

Description

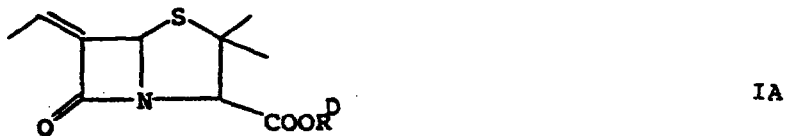
This invention relates to β -lactam compounds and in particular to a class of 6-alkylidene penems which have antibacterial and β -lactamase inhibitory properties. The compounds are therefore useful in the treatment of antibacterial infections, either alone or in combination with other antibiotics.

GB 2 013 674 A (Ciba-Geigy) and EP 0 002 210 A1 (Merck) both disclose 6-substituted 2-penem compounds of the general formula (I):

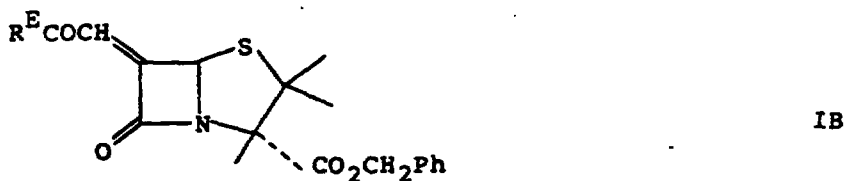


15 in which R^A , R^B and R^C denote hydrogen or certain organic radicals.

6-methylene-penicillanic acid derivatives of the general formulae IA and IB:



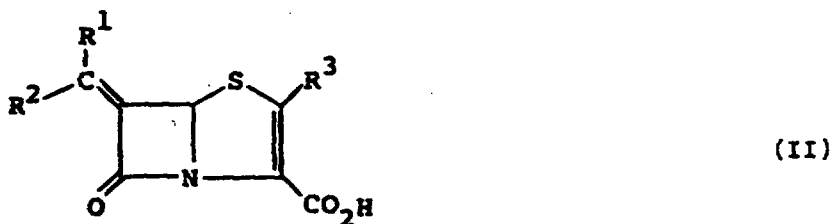
25 in which R^D denotes a protecting group; and



35 in which R^E denotes phenyl or $\text{CH}_2\text{O}(\text{C}_6\text{H}_5)$ have been described in US 4 123 539 and *J. Org. Chem.* 38, 3227—3228 (1973), respectively as intermediates in the preparation of various penicillin derivatives.

It has now been found that it is possible to prepare 6-alkylidene derivatives of 2-penems, and that such compounds possess antibacterial activity, and that they also inhibit β -lactamases and have a synergistic effect in combination with other β -lactam antibiotics. 6-Alkylidene-2-penems are novel compounds.

40 Accordingly, the present invention provides a compound of formula (II):



50 or a pharmaceutically acceptable salt or *in-vivo* hydrolysable ester thereof, in which:

each of R^1 and R^2 , which may be the same or different, denotes a hydrogen atom, a (C_{1-10}) hydrocarbon group optionally substituted by a functional group, or a heterocyclic group; and

R^3 denotes a hydrogen atom or a group of the formula $-\text{R}^A$ or $-\text{SR}^A$; in which:

55 R^A denotes a (C_{1-10}) hydrocarbon group (other than an alkyl group), a heterocyclic group, or an unsubstituted or substituted (C_{1-10}) alkyl group in which the optional substituents are selected from hydroxy, halogen, mercapto, carboxy, (C_{1-6}) alkoxy, (C_{1-6}) alkanoyloxy, (C_{1-6}) alkylthio, amino, monoalkylamino, dialkylamino, alkanoylamino, (C_{1-6}) alkoxycarbonyl, and heterocyclithio groups.

60 R^1 and R^2 may be the same or different and each suitably denotes a hydrogen atom or a (C_{1-10}) hydrocarbon group optionally substituted by a functional group, advantageously a hydrogen atom or a (C_{1-10}) hydrocarbon group. Suitable (C_{1-10}) hydrocarbon groups include (C_{1-6}) alkyl groups and phenyl groups. Suitable (C_{1-6}) alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and tert-butyl groups.

65 Preferably, each of R^1 and R^2 , which may be the same or different, denotes a hydrogen atom, or a methyl, ethyl, or phenyl group.

Also preferably, one of R¹ and R² denotes a hydrogen atom.

Suitably, one of R¹ and R² denotes a hydrogen atom and the other denotes a methyl group.

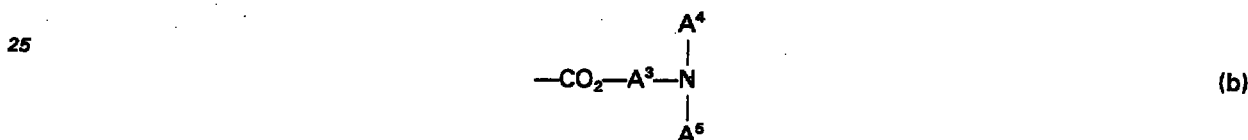
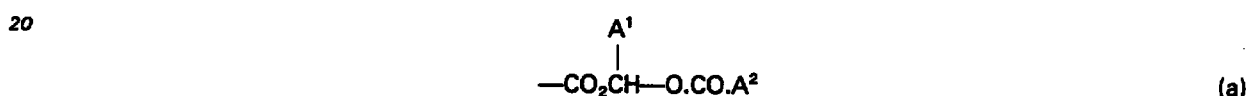
R³ may suitably denote a hydrogen atom, an unsubstituted or substituted (C₁₋₁₀)alkyl group, or an unsubstituted or substituted (C₁₋₁₀)alkylthio group, the substituents of said alkyl and alkylthio groups being selected from hydroxy, halogen, mercapto, carboxy, (C₁₋₆)alkoxy, (C₁₋₆)alkanoyloxy, (C₁₋₆)alkylthio, amino, monoalkylamino, dialkylamino, alkanoylamino, and (C₁₋₆)alkoxycarbonyl groups.

Examples of such groups R³ include hydrogen, methyl, ethyl, propyl, methylthio, ethylthio, hydroxymethyl, methoxymethyl, ethoxymethyl, acetoxymethyl, (1 or 2)-acetoxylethyl, aminomethyl, 2-aminoethyl, acetamidomethyl, 2-acetamidoethyl, carboxymethyl, hydroxymethylthio, 2-hydroxyethylthio, methoxymethylthio, 2-methoxyethylthio, acetoxymethylthio, aminomethylthio, 2-aminoethylthio, acetamidomethylthio, 2-acetamidoethylthio, carboxymethylthio, and pyridylthio.

Particular examples of groups R³ include hydrogen, aminomethyl, aminoethyl, methylthio, ethylthio, 2-aminoethylthio, 2-hydroxyethylthio, methyl, ethyl, acetamidoethyl, and pyridylthio.

Pharmaceutically acceptable *in-vivo* hydrolysable esters are those esters which hydrolyse in the human body to produce the parent acid or its salt. Such esters may be identified by administration to a test animal such as a rat or mouse by intravenous administration and subsequent examination of the test animal's body fluids for the presence of the compound of the formula (II) or its salt.

Suitable ester groups of this type include those of part-formulae (a), (b) and (c):



in which

A¹ denotes hydrogen, methyl, or phenyl;

A² denotes (C₁₋₆)alkyl, (C₁₋₆)alkoxy or phenyl; or

A¹ and A² together denote a 1,2-phenylene group optionally substituted by one or two methoxy groups;

A³ denotes (C₁₋₆)alkylene optionally substituted by a methyl or ethyl group;

each of A⁴ and A⁵, which may be the same or different denotes (C₁₋₆)alkyl; and

A⁶ denotes (C₁₋₆)alkyl.

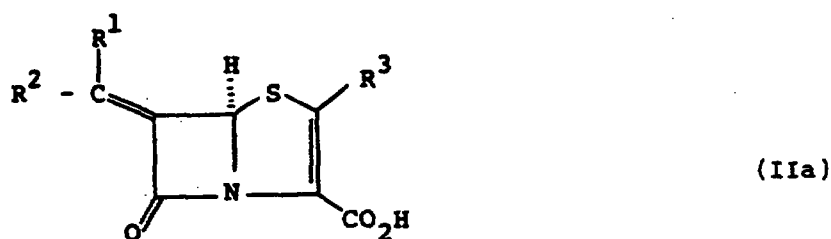
Examples of suitable *in-vivo* hydrolysable ester groups include acetoxymethyl, pivaloyloxymethyl, α-acetoxyethyl, α-acetoxybenzyl, α-pivaloyloxyethyl, ethoxycarbonyloxymethyl, α-ethoxycarbonyloxyethyl, dimethylaminomethyl, diethylaminomethyl, diethylaminoethyl, phthalidyl and dimethoxyphthalidyl groups.

Suitable pharmaceutically acceptable salts of the 3-carboxylic acid group of the compound of formula (II) include metal salts, for example aluminium salts, alkali metal salts (e.g. sodium or potassium salts), and alkaline earth metal salts (e.g. calcium or magnesium salts), ammonium salts, and substituted ammonium salts, for example those with lower alkylamines (e.g. triethylamine), hydroxy-lower alkylamines (e.g. 2-hydroxyethylamine, bis(2-hydroxyethyl)amine or tri(2-hydroxyethyl)amine), cycloalkylamines, (e.g. bicyclohexylamine), procaine, dibenzylamine, N,N-dibenzylethylenediamine, 1-phenamine, N-ethylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylene-diamine, or bases of the pyridine type (e.g. pyridine, collidine and quinoline), or other amines which have been used to form salts with known penicillins.

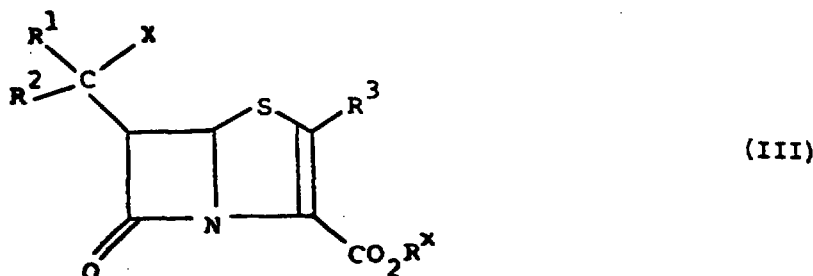
Specific compounds of this invention include the following compounds of the general formula II and their pharmaceutically acceptable salts:

- 6-(Z)-ethylidene-2-ethylthiopenem-3-carboxylic acid;
 - 6-(E)-ethylidene-2-ethylthiopenem-3-carboxylic acid;
 - 6-(Z)-ethylidenepenem-3-carboxylic acid;
 - 6-(Z)-ethylidene-2-n-propylpenem-3-carboxylic acid;
 - 6-ethylidene-2-(2-acetamidoethylthio)penem-3-carboxylic acid;
 - 6-(Z)-ethylidene-2-methylpenem-3-carboxylic acid;
 - 6-ethylidene-2-(2-pyridylthio)penem-3-carboxylic acid;
 - 6-ethylidene-2-(2-aminoethylthio)penem-3-carboxylic acid;
 - 6-(Z)-benzylidene-2-ethylthiopenem-3-carboxylic acid; and
 - 6-isopropylidene-2-ethylthiopenem-3-carboxylic acid; and also
- the compound 6-ethylidene-2-ethylsulphinylpenem-3-carboxylic acid and its pharmaceutically acceptable salts.

The compounds of formula (II) may exist in two optically active forms and it is to be understood that both such forms as well as racemic mixtures thereof are embraced by the present invention. It is believed that the more active form is that of structure (IIa):

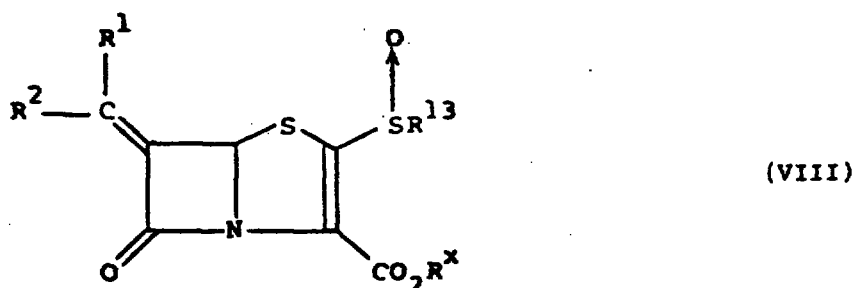


The compounds of this invention may be prepared by a process which comprises either:
(a) elimination of the elements of a compound of the formula H—X from a compound of formula (III):



in which R¹, R² and R³ are as defined above, X denotes a leaving group, and R^x denotes a hydrogen atom or a carboxyl-blocking group; or

(b) when R³ denotes a group of the formula —SR^a, reaction of a sulfoxide of formula (VIII):



in which R¹, R² and R^x are as defined above, and R¹³ denotes an organic group different from the group R^a (R^a being defined as above); with a thiol of formula (IX) or a reactive derivative thereof:



and, after step (a) or (b), if necessary, carrying out one or more of the following steps:

- (i) removal of any carboxyl blocking group R^x;
- (ii) converting the product to a pharmaceutically acceptable salt or *in-vivo* hydrolysable ester.

Suitable carboxyl-blocking derivatives for the groups —CO₂R^x include salt, ester, and anhydride derivatives of the carboxylic acid. The derivative is one which may readily be cleaved at a later stage of the reaction. The salts need not be pharmaceutically acceptable. Suitable salts include inorganic salts, for example, metal salts, for example silver salts, mercuric salts, and alkali metal salts (e.g. lithium or sodium salts), and tertiary amine salts, for example those with tri-lower-alkylamines, N-ethyl-piperidine, or dimethylpiperazine. A preferred salt is that with triethylamine.

Suitable ester-forming carboxyl-blocking groups R^x are those which may be removed under conventional conditions. Examples of such groups include benzyl, p-methoxy-benzyl, 2,4,6-trimethylbenzyl, 3,5-di-t-butyl-4-hydroxybenzyl, benzoylmethyl, p-nitrobenzyl, 4-pyridylmethyl, 2,2,2-trichloroethyl, 2,2,2-tribromoethyl, t-butyl, t-amyl, diphenylmethyl, triphenylmethyl, adamantyl, 2-benzyloxyphenyl, 4-methylthiophenyl, tetrahydrofur-2-yl, tetrahydropyran-2-yl, pentachlorophenyl, p-toluenesulphonyl, methoxymethyl, a silyl, stannyl or phosphorus-containing group, an oxime radical of formula —N=CHR^o where R^o is aryl or heterocyclyl, or an *in-vivo* hydrolysable ester radical as discussed above.

The carboxyl group may be regenerated from any of the above esters by usual methods appropriate to the particular R^x group, for example, by acid-catalysed hydrolysis, base-catalysed hydrolysis, enzymically-catalysed hydrolysis, or hydrogenation. The hydrolysis must of course be carried out under conditions to which the groups on the rest of the molecule are stable.

5 When it is desired to produce a compound of formula (II) in the form of a free acid or salt by the process of this invention, it is convenient to use a starting compound in which R^x is a carboxyl-blocking group. For the preparation of a compound of formula (II) in the form of a pharmaceutically acceptable ester, it is convenient to employ a starting compound in which R^x represents the desired ester group.

