2H, 4.77brs1H, 5.00s1H, 4.95—5.40m1H, 6.97s2H.

Example IV-3

In a procedure similar to that described above in Example IV-1, diphenylmethyl 7β - (α - p - carbomoyloxyphenyl - α - diphenylmethoxycarboxylacetamido)-7α - methioxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl 1 - oxadethia - 3 - cephem-4 - carboxylate (175 mg) is treated with trichloroacetyl isocyanide (0.4 ml) at 0°C in methylene chloride (2 ml) and at room temperature for 4 hours to give N^3 -trichloroacetylureidocarbonyloxyphenyl derivative, which is hydrolyzed with wet silica gel (10 g) for 1 hour in methylene chloride at room temperature to give diphenylmethyl 7β-(α - p - ureidocarbonyloxyphenyl - α - diphenylmethoxycarbonylacetamido) - 7α-methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylate (145 mg). Colorless foam: Yield: 79%.

IR: $\nu_{max}^{CHCl_3}$ 3500, 1790, 1758, 1725, 1700sh cm^{-1}.

NMR: δ^{CDCl_3} 3.43s3H, 3.68s3H, 4.21brs2H, 4.43brs2H, 4.83brs1H, 5.03s1H, 5.80—6.70m2H, 6.95s2H, 8.23brs1H, 9.20brs1H, 6.95s2H.

V. Protection

Example V-1

To a suspension of 7β - (α - carboxy - α - phenylacetamido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid (400 mg) in methylene chloride (20 ml) is added diphenyldiazomethane (700 mg), and the mixture is stirred at room temperature for 30 minutes. The residue obtained by concentration under reduced pressure is chromatographed on silica gel (40 g) containing 10% water, and eluted with a mixture of benzene and ethyl acetate (1:1) to give diphenylmethyl 7β - (α - diphenylmethoxycarbonyl - α - phenylacetamido) - 3 - (1-methyltetrazol - 5 - yl) - thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylate (322 mg). mp. 107—109°C. Yield: 47.4%. (In another experiment, 95% yield of the product was obtained).

Example V-2

To a suspension of 7β - (α - carboxy - α - phenylacetamido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid (50 mg) in a mixture of acetone (30 ml) and methanol (5 ml) is added a solution of sodium acetate (17.6 mg) in methanol (2 ml), and the mixture is stirred at room temperature for 1 hour. The reaction mixture is evaporated under reduced pressure, and the residue is washed with acetone to give disodium 7β - (α - carboxy - α - phenylacetamido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4-carboxylate (57 mg).

IR: ν_{max}^{KBr} 3425, 1746, 1660br, 1610br, 1410 cm^{-1}.

Example V-3

The products of above Examples having free carboxy are dissolved in aqueous

sodium hydrogencarbonate to give the corresponding sodium salts, of which the antibacterial activity is examined. These compounds are more active than the corresponding compounds having sulfur atom instead of oxygen atom at position 1 of the ring system. Those having 7α-methoxy are stronger antibiotics against gram negative bacteria resistant to common cephalosporins and also strongly active against *Pseudomonas aeruginosa* strains.

Example V-4

To a solution of 7β - [α - (3 - thienyl) - α - carboxyacetamido] - 7α - methoxy-3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid (2.04 g) in methanol (20 ml) is added a solution of sodium 2-ethylhexanoate in methanol (2 mole/liter; 10 ml) at room temperature. After stirring for 10 minutes, the reaction mixture is diluted with ethyl acetate (100 ml), stirred for 5 minutes, and filtered to collect separated solid, which are washed with ethyl acetate, and dried to give disodium salt of 7β - [α - (3 - thienyl) - α - carboxyacetamido] - 7α-methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4-carboxylic acid (1.90 g). Yield: 86.7%. Colourless powder mp. decomposition from 150°C.

IR: ν_{max}^{KBr} 1768, 1680, 1612 cm^{-1}.

UV: $\lambda_{max}^{CH_3OH}$ 271 nm (ε=9420).

Example V-5

To a solution of 7β - (α - p - hydroxyphenyl - α - carboxyacetamido) - 7α-methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylic acid (359 mg) in methanol (7 ml) is added a solution of sodium 2-ethylhexanoate in methanol (2 mole/liter; 1.73 ml) at room temperature. After stirring for 10 minutes, the reaction mixture is diluted with ethyl acetate, stirred for 5 minutes, and filtered to collect separated solid, which is washed with ethyl acetate, and dried to give disodium salt of 7β - (α - p - hydroxyphenyl - α - carboxyacetamido) - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia-3 - cephem - 4 - carboxylic acid (342 mg). Yield: 88.8%. Colorless powder. mp. decomposition from 170°C.

IR: ν_{max}^{Nujol} 1768, 1675, 1608 cm^{-1}.

UV: $\lambda_{max}^{CH_3OH}$ 273 nm (ε=11100).

Example V-6

To a solution of 7β - [α - p - hydroxyphenyl - α - carboxyacetamido] - 7α-methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylic acid (836 mg) in a mixture of methylene chloride (15 ml), ethyl acetate (15 ml) and methanol (10 ml) is added diphenyldiazomethane (950 mg). After stirring for 30 minutes at room temperature, the mixture is concentrated under reduced pressure, and washed with n-hexane. The product is chromatographed on silica gel (90 g) containing 10% water, and eluted with a mixture of benzene and ethyl acetate (1:1) to give diphenylmethyl 7β - (α - p - hydroxyphenyl - α - diphenylmethoxycarbonylacetamido) - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl-1 - oxadethia - 3 - cephem - 4 - carboxylate (1.270 g). Yield: 95%.

IR: $\nu_{max}^{CHCl_3}$ 3585, 3315, 1790, 1722, 1700sh cm^{-1}.

VI. Compositions and their Use

Example VI-1

Disodium salt of 7β - (α - p - hydroxyphenyl - α - carboxyacetamido) - 7α-methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylc acid (100 mg) in a 5 ml vial is dissolved in sterilized water for injection (1 ml) before use, and given to an adult patient suffering from pyelitis by way of intravenous injection.

Example VI-2

Lyophilizate from a solution of 7β - [α - (3 - thienyl) - α - carboxyacetamido]-7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylic acid (1 g) neutralized to pH 7.0 with sodium hydrogen carbonate is placed in a 150 ml vial. The lyophilizate is dissolved in sterilized water for injec-

tion (100 ml) and dripped intravenously to an adult patient immediately after or during a surgical operation of cancer for preventing and treating post operative bacterial infection.

Example VI-3

Microcrystalline 7β - [α - carbamoyloxyphenyl - α - carboxyacetamido] - 7α-methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylic acid (200 mg) in a 5 ml vial is suspended in sterilized water for injection containing 2 mg of procaine (2 ml), and given intramuscularly to a patient suffering from suppurative inflammation caused by *Staphylococcus aureus*.

Example VI-4

Crystalline 7β - [α - (3 - thienyl) - α - (5 - indanyl)oxycarbonylacetamido] - 3-(1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid (200 mg) is dissolved in sesame oil (0.25 ml) and filled in a hard gelatin capsule. Each one capsule is given orally at 4 hour intervals to a patient suffering from upper respiratory tract infection caused by *Streptococcus pyogenes*.

Example VI-5

Powdered 7β - (α - p - hydroxyphenyl - α - (5 - indanyl)oxycarbonylacetamido]-7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylic acid (100 mg) is mixed well with corn starch (150 mg) and talc (10 mg), powdered, and encapsulated in a hard gelatin capsule (250 mg volume). Each one capsule is administered orally at 3 hour intervals to an adult patient suffering from urinary tract infection caused by *Escherichia coli*.