10 In the compound of formula (III) the leaving group X may be a hydroxy group, in which case the elimination step is a dehydration step and may be carried out by treating a compound of formula (III) with a compound of formula (IV):



15 in which R^4 and R^5 are independently aryl, or (C_{1-6}) alkyl optionally substituted with aryl; and a compound of formula (V):



20 in which a, b and c are independently 0 or 1, and R^6 , R^7 and R^8 are independently aryl or (C_{1-6}) alkyl optionally substituted with aryl.

25 In the compounds of the formula (IV), R^4 and R^5 are preferably selected from methyl, ethyl, propyl, butyl, phenyl and benzyl, the ethyl and t-butyl groups being preferred. Thus a preferred compound of formula (IV) is diethyl azodicarboxylate. It is often convenient that R^4 and R^5 represent the same group.

Preferred compounds of the formula (V) include triarylphosphines and trialkylphosphites. Preferred groups R^6 , R^7 and R^8 include methyl, ethyl, n-propyl, n-butyl, benzyl, phenyl and methoxyphenyl.

30 Conveniently, R^6 , R^7 and R^8 represent the same group. A particularly preferred compound of the formula (V) is triphenylphosphine.

Generally, the approximate two equivalents of the compounds of the formulae (IV) and (V) are used per mole of compound (III).

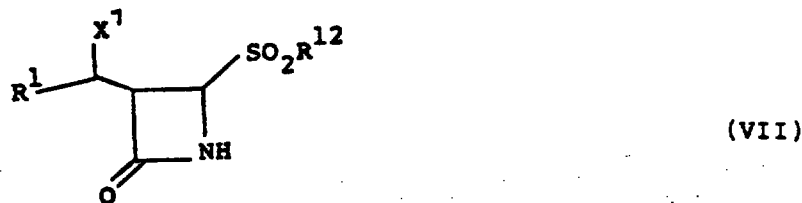
35 The dehydration reaction is generally carried out at a non-extreme temperature, such as -20 to $+100^\circ\text{C}$. We have found it convenient to begin the reaction at a depressed temperature, such as 0°C , and then to allow the temperature to rise to about room temperature.

The reaction is suitably performed in an inert aprotic organic solvent. Suitable solvents include tetrahydrofuran, dioxane, ethyl acetate, benzene and the like.

40 Suitable groups for the leaving group X in the compound of formula III (other than hydroxy groups) include halogen; a group of formula $-O-SO_2(O)_nR^9$ or $-O-CO-(O)_nR^9$ wherein n is zero or 1 and R^9 is aryl or (C_{1-6}) alkyl optionally substituted with aryl; and a group of formula $-OPO(OR^{10})_2$ wherein R^{10} is (C_{1-6}) alkyl or aryl.

Preferred groups of formula $-OCO(O)_nR^9$ are those wherein n is zero and R^9 is (C_{1-6}) alkyl, in particular acetoxy.

45 The compounds of formula (III) in which X denotes a leaving group other than a hydroxy group may be prepared from the compounds of formula (III) in which X denotes a hydroxy group by replacing the hydroxy group by another leaving group X. Alternatively the other leaving group X^1 can be introduced into the molecule at an earlier stage in the synthesis of the penem nucleus. In particular the groups $-OSO_2(O)_nR^9$ and $-OCO(O)_nR^9$ can be introduced at the beginning of, or at any stage during, the synthesis 50 of the penem. In each case, the leaving group (other than a hydroxy group) X^1 is introduced by replacing a hydroxyl group. One particular novel intermediate useful for this purpose is the compound of formula (VII):



60 wherein R^1 is as defined with respect to formula (II) above, R^{12} represents methyl or benzyl, and X^1 denotes a leaving group (other than a hydroxy group).

The elimination of the elements of a compound of the formula $H-X^1$ is most conveniently brought about by treatment of a compound of the formula (III) in which X^1 denotes a leaving group (other than a 65 hydroxy group) with a base in an aprotic medium. The base employed will be a base of low nucleophilicity

so that in general primary and secondary amines will not be suitable. Suitable bases include powdered inorganic bases such as alkali metal carbonates, bicarbonates or hydroxides, for example powdered potassium carbonate, or hydrides or 1,8-diazabicyclo[5.4.0]undec-7-ene. Suitable solvents for use in this reaction include dimethylformamide, hexamethylphosphoramide, dichloromethane, tetrahydrofuran and the like.

The elimination may be effected at a non-extreme temperature such as -20 to $+70^{\circ}\text{C}$, for example $+10$ to $+25^{\circ}\text{C}$. The reaction may be conveniently effected at ambient temperature.

The compounds of this invention in which R^3 denotes a group of the formula SR^a may also be prepared by the reaction of a sulfoxide of formula (VIII) above with a thiol of formula (IX) above or a reactive derivative thereof.

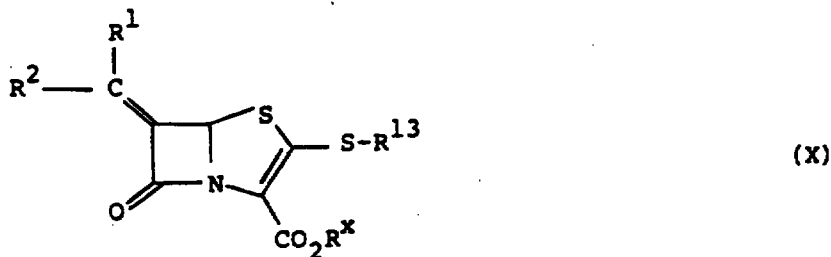
This process may be carried out in any inert solvent such as N,N-dimethylformamide (DMF), tetrahydrofuran (THF), dioxane, hexamethylphosphoramide (HMPA) or glyme. The solvent DMF is preferred. A low temperature is preferred, suitably below 0°C , preferably below -20°C especially from about -30°C to about -70°C .

When the thiol compound of formula (IX) itself is employed, the reaction is generally carried out in the presence of a base, although this is not essential. Examples of suitable bases include sodium hydride, potassium hydride, sodium amide, potassium amide, sodium hydroxide, potassium hydroxide, sodium ethoxide, sodium methoxide, potassium butoxide, triethylamine, and tripropylamine. Advantageously, the base is used in an amount of at least 0.9 equivalent, preferably 1.0 to 1.2 equivalents, per mole of the thiol compound.

Instead of using the base in the reaction, a reactive derivative of the thiol compound of formula (IX) may be used. Preferably the reactive derivative is a salt of the thiol (IX), in particular a salt with an alkali metal, preferably sodium or potassium.

The amount of the thiol compound of formula (IX) or its reactive derivative is not critical. Generally, however, it is used in an amount of at least 1.0 mole, preferably 1.1 to 1.5 moles, per mole of the compound of formula (VIII).

Compounds of formula (VIII) may be prepared by S-oxidation of a compound of formula (X):



in which

R^1 , R^2 , R^4 and R^x are as defined above; with a mild oxidising agent.

Suitable mild oxidising agents include perbenzoic acid, hydrogen peroxide, selenium dioxide or sodium metaperiodate. Substituted perbenzoic acids such as m-chloroperbenzoic acid are most preferred.

The present invention also provides a pharmaceutical composition which comprises a compound of the formula (II) as hereinbefore defined or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof and a pharmaceutically acceptable carrier.

If the compound of the invention present in such a composition is in the form of a salt then suitable salts include pharmaceutically acceptable alkali metal or alkaline earth metal salts, or a salt with a pharmaceutically acceptable nitrogenous base. Particularly suitable salts include the sodium salt and the potassium salt.

The compositions may be formulated for administration by any route, for example oral, topical or parenteral, although oral administration is preferred. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils).

for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and if desired convention flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

- 5 For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle.

Unit-dose forms according to this invention will normally contain from 50 to 500 mg of a compound of this invention, for example about 62.5, 100, 125, 150, 200, 250 or 300 mg. Such compositions may be
10 administered up to 6 times a day or more conveniently 2, 3 or 4 times a day so that the total daily dose for a 70 kg adult is about 200 to 2000 mg, for example about 400, 600, 750, 1000 or 1500 mg.

The compositions of this invention may be used to treat infections of the respiratory tract, urinary tract or soft tissues in humans, mastitis in cattle or the like.

- 15 The present invention also provides synergistic pharmaceutical compositions which comprise a pharmaceutical composition as hereinbefore described which also contains a penicillin or a cephalosporin.

Suitable penicillins for inclusion in the compositions of this invention include benzyl penicillin, phenoxymethylpenicillin, ampicillin, amoxycillin, ticarcillin, suncillin, sulbenicillin, azlocillin, mezlocillin, apalcillin, piperacillin or pro-drugs of these compounds.

- 20 Particularly suitable penicillins for inclusion in orally administrable compositions of this invention include ampicillin and its orally administrable pro-drugs, amoxycillin and its orally administrable pro-drugs and orally administrable pro-drugs of carbenicillin. Thus particularly suitable penicillins include ampicillin anhydride, ampicillin trihydrate, sodium ampicillin, talampicillin hydrochloride, pivampicillin hydrochloride, bacampicillin hydrochloride; amoxycillin trihydrate, sodium amoxycillin; and the sodium salts of the phenyl and 5-indanyl α -esters of carbenicillin.

- 25 A preferred penicillin for inclusion in the orally administrable compositions of this invention is amoxycillin trihydrate. A further preferred penicillin for inclusion in the orally administrable compositions of this invention is ampicillin trihydrate.

Particularly suitable penicillins for inclusion in injectably administrable compositions of this invention include injectable salts such as the sodium salt of ampicillin, amoxycillin, carbenicillin and ticarcillin.

- 30 A preferred penicillin for inclusion in the injectably administrable compositions of this invention is sodium amoxycillin. A further preferred penicillin for inclusion in the injectably administrable compositions of this invention is sodium ampicillin.

Particularly suitable cephalosporins for inclusion in the compositions of this invention include cephaloridine, cephalexin, cephradine, cefazolin and cephalothin.

- 35 A particularly suitable cephalosporin for inclusion in the orally administrable compositions of this invention is cephalexin.

Particularly suitable cephalosporins for inclusion in the injectably administrable compositions of this invention include cephaloridine, cefazolin and cephradine, generally as their pharmaceutically acceptable salt such as the sodium salt.

- 40 The weight ratio between compound of this invention and penicillin or cephalosporin is generally from 10:1 to 1:10, or more usually from 5:1 to 1:5 and normally from 3:1 to 1:3.

The penicillin or cephalosporin is generally utilised in its conventionally administered amount.

The present invention furthermore provides the use of a compound according to the invention for the preparation of a medicament having β -lactamase inhibitory activity.

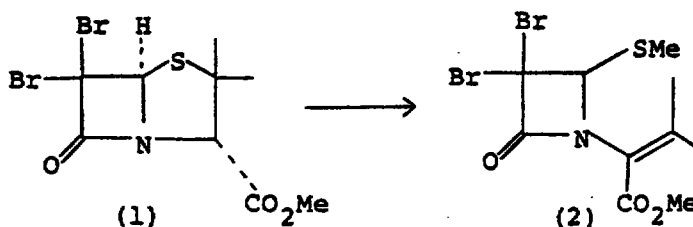
- 45 The following examples illustrate this invention.

Preparation 1(a)

(4RS)13,3-Dibromo-1(1-methoxycarbonyl-2-methylprop-1-enyl)-4-methylthioazetidin-2-one

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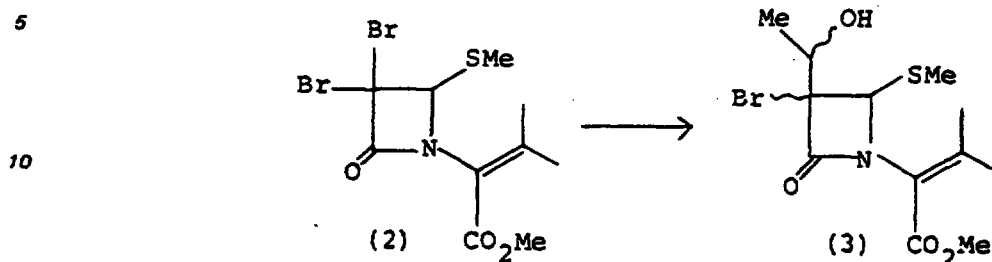
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- 60 A mixture of methyl 6,6-dibromopenicillanate (J. P. Clayton, *J. Chem. Soc. (C)*, 1969, 2123) (42.0 g), methyl iodide (42 ml) and finely powdered sodium hydroxide (5.4 g) in dry tetrahydrofuran (400 ml) was stirred at room temperature for 2.5 hours. The mixture was filtered and the filtrate concentrated. The resulting solution was diluted with ethyl acetate (1 litre) and washed with brine (3 x 100 ml). The dried (MgSO₄) organic layer was evaporated and the residue chromatographed on silica gel eluting with ethyl acetate/petroleum ether mixtures to give the secopenicillanate (2) (25.8 g) as an oil, $v_{\max}$ (CHCl₃) 1785, 1725;
65 δ ppm (CDCl₃) 2.00 (3H, s), 2.23 (3H, s), 2.32 (3H, s), 3.82 (3H, s), 5.52 (1H, s).

Preparation 1(b)

(3E, 4RS)-3-Bromo-3[1-(E)-hydroxyethyl]-1(1-methoxycarbonyl-2-methylprop-1-enyl)-4-methylthioazetidin-2-one



15 a) Using methyl magnesium bromide

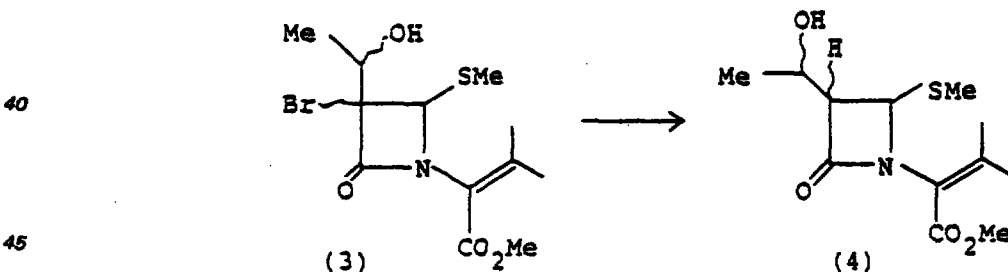
A solution of methyl magnesium bromide (2M in diethyl ether, 14.2 ml) was added, dropwise over five minutes, to a stirred solution of the dibromosecopenicillanate (2) (10.0 g) in dry tetrahydrofuran (200 ml) at -76°C . After stirring at -76°C for a further twenty minutes a solution of acetaldehyde (3 ml) in dry tetrahydrofuran (10 ml) was added dropwise over five minutes. The mixture was stirred at -76°C for a further ten minutes, treated with a saturated solution of ammonium chloride (10 ml), and allowed to attain room temperature. The mixture was diluted with ethyl acetate and the organic phase separated. The organic layer was washed with brine, dried (MgSO_4), and evaporated to give a crude gum. Chromatography of the crude product on silica gel eluting with ethyl acetate/petroleum ether mixtures gave the bromohydrin (3) (7.28 g), a 9:1 mixture of isomer, as a viscous oil, v_{max} (CHCl_3) 3600—3100, 1765, 1725 cm^{-1} ; δ ppm (CDCl_3) 1.43 (3H, d, J 6 Hz), 2.04 (3H, s), 2.13 (3H, s), 2.28 (3H, s), 2.53, 2.53 br (1H, d, J approximately 4 Hz, exch D_2O), 3.78 (3H, s), 4.05—4.40 (1H, m, collapsing to 4.21, q, J 6 Hz on exch D_2O), 5.25 (0.9H, s), 5.32 (0.1H, s).

b) Using n-butyl lithium

30 The above experiment was repeated using n-butyl lithium (one equivalent) in place of methyl magnesium bromide to give, after chromatography, the bromohydrin (3) in 36% yield.