Example VI-6

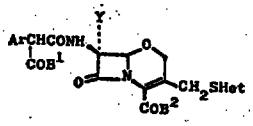
Mixed powder of 7β - [α - p - carbamoyloxyphenyl - α - (5 - indanyloxy(carbonylacetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1-oxadethia - 3 - cephem - 4 - carboxylic acid (10 g), lactose (50 g), corn starch (2 g), magnesium stearate (0.3 g), sucrose (10 g), and necessary amount of acacia and talc is granulated. The granule is mixed with water before use to obtain a suspension, and one tea spoonful amount of the suspension is given orally to an infant suffering from pneumonia caused by *Klebsiella pneumoniae*.

Insofar as the present invention includes within the scope thereof a method for inhibiting the growth of bacteria in an environment, we make no claim to the use of such a method for the treatment or prevention of a disease in a human being.

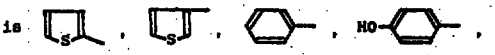
Subject to the foregoing disclaimer:

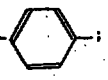
WHAT WE CLAIM IS:—

1. A compound of the formula:

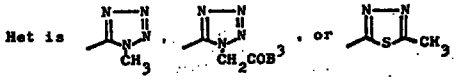


(I)

wherein Ar is  ;

or Acyl-O-  ;

COB^1 and COB^2 are each independently carboxy or protected carboxy;

Het is 

COB^3 being carboxy or protected carboxy; and

Y is hydrogen or methoxy; provided that when Y is methoxy, Het is



2. A compound as claimed in claim 1, wherein Acyl is alkanoyl containing from 1 to 5 carbon atoms, carbamoyl, N-alkylcarbamoyl containing from 2 to 6 carbon atoms or ureidocarbonyl.

tion (100 ml) and dripped intravenously to an adult patient immediately after or during a surgical operation of cancer for preventing and treating post operative bacterial infection.

Example VI-3

Microcrystalline 7β - [α - carbamoyloxyphenyl - α - carboxyacetamido] - 7α-methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylic acid (200 mg) in a 5 ml vial is suspended in sterilized water for injection containing 2 mg of procaine (2 ml), and given intramuscularly to a patient suffering from suppurative inflammation caused by *Staphylococcus aureus*.

Example VI-4

Crystalline 7β - [α - (3 - thienyl) - α - (5 - indanyl)oxycarbonylacetamido] - 3-(1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid (200 mg) is dissolved in sesame oil (0.25 ml) and filled in a hard gelatin capsule. Each one capsule is given orally at 4 hour intervals to a patient suffering from upper respiratory tract infection caused by *Streptococcus pyogenes*.

Example VI-5

Powdered 7β - (α - p - hydroxyphenyl - α - (5 - indanyl)oxycarbonylacetamido]-7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylic acid (100 mg) is mixed well with corn starch (150 mg) and talc (10 mg), powdered, and encapsulated in a hard gelatin capsule (250 mg volume). Each one capsule is administered orally at 3 hour intervals to an adult patient suffering from urinary tract infection caused by *Escherichia coli*.

Example VI-6

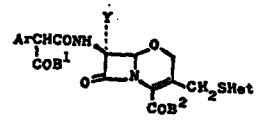
Mixed powder of 7β - [α - p - carbamoyloxyphenyl - α - (5 - indanyloxy(carbonylacetamido] - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1-oxadethia - 3 - cephem - 4 - carboxylic acid (10 g), lactose (50 g), corn starch (2 g), magnesium stearate (0.3 g), sucrose (10 g), and necessary amount of acacia and talc is granulated. The granule is mixed with water before use to obtain a suspension, and one tea spoonful amount of the suspension is given orally to an infant suffering from pneumonia caused by *Klebsiella pneumoniae*.

Insofar as the present invention includes within the scope thereof a method for inhibiting the growth of bacteria in an environment, we make no claim to the use of such a method for the treatment or prevention of a disease in a human being.

Subject to the foregoing disclaimer:

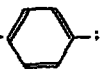
WHAT WE CLAIM IS:—

1. A compound of the formula:

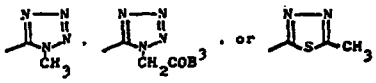


(I)

wherein Ar is 

or Acyl-O- ;

COB^1 and COB^2 are each independently carboxy or protected carboxy;
Het is

Het is 

COB^3 being carboxy or protected carboxy; and
Y is hydrogen or methoxy; provided that when Y is methoxy, Het is



2. A compound as claimed in claim 1, wherein Acyl is alkanoyl containing from 1 to 5 carbon atoms, carbamoyl, N-alkylcarbamoyl containing from 2 to 6 carbon atoms or ureidocarbonyl.

3. A compound as claimed in claim 1, wherein Acyl is 1—5C alkanoyl, 8—12C aralkanoyl, 7—9C aroyl, 2—5C alkoxycarbonyl, 8—20C aralkoxycarbonyl, carbamoyl, 2—6C N-alkylcarbamoyl or ureidocarbonyl.

4. A compound as claimed in claim 1, wherein Acyl is formyl, acetyl, propionyl, butyryl, isobutyryl, enanthoyl, phenylacetyl, phenylpropionyl, benzoyl, toluoyl, carbethoxycarbonyl, benzyloxycarbonyl, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N-isobutylcarbamoyl, N,N-dimethylcarbamoyl, carbamoylcarbamoyl or N^{α}-methylureidocarbonyl.

5. A compound as claimed in any one of claims 1 to 4, wherein COB^1, COB^2, and COB^3, if preesnt, are each independently carboxy or protected carboxy in the form of a pharmaceutically acceptable salt.

6. A compound as claimed in any one of claims 1 to 4, wherein COB^1 is 5-indanyloxycarbonyl, phenoxycarbonyl, tolyloxycarbonyl or dimethylphenoxycarbonyl.

7. A compound as claimed in any one of claims 1 to 4 or 6, wherein COB^2 is benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-methylbenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, benzhydryloxycarbonyl, t-butoxycarbonyl or 2,2,2-trichloroethoxycarbonyl.

8. A compound as claimed in any one of claims 1 to 4, wherein COB^1, COB^2, and COB^3, if present, are each independently any protected carboxy group referred to hereinbefore.

9. 7β - (α - p - acetoxyphenyl - α - carboxyacetamido) - 3 - (1 - methyltetrazol-5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid.

10. 7β - (α - p - carbamoyloxyphenyl - α - carboxyacetamido) - 3 - (2 - methyl-1,3,4 - thiadiazol - 5 - yl) - thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid.

11. 7β - (α - p - carbamoyloxyphenyl - α - carboxyacetamido) - 7α - methoxy-3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid.

12. 7β - (α - p - N - methylcarbamoyloxyphenyl - α - carboxyacetamido) - 7α-methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylic acid.

13. 7β - (α - p - ureidocarbonyloxyphenyl - α - carboxyacetamido) - 7α - methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4-carboxylic acid.

14. 7β - [α - phenyl - α - (5 - indanyloxy)carbonylacetamido] - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid.

15. 7β - [α - phenyl - α - (5 - indanyloxy)carbonylacetamido] - 7α - methoxy-3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid.

16. 7β - [α - (3 - thienyl) - α - (5 - indanyloxy)carbonylacetamido] - 7α-methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylic acid.

17. 7β - [α - (3 - thienyl) - α - phenoxycarbonylacetamido] - 7α - methoxy - 3-(1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid.

18. 7β - [α - (3 - thienyl) - α - (3,4 - dimethylphenoxy)carbonylacetamido] - 7α-methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylic acid.