Preparation 1(c)

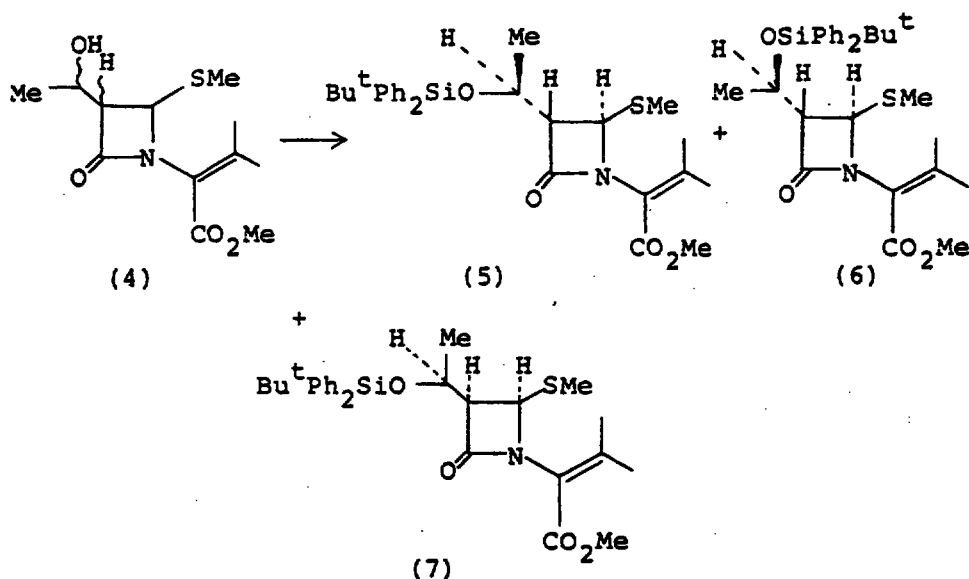
35 (3RS, 4RS) and 3RS, 4SR)-3[1-(E)-Hydroxyethyl]-1(1-methoxycarbonyl-2-methylprop-1-enyl)-4-methylthioazetidin-2-one



The bromohydrin (3) (7.04 g) was stirred with zinc-silver couple (prepared from 2.60 g zinc dust according to the method of R. D. Clark and C. H. Heathcock, J. Org. Chem., 1973, 3659) in methanol (100 ml) containing glacial acetic acid (0.57 ml) at room temperature for 10 minutes (the mixture was initially cooled with an ice-water bath in order to moderate a slightly exothermic reaction). The mixture was filtered through Kieselguhr, the residue being washed with a little methanol. The combined filtrates were evaporated to low volume and diluted with ethyl acetate. The solution was washed successively with N-hydrochloric acid, brine, dilute sodium bicarbonate solution, and brine. The dried (MgSO_4) organic layer was evaporated and the residual gum, chromatographed on silica gel eluting with ethyl acetate/petroleum ether mixtures to give a 3:1 mixture of the *cis*- and *trans*-hydroxyethylazetidinones (4) (4.64 g) as a gum, v_{max} (CHCl_3) 3600—3200, 1750, 1720 cm^{-1} ; δ ppm (CDCl_3) 1.32 and 1.42 (3H, each d, J 6 Hz), 1.98 and 2.00 (3H, each s), 2.10, 2.17 and 2.24 (6H, each s), 2.35—2.90 (1H, broad signal, exch D_2O), 3.14 (1H, dd, J 2 and 5 Hz), 3.41 (1H, dd, J 5 and 9 Hz), 7.75 (3H, s), 4.00—4.40 (1H, m, simplifies on exch D_2O), 4.90 (1H, d, J 2 Hz), 5.04 (1H, d, J 5 Hz).

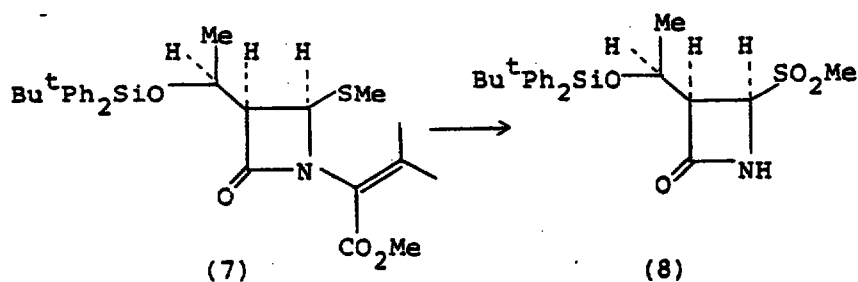
Preparation 1(d)

3-(1-t-Butyldiphenylsilyloxyethyl)-1-(1-methoxycarbonyl-2-methylprop-1-enyl)-4-methylthioazetidin-2-one



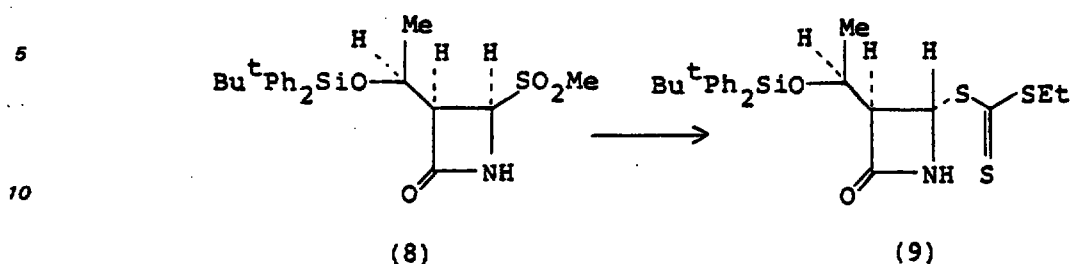
The mixture of *cis*- and *trans*-hydroxyethylazetidinones (4) (2.00 g) was dissolved in dry dimethylformamide (20 ml) and treated with imidazole (1.10 g) and *t*-butyldiphenylsilyl chloride (2.21 g). The mixture was kept at room temperature for 18 hours, diluted with ethyl acetate, and washed successively with *N*-hydrochloric acid, brine, saturated sodium bicarbonate solution, and brine. The dried (MgSO_4) organic layer was evaporated and the residue chromatographed on silica gel eluting with ethyl acetate/petroleum ether mixtures to give two fractions. The less polar fraction, the (3*RS*, 4*SR*)-3-[1(*RS*)-*t*-butyldiphenylsilyloxyethyl]azetidinone (5), contaminated with approximately 15% of the (3*RS*, 4*SR*)-3-[1(*SR*)-*t*-butyldiphenylsilyloxyethyl]azetidinone (6) was obtained as a gum (1.15 g), ν_{max} (CHCl_3) 1750, 1725 cm^{-1} ; δ ppm (CDCl_3) 1.0—1.3 (12H, m), 1.94 (3H, s), 2.05 and 2.08 (3H, each s), 2.19 (3H, s), 3.10 (dd, *J* 3 and 6 Hz) and 3.25 (dd, *J* 3 and 5 Hz) together 1H, 3.63 (0.15H, s), 3.69 (0.85H, s), 4.15—4.50 (1H, m), 5.11 (1H, d, *J* 3 Hz), 7.2—7.8 (10H, m). The more polar fraction, the (3*RS*, 4*RS*)-3-[1-(*SR*)-*t*-butyldiphenylsilyloxyethyl]azetidinone (7) (2.20 g), was obtained as a gum, ν_{max} (CHCl_3) 1750, 1720 cm^{-1} ; δ ppm (CDCl_3) 1.05 (9H, s), 1.24 (3H, d, *J* 6 Hz), 2.00 (6H, s), 2.20 (3H, s), 3.58 (1H, dd, *J* 6 and 6 Hz), 3.73 (3H, s), 4.36 (1H, dq, *J* 6 and 6 Hz), 4.98 (1H, d, *J* 6 Hz), 7.2—7.9 (10H, m). (Found, $\text{M}^+ - \text{Bu}^t$ 454.1479. $\text{C}_{24}\text{H}_{28}\text{NO}_4\text{SSi}$ requires 454.1508).

Preparation 1(e)

(3*RS*, 4*RS*)-3-[1-(*SR*)-*t*-Butyldiphenylsilyloxyethyl]-4-methylsulphonylazetidin-2-one

A solution of *m*-chloroperbenzoic acid (1.60 g) in ethyl acetate (10 ml) was added dropwise over 10 minutes to a stirred, ice-bath cooled, solution of the (3*RS*, 4*RS*) azetidinone (7) (2.16 g) in ethyl acetate (50 ml). The mixture kept at room temperature for 2½ hours and washed with saturated sodium bicarbonate solution (2 × 15 ml) and brine (3 × 15 ml). The dried (MgSO_4) organic layer was diluted to 100 ml with ethyl acetate, cooled to -20°C , and ozonised oxygen passed for 30 minutes. The excess ozone was removed by passage of argon and the mixture treated with methanol (50 ml). The mixture was kept at room temperature for 40 hours and evaporated to give a crude gum which was chromatographed on silica gel eluting with ethyl acetate/petroleum ether mixtures to give the sulphone (8) (1.57 g) as a waxy solid, ν_{max} (CHCl_3) 3400, 1790 cm^{-1} ; δ ppm (CDCl_3) 1.01 (9H, s), 1.23 (3H, d, *J* 6 Hz), 2.91 (3H, s), 3.77 (1H, dd, *J* 5 and 8 Hz), 4.67 (1H, d, *J* 5 Hz), 4.87 (1H, dq, *J* 6 and 8 Hz), 6.88 br (1H, s), 7.3—7.8 (10H, m). (Found: $\text{M}^+ - \text{Bu}^t$ 374.0897. $\text{C}_{18}\text{H}_{20}\text{NO}_4\text{SSi}$ requires 374.0882).

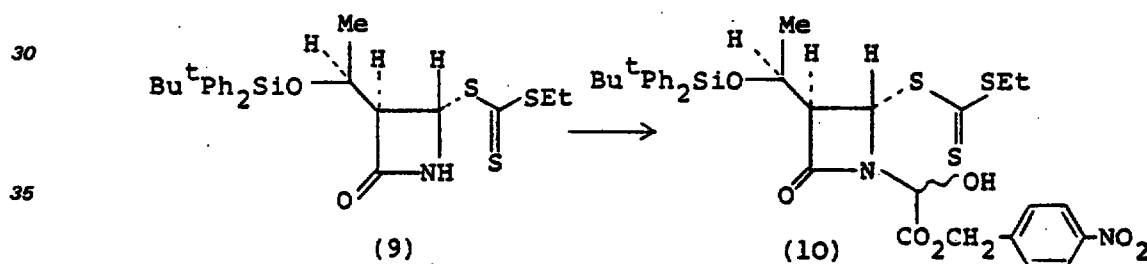
Preparation 1(f)

(3RS, 4SR)-3[1-(SR)-*t*-Butyldiphenylsilyloxyethyl]-4-ethylthiocarbonylthioazetidin-2-one

A mixture of the sulphone (8) (1.49 g) in methylene chloride (25 ml) and potassium ethyl
 15 trithiocarbonate (670 mg) in water (5 ml) was stirred vigorously at room temperature. After 4 hours the
 organic phase was separated and the aqueous layer extracted with methylene chloride (5 ml). The
 combined organic layers were washed with brine (3 × 5 ml), dried (MgSO₄) and evaporated.
 Chromatography of the residue on silica gel eluting with ethyl acetate/petroleum ether mixtures gave the
 20 trithiocarbonate (9) (1.29 g) as a yellow solid, mp 110–111°C (needles ex ethyl acetate/petroleum ether),
 λ_{max} (EtOH) 301 nm. (ϵ_m 14,800); ν_{max} (CHCl₃) 3410, 1770 cm⁻¹; δ ppm (CDCl₃) 1.02–1.12 (12H, s + partially
 obscured d), 1.38 (3H, t, J 7Hz), 3.19 (1H, dd, J 2 and 4½Hz), 3.35 (2H, q, J 7Hz), 4.1–4.5 (1H, m), 5.63 (1H, d, J
 2Hz), 6.59 br (1H, s), 7.3–7.8 (10H, m). (Found: C, 59.3; H, 6.5; N, 2.9; S, 19.4. C₂₄H₃₁NO₂S₃Si requires C,
 58.9; H, 6.3; N, 2.9; S, 19.6%).

25

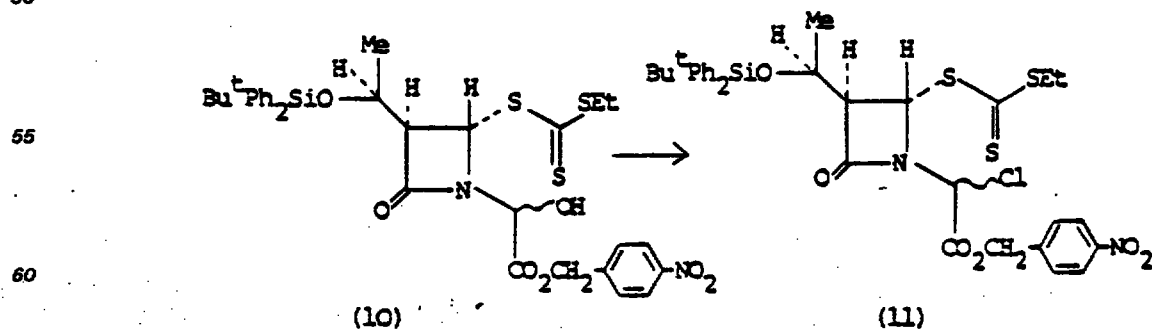
Preparation 1(g)

(3RS, 4SR)-3[1-(SR)-*t*-Butyldiphenylsilyloxyethyl]-4-ethylthiocarbonylthio-1-(1-hydroxy-1-*p*-nitrobenzyloxycarbonylmethyl)azetidin-2-one

The trithiocarbonate (9) (1.25 g) and *p*-nitrobenzyl glyoxylate monohydrate (1.16 g) were refluxed in
 40 benzene (50 ml) under argon for 30 hours with provision for removal of water. The mixture was evaporated
 and the residual gum chromatographed on silica gel eluting with ethyl acetate/petroleum ether to give the
 hydroxy-ester (10) (1.51 g), a mixture of stereoisomers, as a gum, ν_{max} (CHCl₃) 3500 br, 3400 br, 1775, 1750
 (slight shoulder) cm⁻¹; δ ppm (CDCl₃) 1.02 (9H, s), 1.35 (3H, t, J 7Hz), 3.24–3.49 (3H, m), 3.6–3.9 br (1H, m,
 45 exch D₂O), 4.2–4.5 (1H, m), 5.15–5.46 (2½ H, m), 5.5–5.7 br (½H, m, collapses to 5.58, s, on exch D₂O),
 6.30 and 6.35 (1H, each d, J 2½Hz), 7.2–7.8 (12H, m), 8.18 and 8.21 (2H, each d, J 8Hz).

50

Preparation 1(h)

(3RS, 4SR)-3[1-(SR)-*t*-Butyldiphenylsilyloxyethyl]-1-(1-chloro-1-*p*-nitrobenzyloxycarbonylmethyl)-4-ethylthiocarbonylthioazetidin-2-one

A solution of thionyl chloride (384 mg) in dry tetrahydrofuran (5 ml) was added dropwise over 5
 65 minutes to a stirred mixture of the hydroxy-ester (10) (1.50 g) and 2,6-lutidine (345 mg) in dry

tetrahydrofuran (30 ml) at -10°C . The mixture was stirred at -10°C for 10 minutes, filtered, and evaporated. The residual gum was re-evaporated from dry toluene (2×5 ml) to give the chloro-ester (11) (1.55 g) as a gum, ν_{max} (CHCl_3) 1785 cm^{-1} .

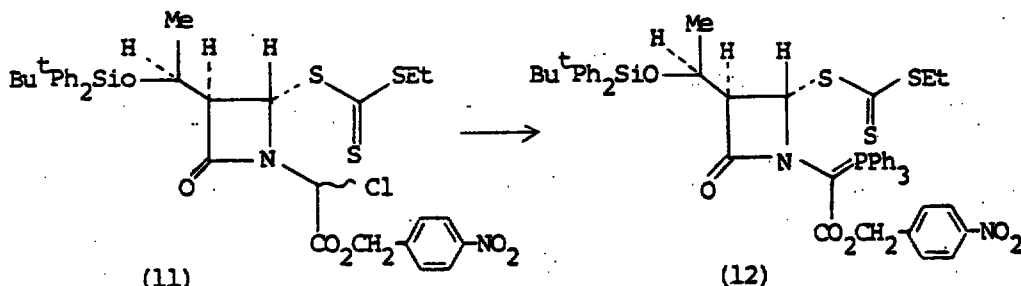
5

Preparation 1(i)

(3RS, 4SR)-3[1-(SR)-t-Butyldiphenylsilyloxyethyl]-4-ethylthiothiocarbonylthio-1-(1-p-nitrobenzyloxycarbonyl-1-triphenylphosphoranylidene-methyl)azetidin-2-one

10

15



20 A mixture containing the chloro-ester (11) (1.55 g), triphenylphosphine (1.13 g), and 2,6-lutidine (278 mg) in dry dioxan (30 ml) was stirred at 60°C under dry argon for 72 hours. The mixture was cooled, filtered, and the filtrate concentrated. The mixture was diluted with ethyl acetate (50 ml) and washed with N-hydrochloric acid, brine, saturated sodium bicarbonate solution, and brine. The dried (MgSO_4) organic layer was evaporated and the residue chromatographed on silica gel eluting with ethyl acetate/petroleum ether mixtures to give the phosphorane (12) (1.17 g) as an amorphous solid, ν_{max} (CHCl_3) $1745, 1610\text{ cm}^{-1}$.

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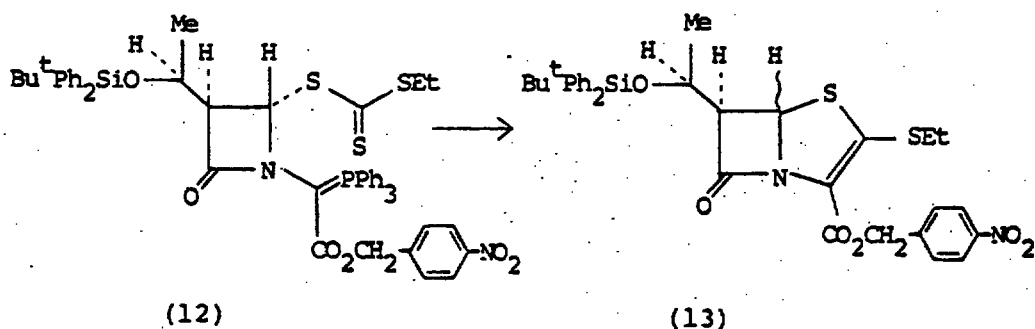
Preparation 1(j)

(5RS, 6SR, 8RS) and (5RS, 6RS, 8SR)-p-Nitrobenzyl-6(1-t-Butyldiphenylsilyloxyethyl)-2-ethylthiopentem-3-carboxylate

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35

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45 A solution of the phosphorane (12) (1.03 g) in xylene (1000 ml) was refluxed under argon for 7 hours. The mixture was evaporated and the residue chromatographed on silica gel eluting with ethyl acetate/petroleum ether mixtures to give the penem ester (13) (440 mg), a 4:1 mixture of (5RS, 6SR, 8RS) and (5RS, 6RS, 8SR) isomers, as an amorphous solid, ν_{max} (CHCl_3) 1790 and 1690 cm^{-1} ; δ ppm (CDCl_3) 0.99 and 1.01 (9H, each s), 1.13 (d, J 6Hz), 1.30 (t, J 7Hz) and 1.35 (t, J 7Hz) together 6H, 2.65 – 3.15 (2H, m), 3.55 – 3.95 (1H, m), 3.95 – 4.50 (1H, m), 5.15 and 5.43 (2H, ABq, J 14Hz), 5.49 (0.8H, d, J $1\frac{1}{2}$ Hz), 5.65 (0.2H) d, J 4Hz), 7.2 – 7.8 (12H, m), 8.14 and 8.16 (2H, each d, J 9Hz). Unchanged phosphorane (12) (161 mg) was also isolated in this experiment.

50

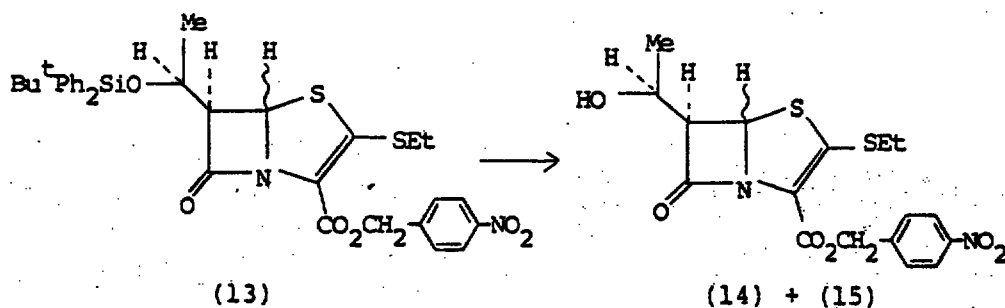
Preparation 1(k)

(5RS, 6SR, 8RS) and (5RS, 6RS, 8SR)-p-Nitrobenzyl 2-Ethylthio-6(1-hydroxyethyl)-penem-3-carboxylate

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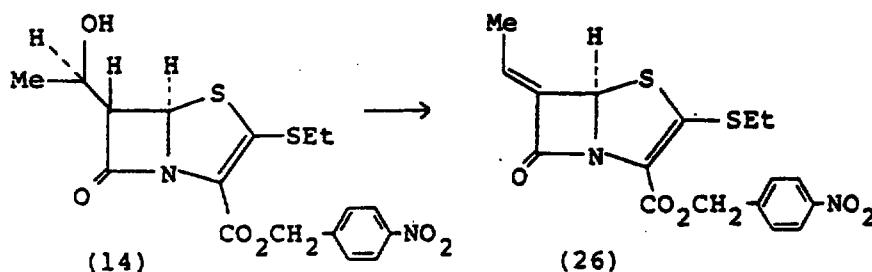
65



Tetra-n-butylammonium fluoride (2.44 ml of a solution containing 0.5 mM n-Bu₄NF.3H₂O/ml tetrahydrofuran, dried of Molecular Sieves Type 4A for 24 hours) was added over 5 minutes to an ice-bath cooled solution of the penem silyl ethers (13) (395 mg) in dry tetrahydrofuran (20 ml). The mixture was kept at ice-bath temperature for 30 minutes and then allowed to attain room temperature during a further 30 minutes. The mixture was diluted with ethyl acetate (50 ml) and washed with 5% citric acid (5 ml) and brine (3 × 10 ml). The dried (MgSO₄) organic layer was evaporated and the residue chromatographed on silica gel eluting with ethyl acetate/petroleum ether mixtures to give the hydroxyethyl penem (105 mg), a mixture of *cis*- and *trans*-isomers, as a solid. Crystallisation of the mixture from ethyl acetate/petroleum ether gave the pure (5RS, 6SR, 8RS) penem (14) (68 mg) as fine needles, mp 131–134°C, λ_{max} (EtOH) 262 nm (ϵ_m 15,100) and 339 nm (9,800); ν_{max} (CHCl₃) 3600–3200, 1790, 1730 and 1690 cm⁻¹; δ ppm (CDCl₃) 1.35 (d, J 6Hz) and 1.36 (t, J 7Hz) together 6H, 2.0 approximately (1H, brs), 2.80–3.15 (2H, m), 3.71 (1H, dd, J 1.6 and 6.6Hz), 4.0–4.4 (1H, m), 5.18 and 5.46 (2H, ABq, J 14Hz), 5.64 (1H, d, J 1.6Hz), 7.60 (2H, d, J 8Hz), 8.19 (2H, d, J 8Hz), signals at 1.24 (t, J 7Hz), 2.01 (s), and 4.09 (1, J 7Hz) indicated the presence of approximately 0.5 mole of ethyl acetate of crystallisation; (Found: M⁺, 410.0593. C₁₇H₁₈N₂O₆S₂ requires M, 410.0606). Evaporation of the mother liquors gave the (5RS, 6RS, 8SR) penem (15) (35 mg) contaminated with approximately 20% of the *trans*-isomer (14) as an amorphous solid, δ ppm (CDCl₃) (*inter alia*) 3.84 (0.8H, dd, J 3.9 and 10.1Hz), 5.73 (0.8H, d, J 3.9Hz).

Example 1(a)

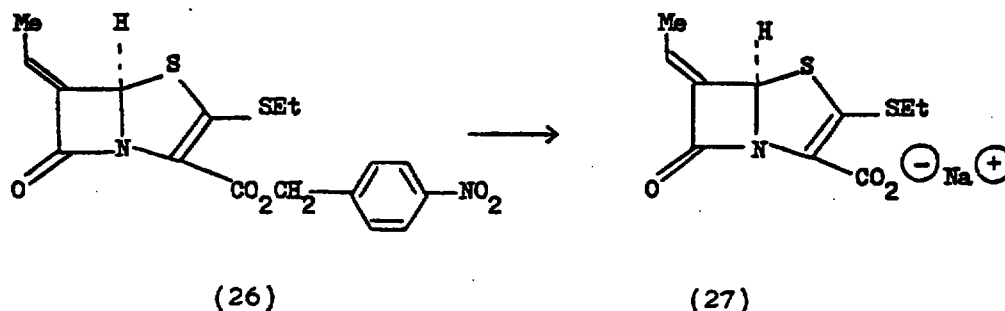
(5RS)-p-Nitrobenzyl(Z)-6-ethylidene-2-ethylthiopenem-3-carboxylate



The *trans*-penem ester (14) (82 mg) was dissolved in dry methylene chloride (5 ml), cooled in an ice-bath, and treated with triphenylphosphine (52 mg) and diethyl azodicarboxylate (35 mg). The mixture was allowed to attain room temperature during 15 minutes. The mixture was re-cooled in an ice-bath and treated with triphenylphosphine (52 mg) and diethyl azodicarboxylate (35 mg). The mixture was again allowed to attain room temperature during 15 minutes and evaporated. The crude product was chromatographed on silica gel eluting with chloroform to give the (Z)-ethylidenepenem ester (26) (44 mg) as a solid, mp 169–171°C (fine yellow needles ex ethyl acetate/petrol), λ_{max} (EtOH) 260 (ϵ_m 14,520) and 322 nm (7,980); ν_{max} (CHCl₃) 1785, 1700, br cm⁻¹; δ ppm (CDCl₃) 1.36 (3H, t, J 7Hz), 1.82 (3H, d, J 7Hz), 2.75–3.15 (2H, m), 5.19 and 5.49 (2H, ABq, J 14Hz), 6.16 (1H, s), 6.44 (1H, q, J 7Hz, showing further fine coupling J <1Hz), 7.63 (2H, d, J 8Hz), 8.19 (2H, d, J 8Hz). (Found: M⁺, 392.0503. C₁₇H₁₆N₂O₅S₂ requires M, 392.0500).

Example 1(b)

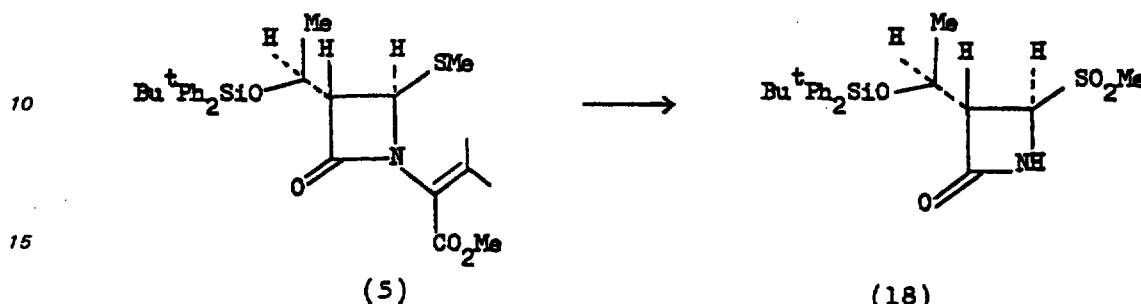
(5RS)-Sodium(Z)-6-Ethylidene-2-ethylthiopenem-3-carboxylate



The (Z)-ethylidenepenem ester (26) (33 mg) was dissolved in a mixture of dioxan (8 ml) and water (2 ml) and hydrogenated over 5% palladium/charcoal catalyst (48 mg) at S.T.P. for one hour. Further catalyst (33 mg) was added and the hydrogenation continued for a further one and a half hours. A 1% sodium hydrogencarbonate solution (0.71 ml) was added and the mixture filtered through Kieselguhr, the residual catalyst being washed with a little 50% aqueous dioxan. The combined filtrates were evaporated and the residue chromatographed on Biogel P2 eluting with water. The appropriate fractions were evaporated and the residue re-evaporated from ethanol (2 ml) and dry toluene (2 × 2 ml) to give, after trituration with dry

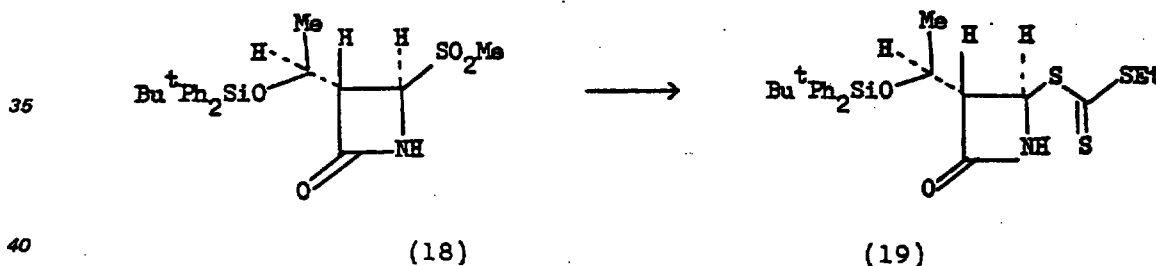
ether, the *Z*-ethylidenepenem sodium salt (27) (10 mg) as an amorphous solid, $\lambda_{\max}$ (H₂O) 305 n.m. (ϵ_m 3280); δ ppm (D₂O) 1.19 (3H, t, *J* 7Hz), 1.71 (3H, d, *J* 7Hz), 2.4—3.1 (2H, m), 6.19 (1H, s), 6.44 (1H, q, *J* 7Hz).