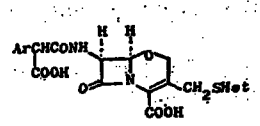
19. 7β - (α - p - hydroxyphenyl - α - (5 - indanyloxy)carbonylacetamido) - 7α-methoxy - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem-4 - carboxylic acid.

20. A compound as claimed in claim 1 substantially as hereinbefore described in any one of the Examples.

21. A salt of a compound as claimed in any one of claims 1 to 20.

22. A salt as claimed in claim 21 which is a pharmaceutically acceptable salt.

23. A compound of the formula:



(IX)

wherein

Ar is phenyl, p-hydroxyphenyl, 2-thienyl, or 3-thienyl;

Het is 1-methyltetrazol-5-yl, 1-carboxymethyltetrazol-5-yl, or 2-methyl-1,3,4-thiadiazol-5-yl, and derivatives thereof at the carboxy.

24. A compound as claimed in claim 23, wherein derivatives thereof at the carboxy are alkali metal salts.

25. A compound as claimed in claim 23, wherein derivatives thereof at the carboxy are diphenylmethyl, p-nitrobenzyl, indanyl, alkanoyloxymethyl, or benzyl esters.

26. 7β - [α - (2 - thienyl) - α - carboxyacetamido] - 3 - (1 - methyltetrazol - 5-yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid.

27. 7β - [α - (2 - thienyl) - α - carboxyacetamido] - 3 - (1 - carboxymethyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid.

28. 7β - [α - (2 - thienyl) - α - carboxyacetamido] - 3 - (2 - methyl - 1,3,4-thiadiazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid.

29. 7β - [α - (3 - thienyl) - α - carboxyacetamido] - 3 - (1 - methyltetrazol-5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid.

30. 7β - [α - (3 - thienyl) - α - carboxyacetamido] - 3 - (1 - carboxymethyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid.

31. 7β - [α - (3 - thienyl) - α - carboxyacetamido] - 3 - (2 - methyl - 1,3,4-thiadiazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid.

32. 7β - (α - phenyl - α - carboxyacetamido) - 3 - (1 - methyltetrazol - 5 - yl)-thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid.

33. 7β - (α - phenyl - α - carboxyacetamido) - 3 - (1 - carboxymethyltetrazol-5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid.

34. 7β - (α - phenyl - α - carboxyacetamido) - 3 - (2 - methyl - 1,3,4 - thiadiazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid.

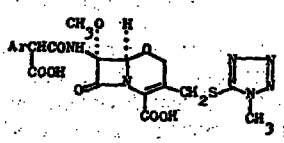
35. 7β - (α - p - hydroxyphenyl - α - carboxyacetamido) - 3 - (1 - methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid.

36. 7β - (α - p - hydroxyphenyl - α - carboxyacetamido) - 3 - (1 - carboxymethyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid.

37. 7β - (α - p - hydroxyphenyl - α - carboxyacetamido) - 3 - (2 - methyl-1,3,4 - thiadiazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid.

38. A compound as claimed in claim 23 substantially as hereinbefore described in any one of the Examples.

39. A compound of the formula:



(XIII)

wherein

Ar is phenyl, p-hydroxyphenyl, p-acyloxyphenyl, 2-thienyl, or 3-thienyl, and derivatives thereof at the carboxy.

40. A compound as claimed in claim 39, wherein the derivatives at the carboxy are alkali metal salts.

41. A compound as claimed in claim 39, wherein the derivatives at the carboxy are diphenylmethyl, p-methoxybenzyl, p-nitrobenzyl, indanyl, alkanoyloxymethyl, t-butyl, or benzyl ester.

45. 7β (α - p - hydroxyphenyl - α - carboxyacetamido(- 7α - methoxy - 3 - (1-methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid.

43. 7β - [α - (3 - thienyl) - α - carboxyacetamido] - 7α - methoxy - 3 - (1-methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid.