Preparation 2(a)

5 (3*RS*, 4*SR*)-3-[1-(*RS*)-*t*-Butyldiphenylsilyloxyethyl]-4-methylsulphonylazetidin-2-one

A solution of *m*-chloroperbenzoic acid (930 mg) in ethyl acetate (5 ml) was added dropwise over five minutes to a stirred, ice-bath cooled, solution of the impure azetidinone (5) (1.25 g) in ethyl acetate (25 ml). The mixture was kept at room temperature for one hour and washed with saturated sodium hydrogen-carbonate solution (2 × 5 ml) and brine (3 × 5 ml). The dried (MgSO₄) organic layer was treated with ozonised oxygen and methanol as in Preparation 1(e) to give, after chromatography, the sulphone (18) (894 mg) contaminated with 15% of the (3*RS*, 4*SR*)-3-[1-(*SR*)-*t*-butyldiphenylsilyloxyethyl] isomer as a gum, $v_{\max}$ (CHCl₃) 3420, 3270 br, 1790 cm⁻¹; δ ppm (CDCl₃) 1.01 and 1.05 (9H, each s), 1.27 (3H, d, *J* 6.1Hz), 2.70 (0.85H, s), 2.91 (0.15H, s), 3.50—3.65 (1H, m), 4.15—4.50 (m) and 4.43 (d, *J* 2.0Hz), together 1.85H, 4.82 (0.15H, d *J* 2Hz), 6.92 (1H, broad s), 7.3—7.8 (10H, m).

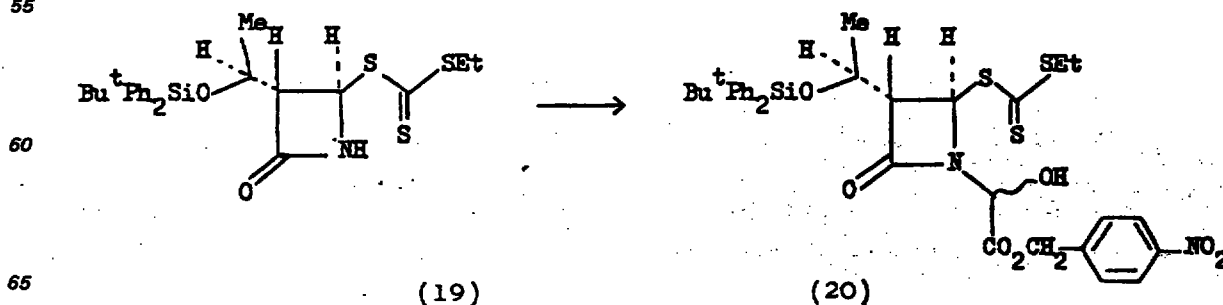
Preparation 2(b)

30 (3*RS*, 4*SR*)-3-[1-(*RS*)-*t*-Butyldiphenylsilyloxyethyl]-4-ethylthiothiocarbonylthioazetidin-2-one

A mixture of the impure sulphone (18) (890 mg) in methylene chloride (15 ml) and potassium ethyl trithiocarbonate (400 mg) in water (3 ml) was stirred vigorously at room temperature. After eighteen hours the mixture was worked up as in Preparation 1(f) to give the trithiocarbonate (19) (450 mg) as a yellow gum, $\lambda_{\max}$ (EtOH) 303 n.m. (ϵ_m 13,700); $v_{\max}$ (CHCl₃) 3420, 1775 cm⁻¹; δ ppm (CDCl₃) 1.05 (9H, s), 1.23 (d, *J* 6Hz) and 1.34 (t, *J* 7Hz) together 6H, 3.15—3.45 (3H, m), 4.22 (1H, dq, *J* 3 and 6Hz), 5.62 (1H, d, *J* 2Hz), 6.59 (1H, brs), 7.3—7.8 (10H, m). (Found: M^+ —Bu^t, 432.0580. C₂₀H₂₂NO₂S₃Si requires 432.0579). The starting sulphone (18) (252 mg) was also isolated in this experiment.

Treatment of the recovered sulphone (18) with fresh potassium ethyl trithiocarbonate gave the trithiocarbonate (19) (126 mg).

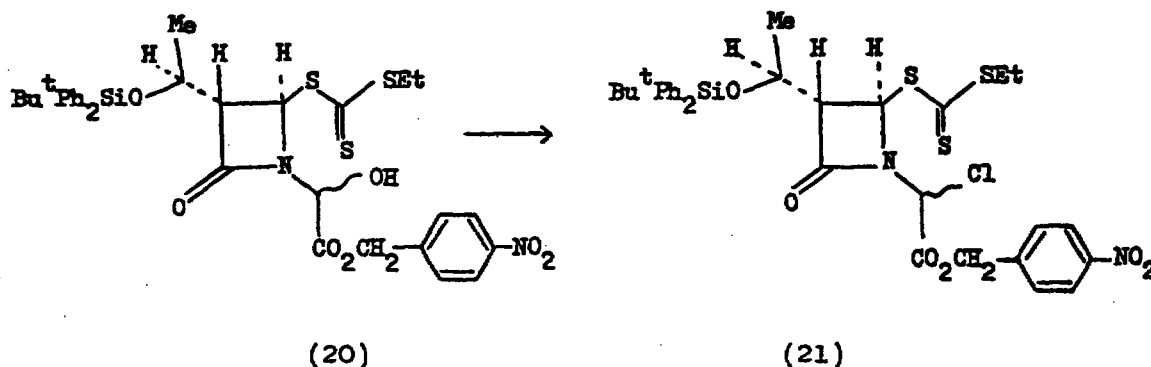
Preparation 2(c)

55 (3*RS*, 4*SR*)-3-[1-(*RS*)-*t*-Butyldiphenylsilyloxyethyl]-4-ethylthiothiocarbonylthio-1(1-hydroxy-1-*p*-nitrobenzyloxycarbonylmethyl)azetidin-2-one

The trithiocarbonate (19) (570 mg) was treated with *p*-nitrobenzyl glyoxylate monohydrate (530 mg) as in Example 7 to give the hydroxy-ester (20) (676 mg), a mixture of stereoisomers, as an amorphous solid, $\nu_{\max}$ (CHCl_3) 3520 br, 1780, 1760 slight shoulder cm^{-1} ; δ ppm (CDCl_3) 1.0–1.5 (15H, m), 3.2–3.5 (3H, m), 3.75 (½H, d, J 9Hz), 3.91 (½H, d, J 9Hz), 4.1–4.5 (1H, m), 5.18–5.50 (2½H, m), 5.56 (½H, d, J 9Hz), 6.15–6.25 (1H, m), 7.2–7.8 (12H, m), 8.21 (2H, d, J 8Hz).

Preparation 2(d)

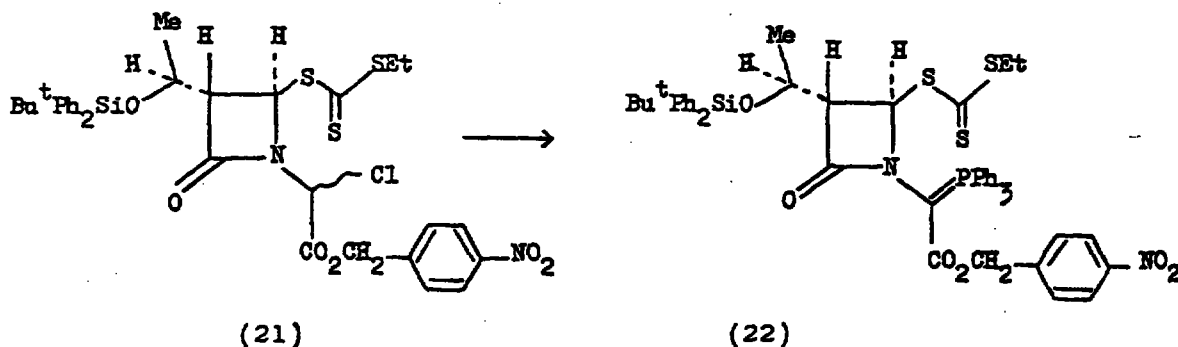
(3RS,4SR)-3-[1-(RS)-*t*-Butyldiphenylsilyloxyethyl]-1-(1-chloro-1-*p*-nitrobenzyloxycarbonylmethyl)-4-ethylthiocarbonylthioazetidin-2-one



A solution of thionyl chloride (169 mg) in dry tetrahydrofuran (2 ml) was added, dropwise over three minutes, to a stirred mixture of the hydroxyester (20) (660 mg) and 2,6-lutidine (152 mg) in dry tetrahydrofuran (10 ml) at -10°C . The mixture was stirred at -10°C for ten minutes, filtered, and evaporated. The residual gum was re-evaporated from dry toluene (2×2 ml) to give the chloro-ester (21) (679 mg) as a gum, $\nu_{\max}$ (CHCl_3) 1790 cm^{-1} .

Preparation 2(e)

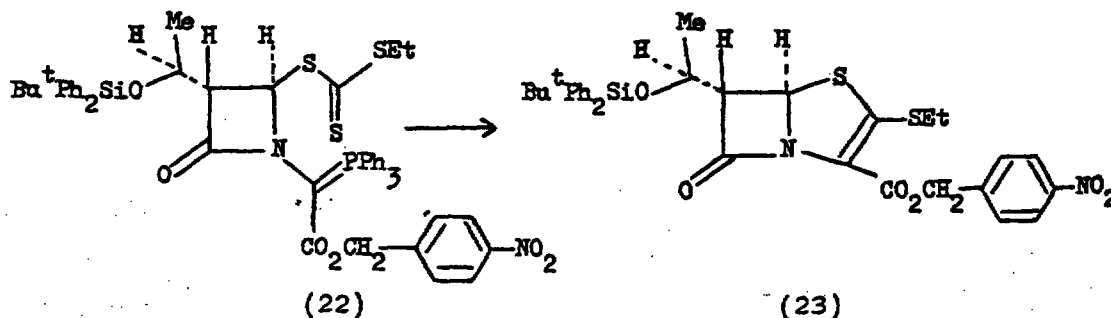
(3RS,4R)-3-[1-(RS)-*t*-Butyldiphenylsilyloxyethyl]-4-ethylthiothiocarbonylthio-1-(1-*p*-nitrobenzyloxycarbonyl-1-triphenylphosphoranylideneethyl)azetidin-2-one



A mixture containing the chloro-ester (21) (679 mg), triphenylphosphine (1.02 g), and 2,6-lutidine (125 mg) in dry dioxan (15 ml) was stirred at 60°C under dry argon for forty-eight hours. The mixture was worked up as in Preparation 1(i) to give the phosphorane (22) (640 mg) as an amorphous solid, $\nu_{\max}$ (CHCl_3) 1750, 1620 cm^{-1} .

Preparation 2(f)

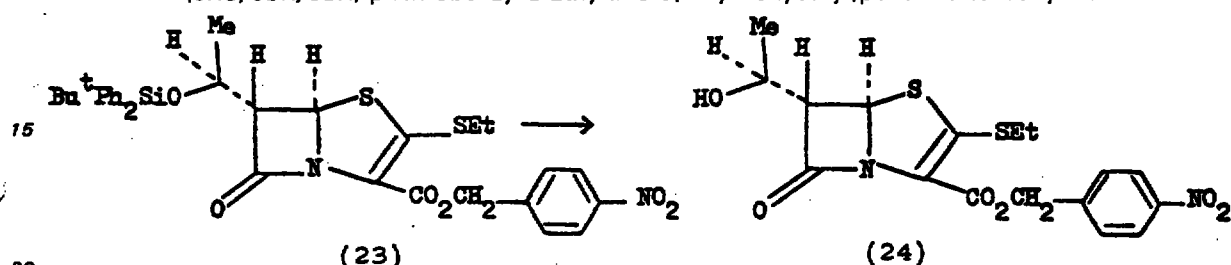
(5RS,6SR,8SR)-*p*-Nitrobenzyl 6(1-*t*-Butyldiphenylsilyloxyethyl)-2-ethylthiopenem-3-carboxylate



A solution of the phosphorane (22) (640 mg) in xylene (640 ml) was refluxed under argon for nine hours. The mixture was evaporated and the residue chromatographed on silica gel eluting with ethyl acetate/petroleum ether mixtures to give the penem ester (23) (229 mg) as a gum, $\lambda_{\max}$ (EtOH) 261 (ϵ_m 13,800) and 339 n.m. (9, 600); $\nu_{\max}$ (CHCl₃) 1790, 1690 cm⁻¹; δ ppm (CDCl₃) 1.00 (9H, s), 1.24 (3H, d, J 6 Hz), 1.34 (3H, t, J 7 Hz), 2.80–3.15 (2H, m), 3.71 (1H, dd, J 3.3 and 1.5 Hz), 4.00–4.40 (1H, m), 5.19 and 5.42 (2H, ABq, J 13 Hz), 5.53 (1H, d, J 1.5 Hz), 7.1–7.8 (12H, m), 8.14 (2H, d, J 8 Hz) (Found: M⁺, 648.1776. C₃₃H₃₆N₂O₆S₂Si requires 648.1781).

Preparation 2(g)

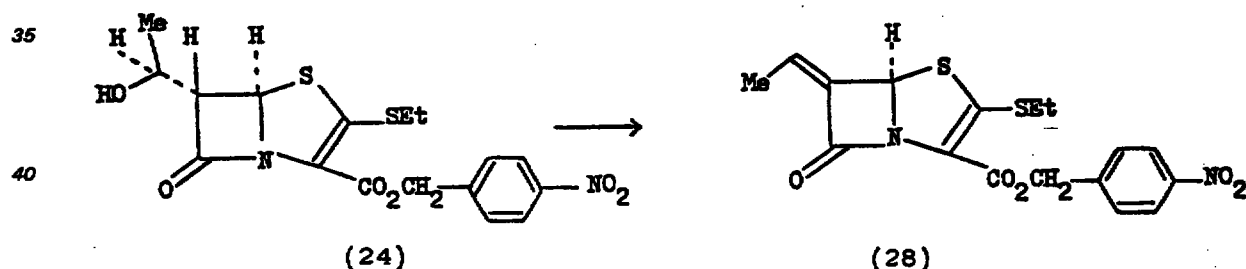
(5RS, 6SR, 8SR)-p-Nitrobenzyl 2-Ethylthio-6(1-hydroxyethyl)penem-3-carboxylate



Tetra-n-butylammonium fluoride (1.39 ml of a solution containing 0.5 mMole n-Bu₄NF·3H₂O/ml tetrahydrofuran, dried over Molecular Sieves Type 4A for twenty-four hours) was added over five minutes to an ice-bath cooled solution of the penem silyl ether (23) (225 mg) in dry tetrahydrofuran (10 ml). The mixture was kept at ice-bath temperature for thirty minutes and then allowed to attain room temperature during a further thirty minutes. Work-up of the mixture as in Preparation 1(k) gave the *trans*-penem ester (24) (52 mg) as a solid, m.p. 170–1°C (yellow needles ex ethyl acetate/petroleum ether), $\lambda_{\max}$ (EtOH) 261 (ϵ_m 15,700) and 340 nm (10,000); $\nu_{\max}$ (CHCl₃) 1790, 1690 cm⁻¹; δ ppm (CDCl₃) 1.28–1.46 (6H, m), approx 1.6 (1H, broad signal), 2.84–3.14 (2H, m), 3.85 (1H, dd, J 1.5 and 4.5 Hz), 3.95–4.45 (1H, m), 5.19 and 5.50 (2H, ABq, J 14 Hz), 5.63 (1H, d, J 1.5 Hz), 7.62 (2H, d, J 8.8 Hz), 8.21 (2H, d, J 8.8 Hz). (Found: M⁺, 410.0615. C₁₇H₁₈N₂O₆S₂ requires M, 410.0606).