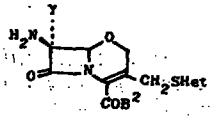
44. 7β - (α - phenyl - α - carboxyacetamido) - 7α - methoxy - 3 - (1 - methyltetrazol 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid.

45. 7β - (α - p - hydroxyphenyl - α - carboxyacetamido) - 7α - methoxy - 3 - (1-methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid.

46. 7β - (α - p - acetoxyphenyl - α - carboxyacetamido) - 7α - methoxy - 3 - (1-methyltetrazol - 5 - yl)thiomethyl - 1 - oxadethia - 3 - cephem - 4 - carboxylic acid.

47. A compound as claimed in claim 39 substantially as hereinbefore described in any one of the Examples.

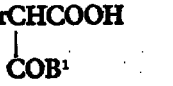
48. A process for preparing a compound as claimed in claim 1, which process comprises reacting an amine of the formula:



(II)

wherein

COB^2, Het and Y are each as defined in claim 1, with an arylmalonic acid of the formula:



(III)

wherein

Ar and COB^1 are each as defined in claim 1, or reactive derivatives thereof.

49. A process as claimed in claim 48 wherein the amino group at position 7 of the amine (II) is protected or activated.

50. A process as claimed in claim 48 or claim 49, wherein the arylmalonic acid (III) is used in the form of the free acid.

51. A process as claimed in claim 50 wherein the reaction is effected in a solvent and in the presence of a condensing reagent.

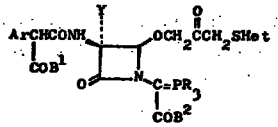
52. A process as claimed in claim 51 wherein the condensing reagent is a N,N'-dialkylcarbodiimide, a carbonyl compound, or acylamine or an isoxazolinium salt.

53. A process as claimed in any one of claims 50 to 52, wherein the reaction is effected at a temperature of from −10°C to 70°C.

54. A process as claimed in claim 48 or claim 49, wherein the arylmalonic acid (III) is used in the form of an anhydride, a reactive ester, a diacylamino ester, a reactive amide or a formimino derivative.

55. A process as claimed in any one of claims 48 to 54, wherein the reaction is effected in the presence of an acid receptor or a molecular sieve.

56. A process for preparing a compound as claimed n cliam 1, which process comprises heating in an inert solvent an azetidinone of the formula:



(IV)

wherein

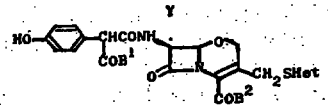
Ar, COB^1, COB^2, Het and Y are each as defined in claim 1 and each of the three groups R is the same or different and is optionally substituted alkyl or aryl.

57. A process for preparing a compound as claimed in claim 1 wherein COB^1, COB^2, and/or COB^3 is carboxy, which process comprises deprotecting a compound as claimed in claim 1 wherein COB^1, COB^2, and/or COB^3 is protected carboxy.

58. A process as claimed in claim 57 wherein the deprotection is effected by a method substantially as hereinbefore described.

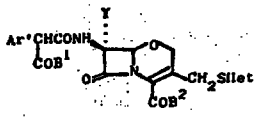
59. A process for preparing a compound as claimed in claim 1, wherein COB^1, COB^2, and/or COB^3 is a carboxylic acid salt group, which process comprises treating a compound as claimed in claim 1 wherein COB^1, COB^2 and/or COB^3 is carboxy with a base.

60. A process for preparing a compound as claimed in claim 1 and having the formula:



(V)

which process comprises removing the protecting group(s) in the moiety Ar' of a compound of the formula:



(VI)

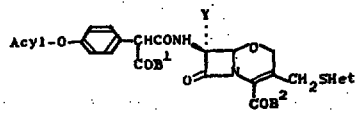
wherein

Ar' is p-protected hydroxyphenyl, and COB^1, COB^2, Het and Y are each as defined in claim 1 but are not necessarily the same in the product as in the starting material.

61. A process as claimed in claim 60, wherein removal of the protecting group(s) is achieved, in the case of cleavage of acylates or ethers, by treatment with an acid or a base in the presence of a cation scavenger, or, in the case of removal of p-nitro-

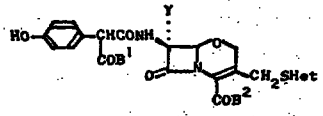
benzyloxycarbonyl or benzyloxycarbonyl groups, by hydrogenation in the presence of platinum or palladium.

62. A process for preparing a compound as claimed in claim 1 and having the formula:



(VII)

which process comprises acylating a compound of the formula:



(VIII)

with an acylating reagent for introducing a group Acyl.

63. A process for preparing a compound as claimed in claim 1 substantially as hereinbefore described in any one of the Examples.

64. A process as claimed in any one of claims 57 to 62 wherein the starting compound as claimed in claim 1 has been prepared by a process as claimed in any one of claims 48 to 56.

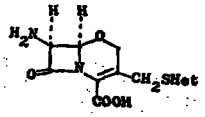
65. A process as claimed in any one of claims 57 to 62 wherein the starting compound as claimed in claim 1 has been prepared by a process as claimed in any one of claims 57 to 62.

66. A compound as claimed in claim 1 which has been prepared by a process as claimed in any one of claims 48 to 65.

67. A salt of a compound as claimed in claim 66.

68. A salt as claimed in claim 67 which is a pharmaceutically acceptable salt.

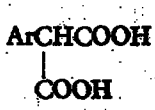
69. A process for preparing a compound as claimed in claim 23, which process comprises reacting an amine of the formula:



(X)

wherein

Het is as defined in claim 23, or a derivative thereof at the carboxy with a malonic acid derivative of the formula:



(XI)

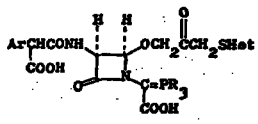
wherein

Ar is as defined in claim 23, or with a reactive derivative thereof in which one of the carboxy groups may be protected.

70. A process as claimed in claim 69, wherein the reaction is effected under conditions as specified in any one of claims 51 to 53 and 55.

71. A process as claimed in claim 69 or claim 70, wherein the malonic acid derivative (XI) is used in the form of an anhydride, a reactive ester, a diacylimino ester, a reactive amide or a formimino derivative.

72. A process for preparing a compound as claimed in claim 23, which process comprises heating in an inert solvent an azetidinone of the formula:



(XII)

wherein

Ar and Het are each as defined in claim 23, and each of the three groups R is the same or different and is optionally substituted alkyl or aryl, or a derivative thereof at the carboxy.

73. A process for preparing a compound as claimed in claim 23 which contains one or more free acid groups, which process comprises deprotecting a compound as claimed in claim 23 wherein one or more of the carboxy groups is protected.

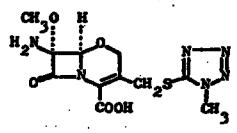
74. A process as claimed in claim 73, wherein the deprotection is effected by a method substantially as hereinbefore described.

75. A process for preparing a compound as claimed in claim 23 in which one or more of the carboxy groups is a carboxylic acid salt group, which process comprises treating a compound as claimed in claim 23 which contains one or more free acid groups with a base.

76. A process for preparing a compound as claimed in claim 23 substantially as hereinbefore described in any one of the Examples.

77. A compound as claimed in claim 23 which has been prepared by a process as claimed in any one of claims 69 to 76.

78. A process for preparing a compound as claimed in claim 39, which process comprises reacting an amine of the formula:



(XIV)

or a derivative thereof at the carboxy with a malonic acid derivative of the formula:



(XV)

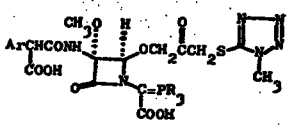
wherein

Ar is as defined in claim 39, or with a reactive derivative thereof in which one of the carboxy groups may be protected.