Example 2(a)

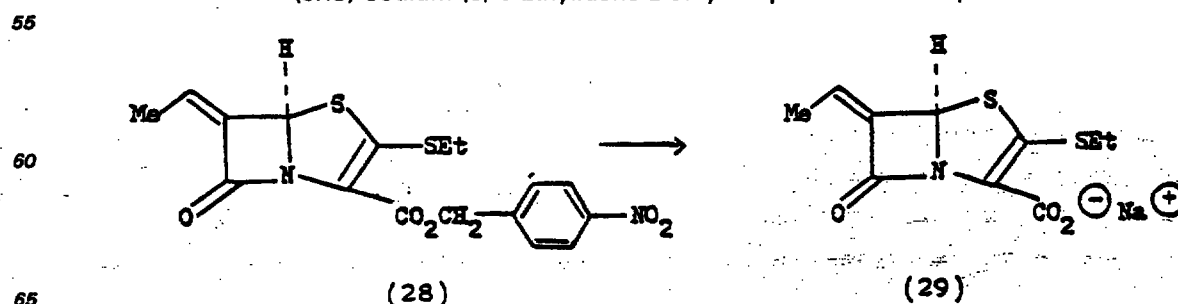
(5RS)-p-Nitrobenzyl (E)-6-Ethylidene-2-ethylthiopenem-3-carboxylate



The *trans*-penem ester (100 mg) was dissolved in dry methylene chloride (10 ml), cooled in an ice-bath, and treated with triphenylphosphine (2 × 64 mg) and diethyl azodicarboxylate (2 × 42 mg) as in Example 1(a). The mixture was evaporated and chromatographed on silica gel eluting with ethyl acetate/petroleum ether mixtures to give the (E)-ethylenopenem ester (28) (48 mg) as a solid, $\lambda_{\max}$ (EtOH) 260 (ϵ_m 14,050) and 322 (7,640); $\nu_{\max}$ (CHCl₃) 1780, 1690 cm⁻¹; δ ppm (CDCl₃) 1.35 (3H, t, J 7 Hz), 2.10 (3H, d, J 7 Hz), 2.8–3.1 (2H, m), 5.20 and 5.50 (2H, ABq, J 14 Hz), 5.98 (1H, q, J 7 Hz), 6.12 (1H, s), 7.64 (2H, d, J 8 Hz), 8.21 (2H, d, J 8 Hz). (Found: M⁺, 392.0463. C₁₇H₁₆N₂O₅S₂ requires M, 392.0500).

Example 2(b)

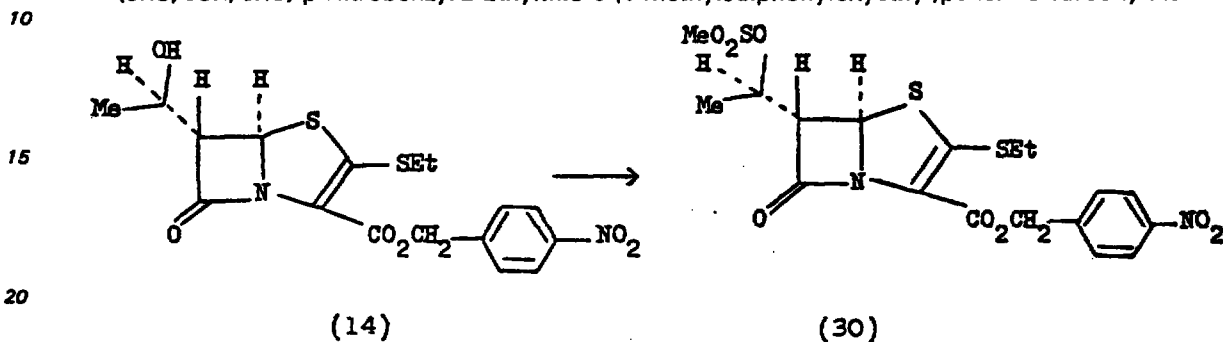
(5RS)-Sodium (e)-6-Ethylidene-2-ethylthiopenem-3-carboxylate



The (E)-ethylidenepenem ester (28) (45 mg) was dissolved in a mixture of dioxan (8 ml) and water (2 ml) and hydrogenated over 5% palladium/charcoal catalyst (68 mg) at S.T.P. for one hour. Further catalyst (45 mg) was added and the hydrogenation continued for a further two and a half hours. A 1% sodium hydrogencarbonate solution (0.96 ml) was added and the mixture worked up as in Example 1(b) to give the (E)-ethylidenepenem sodium salt (29) (14 mg) as an amorphous solid, $\lambda_{\max}$ (H₂O) 212 (ϵ_m 8,410) and 306 n.m. (3,180).

Example 3(a)

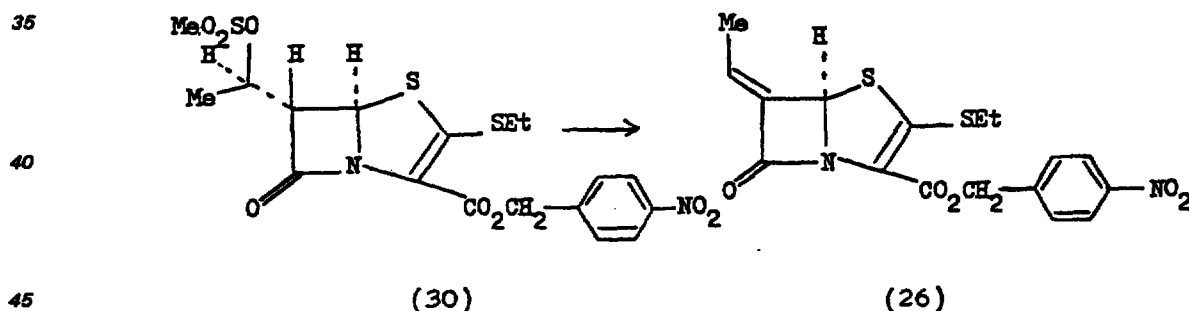
(5RS, 6SR, 8RS)-p-Nitrobenzyl 2-Ethylthio-6-(1-methylsulphonyloxyethyl)penem-3-carboxylate



The *trans*-penem (14) (100 mg) was dissolved in dry methylene chloride (4 ml), cooled in an ice-bath, and treated with triethylamine (37 mg) and methanesulphonyl chloride (42 mg). The mixture was stirred for fifteen minutes and washed with brine. The dried (MgSO₄) organic layer was evaporated and the residue crystallised from ethyl acetate/petroleum ether to give the mesylate (30) (56 mg) as rods, m.p. 114–116°C, $\nu_{\max}$ (CHCl₃) 1795, 1695 cm⁻¹; δ ppm (CDCl₃) 1.37 (3H, t, J 7Hz) 1.58 (3H, d, J 6½Hz), 2.8–3.2 (m) and 3.01 (s) together 5H, 3.92 (1H, dd, J 1½ and 7½Hz), 5.19 and 5.44 (ABq, J 13Hz), partially obscuring a m, together 3H, 5.77 (1H, d, J 1½Hz), 7.59 (2H, d, J 8½Hz), 8.20 (2H, d, J 8½Hz). (Found: M⁺, 488.0373. C₁₈H₂₀N₂O₆S₃ requires M, 488.0379).

Example 3(b)

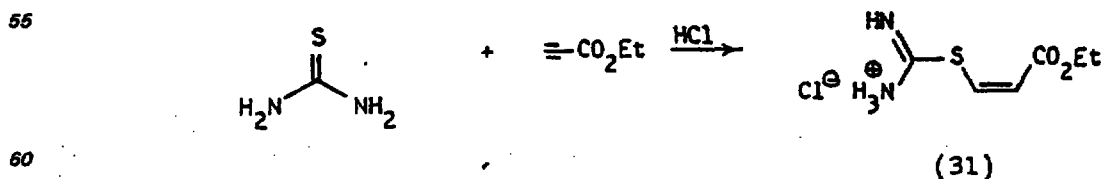
(5RS)-p-Nitrobenzyl (Z)-6-Ethylidene-2-ethylthiopenem-3-carboxylate



The mesylate (30) (2 mg) was dissolved in chloroform (0.2 ml) and treated with 1,5-diazabicyclo [4.3.0] non-5-ene (0.5 mg). The mixture was kept at room temperature for ten minutes and chromatographed to give the (Z)-ethylidene penem (26) (I.R. and U.V. data were in agreement with that described in Example 1(a)).

Preparation 4(a)

(Z)-2-Carboethoxyvinylisothiuronium Chloride

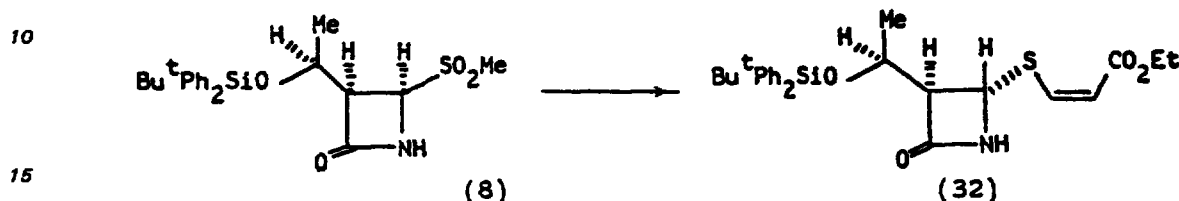


A solution containing ethyl propiolate (9.8 g) in methanol (20 ml) was added to a solution of thiourea (7.6 g) in 2N hydrochloric acid at a rate which allowed the temperature of the exothermic reaction to be maintained at approximately 50°C. After the addition was complete the mixture was stirred for 2 hours and

evaporated. The residue was re-evaporated from dry toluene (3 × 20 ml) and crystallised from propan-2-ol to give the isothiuronium chloride (31) (14.2 g), mp 134–136°C (rods); $\nu_{\max}$ (Nujol) 3600–2500, 1700, 1675, 1660 cm^{-1} ; δ ppm (CD_3SO) 1.28 (3H, t, J 7 Hz), 3.69 Br (1H, s, exch. D_2O), 4.26 (2H, q, J 7 Hz), 6.40 (1H, d, J 10 Hz), 7.96 (1H, d, J 10 Hz), 10.02 br (3H, s, exch. D_2O). (Found: C, 34.1; H, 5.2; N, 13.3; S, 15.2. $\text{C}_6\text{H}_{11}\text{N}_2\text{ClO}_2\text{S}$ requires C, 34.2; H, 5.2; N, 13.3; S, 15.2%).

Preparation 4(b)

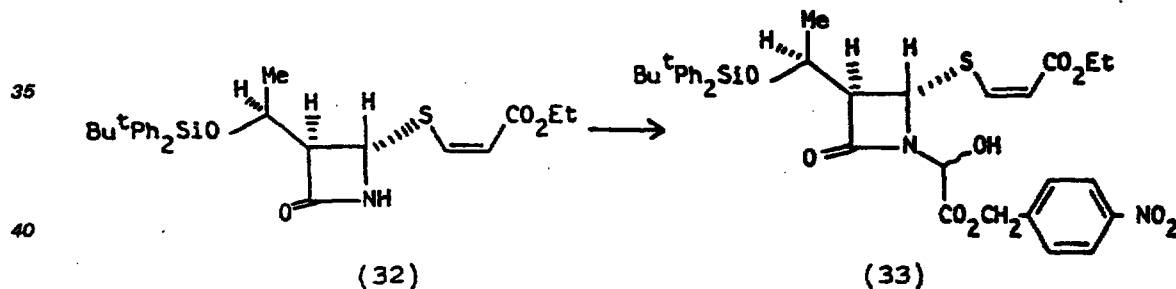
(3RS, 4SR)-3-[1-(SR)-t-Butyldiphenylsilyloxyethyl]-4-[2-(Z)-ethoxycarbonylvinylthio]azetidin-2-one



A 1N solution of sodium hydroxide (8.64 ml) was added, dropwise over 2 minutes, to a stirred solution of the isothiuronium chloride (31) (910 mg) in ethanol (20 ml) at -10°C . The resulting mixture was treated, in 2 minutes, with a pre-cooled (-10°C) solution of the sulphone (8) (1.86 g) in ethanol (40 ml). After stirring at -10°C for 30 minutes the mixture was allowed to attain room temperature (30 minutes), diluted with ethyl acetate (400 ml) and washed with brine (3 × 50 ml). The aqueous washings were back-extracted with ethyl acetate (50 ml). The dried (MgSO_4), combined organic layers were evaporated and the residue chromatographed to give the azetidinone (32) (1.68 g) as an amorphous solid, $\nu_{\max}$ (CHCl_3) 3410, 1775, 1695 cm^{-1} ; δ ppm (CDCl_3) 1.00–1.20 (m) and 1.28 (t, J 7 Hz) together 15H, 3.15–3.28 (1H, m, sharpens to 3.22, dd, J 2.2 and 4.4 Hz on irradiation of the signal at 6.45 ppm), 4.1–4.4 (m) and 4.19 (q, J 7 Hz) together 3H, 4.92 (1H, d, J 2.2 Hz), 5.94 (1H, d, 10 Hz), 6.45 (1H, s), 7.14 (1H, d, J 10 Hz), 7.3–7.8 (10H, m). (Found: $[\text{M}-\text{Bu}]^+$, 426.1201. $\text{C}_{22}\text{H}_{24}\text{NO}_4\text{SSi}$ requires 426.1195).

Preparation 4(c)

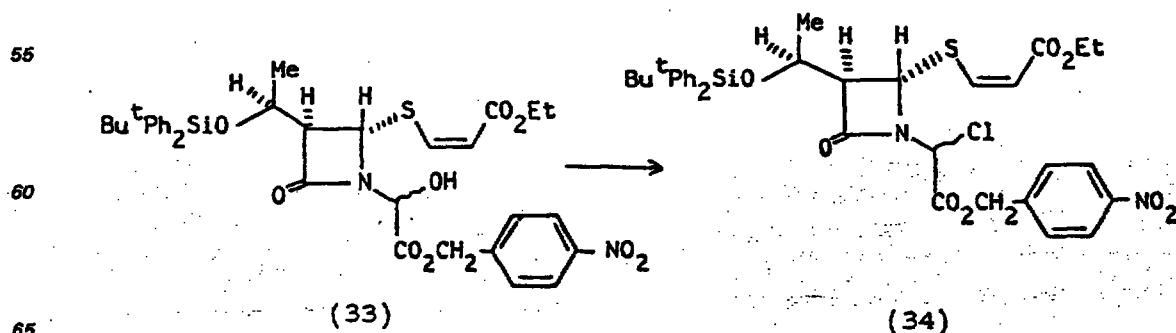
30 (3RS, 4SR)-3[1-(SR)-t-Butyldiphenylsilyloxyethyl]-4-[2-(Z)-ethoxycarbonylvinylthio]-1(1-hydroxy-1-p-nitrobenzyloxycarbonylmethyl)azetidin-2-one



The azetidinone (32) (1.74 g) and p-nitrobenzyl glyoxylate monohydrate (1.63 g) were heated in refluxing benzene (40 ml) under argon for 7 hours with provision for removal of water. The mixture was evaporated and chromatographed to give the hydroxyester (33) (2.25 g), a mixture of stereoisomers, as an amorphous solid, $\nu_{\max}$ (CHCl_3) 3520, 1775, 1760 sh, 1695 cm^{-1} ; δ ppm (CDCl_3) 1.0–1.4 (15H, m), 3.15–3.30 (1H, m), 3.6–3.9 (1H, broad signal, exch. D_2O), 4.0–4.4 (3H, m), 5.0–5.7 (4H, m, simplifies on exch. D_2O), 5.82 and 5.87 (1H, each d, J 10 Hz), 7.02 and 7.11 (1H, each d, J 10 Hz); 7.3–7.8 (12H, m), 8.21 (2H, d, J 8.5 Hz).

Preparation 4(d)

50 (3RS, 4SR)-3[1-(SR)-t-Butyldiphenylsilyloxyethyl]-1-(1-chloro-1-p-nitrobenzyloxycarbonylmethyl)-4-[2-(Z)-ethoxycarbonylvinylthio]azetidin-2-one



A solution of thionyl chloride (573 mg) in dry tetrahydrofuran (10 ml) was added, dropwise over 10 minutes, to a stirred mixture of the hydroxyester (33) (2.22 g) and 2,6-lutidine (515 mg) in dry tetrahydrofuran (40 ml) at -10°C . After stirring at -10°C for a further 10 minutes the mixture was filtered and evaporated. The residue was re-evaporated from dry toluene to give the chloro-ester (34) (2.32 g) as a
 5 gum, v_{max} (CHCl_3) 1785 br, 1695 cm^{-1} .

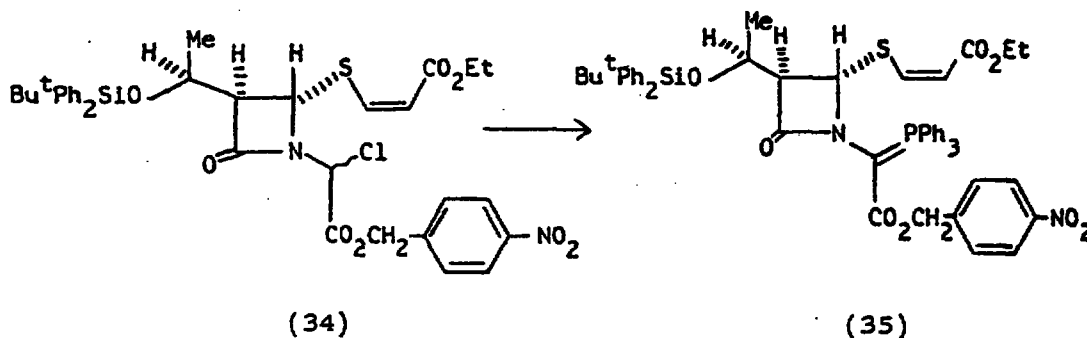
Preparation 4(e)

(3RS, 4SR)-3-[1-(SR)-t-Butyldiphenylsilyloxyethyl]-4-[2-(Z)-ethoxycarbonylvinylthio]-1-(1-p-nitrobenzyloxycarbonyl-1-triphenylphosphoranylidene-methyl)azetidin-2-one

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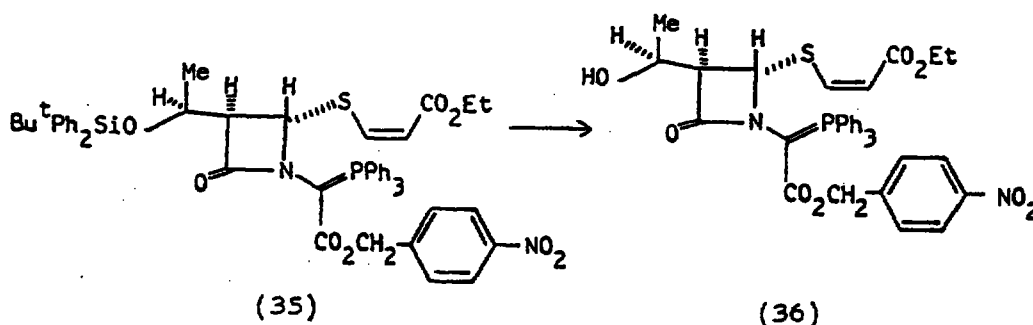
A mixture of the chloroester (34) (2.32 g), triphenylphosphine (3.42 g) and 2,6-lutidine (420 mg) in dry
 25 dioxan (40 ml) was heated at 60°C under dry argon for 16 hours. The mixture was worked up as for preparation 1(ii) to give the phosphorane (35) (2.82 g) as an amorphous solid, v_{max} (CHCl_3) 1750, 1695, 1625 cm^{-1} .

Preparation 4(f)

30 (3RS, 4SR)-4-[2-(Z)-Ethoxycarbonylvinylthio]-3-[1-(SR)-hydroxyethyl]-1-(1-p-nitrobenzyloxycarbonyl-1-triphenylphosphoranylidene-methyl) azetidin-2-one

35

40



45 Hydrogen chloride was passed into an ice-bath cooled solution of the phosphorane (35) (1.32 g) in methanol (25 ml) until the concentration was approximately 15% w/v. The mixture was kept at room temperature for 3 hours, diluted with ethyl acetate (150 ml) and neutralised with saturated sodium bicarbonate solution. The organic layer was separated and washed with brine (3×25 ml). The dried (MgSO_4) organic layer was evaporated and the residue chromatographed to give the phosphorane (36)
 50 (745 mg) as an amorphous solid, v_{max} (CHCl_3) 3700—3100, 1750, 1695, 1620 cm^{-1} .

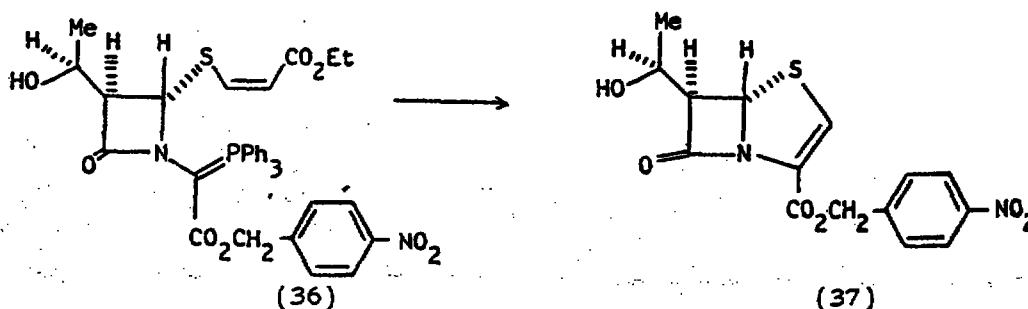
Preparation 4(g)

(5RS, 6SR, 8RS)-p-Nitrobenzyl 6-(1-Hydroxyethyl)penem-3-carboxylate

55

60

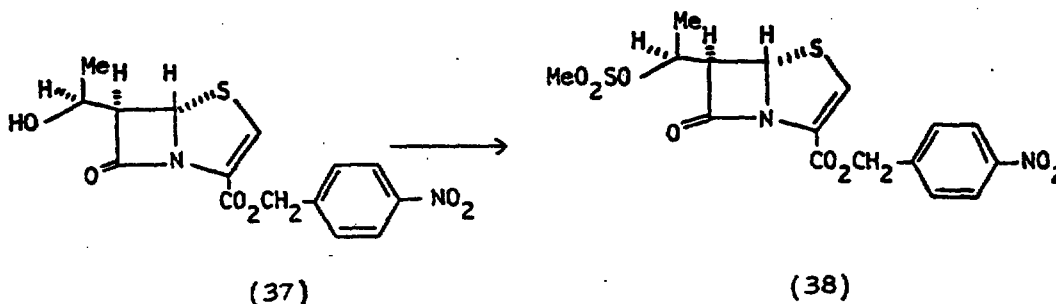
65



The phosphorane (36) (745 mg) was dissolved in ethyl acetate (15 ml) and treated with trifluoroacetic acid (3.27 ml) at room temperature. After 10 minutes the mixture was cooled to -76°C and ozonised oxygen passed till a pale blue colour persisted. Excess ozonised oxygen was removed by passage of argon and the mixture was treated with a solution of triphenylphosphine (280 mg) in ethyl acetate (3 ml). The mixture was allowed to reach 0°C and was neutralised with saturated sodium bicarbonate solution. The organic layer was separated and washed with brine (3×5 ml), dried (MgSO_4) and heated at 50°C under argon for 45 minutes. The mixture was evaporated and the residue chromatographed to give the penem ester (37) (293 mg) as a solid, m.p. $119\text{--}120^{\circ}\text{C}$ (needles ex ethyl acetate/petroleum ether); λ_{max} (EtOH) 262 (ϵ_{m} , 12730) and 317 nm (8490); ν_{max} (CHCl_3) 3600—3100, 1790 cm^{-1} ; δ ppm (CDCl_3) 1.38 (3H, d, J 6.3Hz), 2.10 (1H, d, J 4.7Hz), 3.85 (1H, ddd, J 6.3, 1.5 and 1.0Hz), 4.29 (1H, ddq, J 6.3, 6.3 and 4.7Hz), 5.26 and 5.43 (2H, ABq, J 14Hz), 5.79 (1H, d, J 1.5Hz), 7.34 (1H, d, J 1.0Hz), 7.59 (2H, d, J 8Hz), 8.24 (2H, d, J 8Hz). (Found: C, 51.1; H, 4.0; N, 7.8; S, 8.9; M^+ , 350.0557. $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_6\text{S}$ requires C, 51.4; H, 4.0; N, 8.0; S, 9.0% M, 350.0573).

Example 4(a)

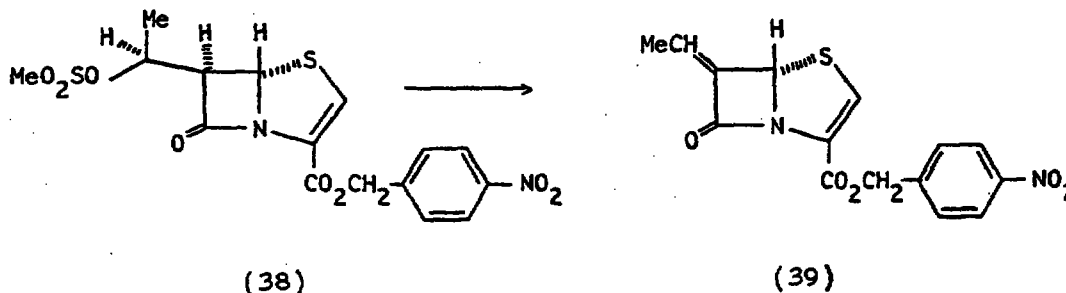
(5RS, 6SR, 8RS)-p-Nitrobenzyl 6-(1-methylsulphonyloxyethyl)-penem-3-carboxylate



A solution of the penem ester (37) (145 mg) in methylene chloride (5 ml) was cooled to -10°C and treated with triethylamine (84 mg) and methanesulphonyl chloride (95 mg). After stirring at -10°C for 15 minutes the mixture was diluted with ethyl acetate (25 ml) and washed with brine (3×5 ml). The dried (MgSO_4) organic layer was evaporated to give the crude mesylate (38) (191 mg) as a gum, ν_{max} (CHCl_3) 1795, 1720 cm^{-1} ; δ ppm (CDCl_3) 1.61 (3H, d, J 7Hz), 3.28 (3H, s), 4.12 (1H, dd, J 2 and 7Hz), 5.20 (dq, J 7 and 7Hz) plus 5.28 and 5.52 (ABq, J 14Hz) together 3H, 5.94 (1H, d, J 2Hz), 7.46 (1H, s), 7.66 (2H, d, J 8Hz), 8.29 (2H, d, J 8Hz).

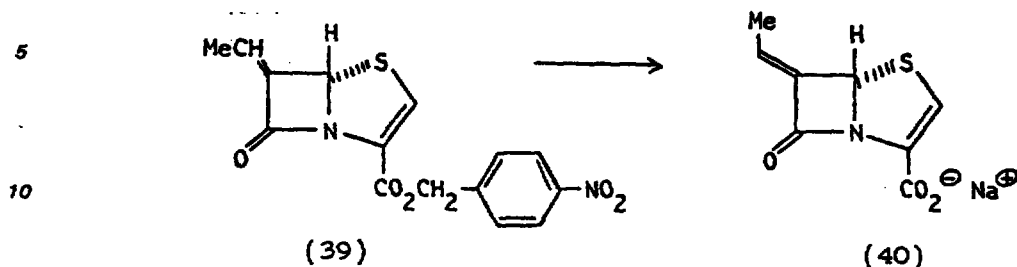
Example 4(b)

(5RS)-p-Nitrobenzyl (Z)-6-Ethylidenepenem-3-carboxylate



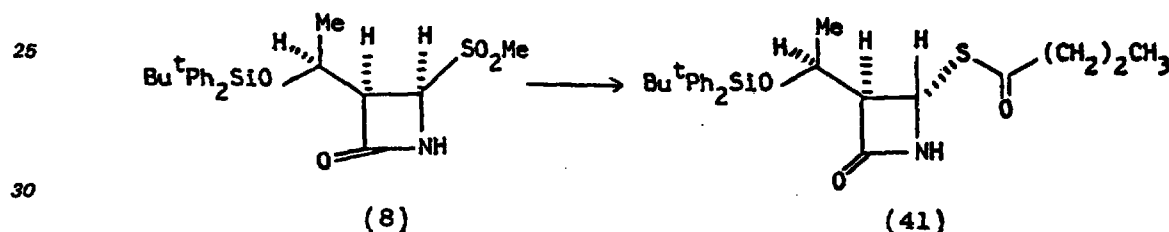
The crude mesylate (38) (191 mg) was dissolved in dry methylene chloride (5 ml), cooled to -10°C and treated with a solution of 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) (63 mg) in dry methylene chloride (1 ml) dropwise over 1 minute. After stirring at -10°C for 10 minutes the mixture was treated with DBU (25 mg). After stirring for a further 10 minutes at -10°C the mixture was diluted with ethyl acetate (30 ml) and washed with 5% citric acid solution (3 ml), brine (2×3 ml), saturated sodium bicarbonate solution (3 ml), and brine (3×3 ml). The dried (MgSO_4) organic layer was evaporated and the residue chromatographed to give the 6-ethylidenepenem ester (39) (113 mg), a 5:2 mixture of (Z) and (E)-isomers as determined by nmr. Fractional crystallization of the mixture from ethyl acetate/petroleum ethers afforded the pure (Z)-isomer, m.p. $164\text{--}166^{\circ}\text{C}$ (rods); λ_{max} (EtOH) 265 (ϵ_{m} , 12010) and 296 nm (inflection); ν_{max} (CHCl_3) 1790 and 1720 cm^{-1} ; δ ppm (CDCl_3) 1.86 (3H, d, J 7.1Hz with further fine coupling), 5.28 and 5.45 (2H, ABq, J 13Hz), 6.32 (1H, d, J 1.1Hz with further fine coupling), 6.53 (1H, dq, J 7.1 and 1.1 Hz), 7.37 (1H, s), 7.61 (2H, d, J 9Hz), 8.24 (2H, d, J 9Hz). (Found: C, 54.2; H, 3.4; N, 8.3; S, 9.5; M^+ , 332.0474. $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_5\text{S}$ requires C, 54.2; H, 3.6; N, 8.4; S, 9.6%; M, 332.0464).