79. A process as claimed in claim 78, wherein the reaction is effected under conditions as specified in any one of claims 51 to 53 and 55.

80. A process as claimed in claim 78 or claim 79, wherein the malonic acid derivative (XV) is used in the form of an anhydride, a reactive ester, a diacylimino, a reactive amide or a formimino derivative.

81. A process for preparing a compound as claimed in claim 39, which process comprises heating in an inert solvent an azetidinone of the formula:



(XVI)

wherein

Ar is as defined in claim 39, and each of the three groups R is the same or different and is optionally substituted alkyl or aryl, or a derivative thereof at the carboxy.

82. A process for preparing a compound as claimed in claim 39 which contains one or more free acid groups, which process comprises deprotecting a compound as claimed in claim 39 wherein one or more of the carboxy groups is protected.

83. A process as claimed in claim 82, wherein the deprotection is effected by a method substantially as hereinbefore described.

84. A process for preparing a compound as claimed in claim 39 in which one or more of the carboxy groups is a carboxylic acid salt group, which process comprises treating a compound as claimed in claim 39 which contains one or more free acid groups with a base.

85. A process for preparing a compound as claimed in claim 39 substantially as hereinbefore described in any one of the Examples.

86. A compound as claimed in claim 39 which has been prepared by a process as claimed in claims 78 to 85.

87. A pharmaceutical or veterinary formulation which comprises a compound as claimed in any one of claims 1 to 20 and 66 or a salt as claimed in any one of claims 21, 22, 67 and 68.

88. A pharmaceutical or veterinary composition which comprises a compound as claimed in any one of claims 1 to 20 and 66 or a salt as claimed in any one of claims 21, 22, 67 and 68 together with a pharmaceutically acceptable or veterinarily acceptable, respectively, diluent, carrier or excipient.

89. A pharmaceutical or veterinary formulation which comprises a compound as claimed in any one of claims 23 to 38 and 77.

90. A pharmaceutical or veterinary composition which comprises a compound as

claimed in any one of claims 23 to 38 and 77 together with a pharmaceutically acceptable or veterinarily acceptable, respectively, diluent, carrier or excipient.

91. A pharmaceutical or veterinary formulation which comprises a compound as claimed in any one of claims 39 to 47 and 86.

92. A pharmaceutical or veterinary composition which comprises a compound as claimed in any one of claims 39 to 47 and 86 together with a pharmaceutically acceptable or veterinarily acceptable, respectively, diluent, carrier or excipient.

93. A pharmaceutical or veterinary composition as claimed in any one of claims 88, 90 and 92 in the form of an injectable composition or a vial.

94. A pharmaceutical or veterinary composition as claimed in any one of claims 88, 90 and 92 in the form of sterilized microcrystals or lyophilizate.

95. A formulation as claimed in any one of claims 87, 89 and 91 or a composition as claimed in any one of claims 88, 90, and 92 to 94 in unit dosage form.

96. A method for inhibiting the growth of bacteria in an environment which method comprises administering to the environment an effective amount of a compound as claimed in any one of claims 1 to 20, 23 to 47, 66, 77 and 86 or a salt as claimed in any one of claims 21, 22, 67 and 68, or of a formulation as claimed in any one of claims 87, 89, 91 and 95, or of a composition as claimed in any one of claims 88, 90 and 92 to 94.

97. A method as claimed in claim 96 when used in the prevention or cure of disease in a non-human animal.

98. A method as claimed in claim 96 when used in the prevention of decay in a perishable substance or material.

99. A method as claimed in claim 96 when used in disinfecting a substance, material, article or building structure.

100. A method as claimed in claim 97 when effected by the use of intravenous injection or a drip.

101. A method as claimed in claim 97 or claim 100 wherein from 0.05 to 50 mg of compound (I) or salt thereof, whether in a formulation or composition or in the free form, is administered per kilogram body weight per day.

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