Example 4(c)
(5RS)-Sodium(Z)-6-Ethylidenepipenem-3-carboxylate



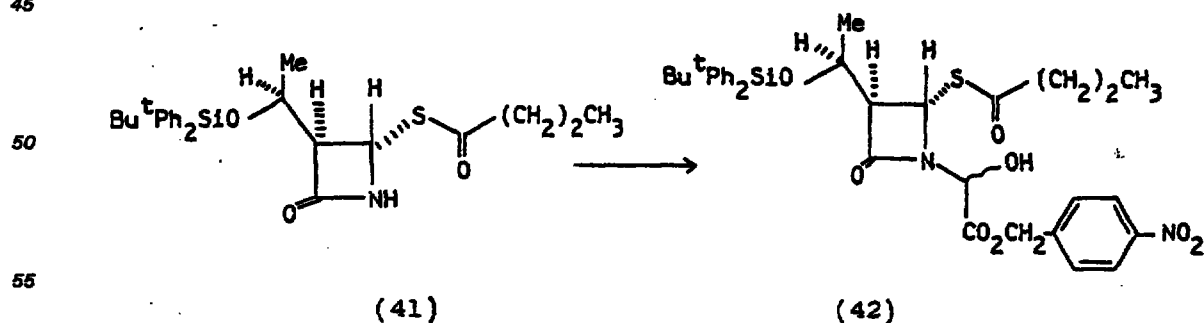
The (Z)-ethylidenepipenem ester (39) (56 mg) was dissolved in a mixture of dioxan (8 ml) and water (2 ml) and hydrogenated over 5% palladium/charcoal catalyst (84 mg) at S.T.P. for 45 minutes. Further catalyst (56 mg) was added and the hydrogenation continued for 30 minutes. A 1% sodium bicarbonate solution (1.42 ml) was added and the mixture worked up as in example (1b) to give the sodium salt (40) (20 mg) as a buff-coloured amorphous solid, $\lambda_{\max}$ (H₂O) 288 nm (ϵ_m 3590); $\nu_{\max}$ (KBr) 3700–2300, 1765, 1700, 1600, 1560 sh. cm^{-1} ; δ ppm (D₂O) 1.64 (3H, d, J 7Hz), 6.20 (1H, s), 6.34 (1H, q, J 7Hz), 6.90 (1H, s).

Preparation 5(a)
(3RS, 4SR)-3-[1-(SR)-t-Butyldiphenylsilyloxyethyl]-4-n-butyrylthioazetidin-2-one



The sulphone (8) (2.00 g) was dissolved in dioxan (40 ml), cooled in an ice-bath, and treated with a solution of thiolbutyric acid (965 mg) in 1N sodium hydroxide (9.28 ml). The mixture was stirred at ice-bath temperature for 40 minutes, diluted with ethyl acetate and washed with brine. The dried (MgSO₄) organic layer was evaporated and chromatographed to give the thiolester (41) (1.73 g) as a solid, m.p. 82–83°C (rods ex petroleum ether); $\nu_{\max}$ (CHCl₃) 3420, 1770, and 1690 cm^{-1} ; δ ppm (CDCl₃) 0.95–1.15 (15H, m), 1.70 (2H, dq, J 7 and Hz), 2.58 (2H, t, J 7Hz), 3.14 (1H, dd, J 2.3 and 4.8Hz), 4.25 (1H, dq, J 4.8 and 6Hz), 5.30 (1H, d, J 2.3Hz), 6.30 br (1H, s, exch. D₂O), 7.3–7.8 (10H, m). (Found: C, 66.3; H, 7.3; N, 3.0; S, 6.7; C₂₅H₃₃NO₃SSi requires C, 65.9; H, 7.3; N, 3.1; S, 7.0%).

Preparation 5(b)
(3RS, 4SR)-3-[1-(SR)-t-Butyldiphenylsilyloxyethyl]-4-n-butyrylthio-1-(1-hydroxy-1-p-nitrobenzyloxy-carbonylmethyl) azetidin-2-one



The thiolester (41) (1.80 g) and p-nitrobenzylglyoxylate monohydrate (1.80 g) were heated in refluxing benzene (40 ml) under argon for 7 hours with provision for removal of water. The mixture was evaporated and chromatographed to give a partial separation of the stereoisomers of the hydroxyester (42). The less polar isomer was obtained as a gum (420 mg), $\nu_{\max}$ (CHCl₃) 3600–3100, 1780, 1760, 1690 cm^{-1} ; δ ppm (CDCl₃) 0.85–1.10 (15H, m), 1.40–1.85 (2H, m), 2.48 (2H, t, J 7Hz), 3.20 (1H, dd, J 2.8 and 4.9Hz), 4.24 (1H, dq, J 4.9 and 6Hz), 4.41 (1H, d, J 11Hz, each D₂O), 5.23 (2H, s), 5.53 (1H, d, J 11Hz collapses to s on ech. D₂O), 5.58 (1H, d, J 2.8Hz), 7.3–7.8 (12H, m), 8.20 (2H, d, J 9Hz). The more polar isomer was also obtained as a gum (681 mg), $\nu_{\max}$ (CHCl₃) 3600–3100, 1775, 1760 sh., 1700 cm^{-1} ; δ ppm (CDCl₃) 0.85–1.10 (15H, m),

1.50—1.85 (2H, m), 2.58 (2H, t, J 7Hz), 3.25 (1H, dd, J 2.7 and 4.9Hz), 3.55—3.80 (1H, br signal, exch. D₂O), 4.25 (1H, dq, J 4.9 and 6Hz), 5.15—5.50 (3H, m, collapses to 5.23, s, plus 5.22 and 5.41, ABq, J 13Hz on exch. D₂O), 5.62 (1H, d, J 2.7Hz), 7.3—7.8 (12H, m), 8.19 (2H, d, J 9Hz). Also obtained was a mixture of the two stereoisomers as a gum (884 mg).

5

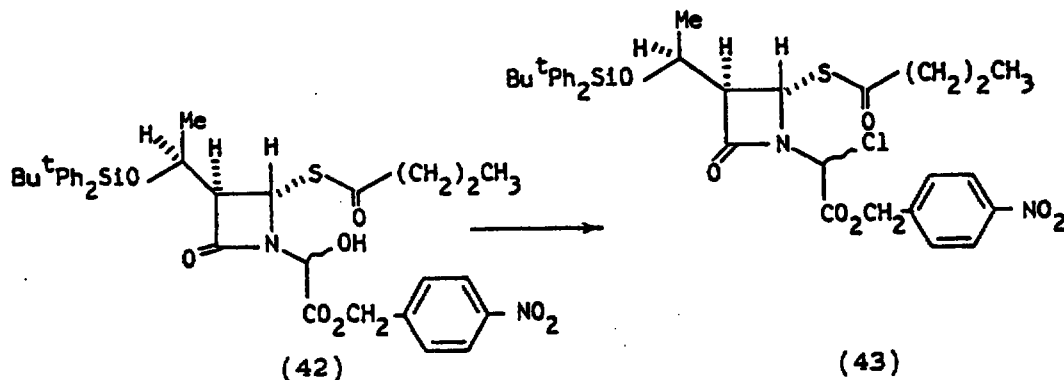
Preparation 5(c)

(3RS, 4SR)-3-[1-(SR)-t-Butyldiphenylsilyloxyethyl]-4-n-butyrylthio-1-(1-chloro-1-p-nitrobenzyloxycarbonylmethyl) azetidin-2-one

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15

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A solution of thionyl chloride (535 mg) in dry tetrahydrofuran (10 ml) was added, dropwise over 10 minutes, to a stirred mixture of the hydroxyester (42) (1.99 g) and 2,6-lutidine (482 mg) in dry tetrahydrofuran (40 ml) at -10°C . After stirring at -10°C for a further 15 minutes, the mixture was filtered and the filtrate evaporated. The residue was re-evaporated from dry toluene (2×5 ml) to give the chloroester (43) (2.08 g) as a gum, v_{max} (CHCl₃) 1785 br, 1700 cm^{-1} .

25

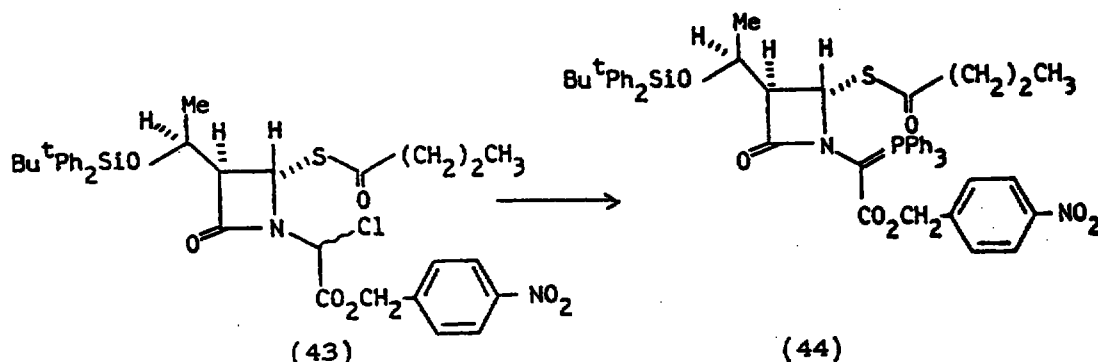
Preparation 5(d)

(3RS, 4SR)-3-[1-(SR)-t-Butyldiphenylsilyloxyethyl]-4-n-butyrylthio-1-(1-p-nitrobenzyloxycarbonyl-triphenylphosphoranylidene)methyl)azetidin-2-one

35

40

45



A mixture of the chloroester (43) (2.08 g), triphenylphosphine (3.14 g) and 2,6-lutidine (384 mg) in dry dioxan (40 ml) was heated at 60°C under dry argon for 22 hours. The mixture was worked up as for preparation 1(i) to give the phosphorane (44) (1.46 g) as an amorphous solid, v_{max} (CHCl₃) 1750, 1695, 1620 and 1610 sh. cm^{-1} . The chloroester (43) (587 mg) which was recovered from this experiment was retreated with triphenylphosphine (900 mg) and 2,6-lutidine (111 mg) in dioxan (10 ml) at 60°C for 30 hours to give, after work-up, the phosphorane (44) (490 mg).

50

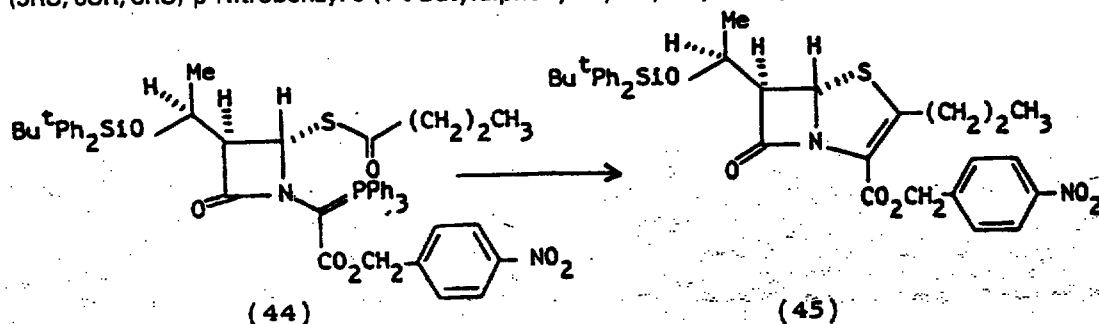
Preparation 5(e)

(5RS, 6SR, 8RS)-p-Nitrobenzyl 6-(1-t-Butyldiphenylsilyloxyethyl)-2-n-propylpenem-3-carboxylate

55

60

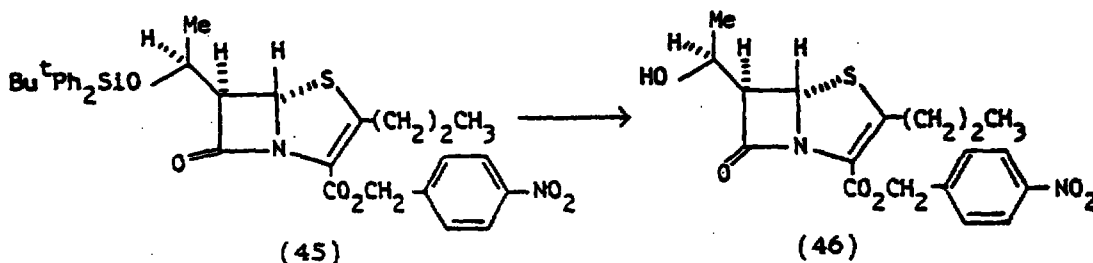
65



The phosphorane (44) (1.75 g) was heated in refluxing toluene (400 mg) under dry argon for 12 hours. The mixture was evaporated and chromatographed to give the penem ester (45) (960 mg) as a solid, m.p. 121—123°C (rods ex ethyl acetate/petroleum ether); $\lambda_{\max}$ (EtOH) 264 (ϵ_m , 12, 285) and 316 nm (8435); $\nu_{\max}$ (CHCl₃) 1785, 1710 cm⁻¹; δ ppm (CDCl₃) 0.85—1.35 (m) plus 1.01 (s) and 1.16 (d, J 6Hz) together 15H, 1.40—1.80 (2H, m), 2.50—3.08 (2H, m), 3.72 (1H, dd, J 5.5 and 2Hz), 4.23 (1H, dq, J 5.5 and 6Hz), 5.15 and 5.43 (2H, ABq, J 14Hz), 5.46 (1H, d, J 2Hz), 7.3—7.8 (12H, m), 8.16 (1H, d, J 8.5Hz). (Found: C, 64.7; H, 6.2; N, 4.4; S, 5.0. C₃₄H₃₈N₂O₆SSi requires C, 64.8; H, 6.0; N, 4.4; S, 5.1%).

Preparation 5(f)

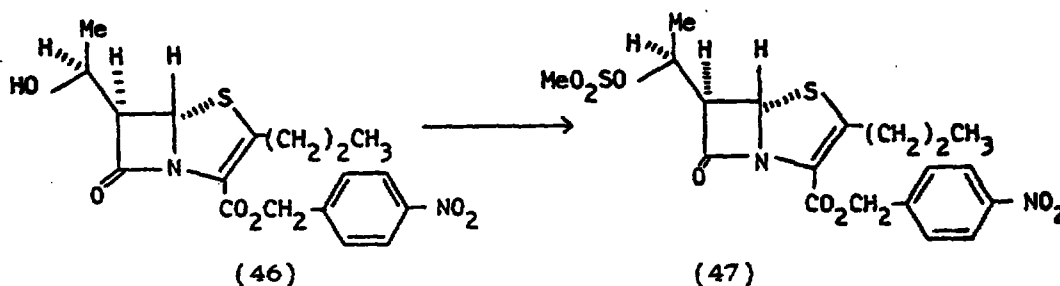
(5RS, 6SR, 8RS)-p-Nitrobenzyl 6-(1-Hydroxyethyl)-2-n-propylpenem-3-carboxylate



Tetra-n-butylammonium fluoride (6.04 ml of a solution containing 0.5 m.Mole n-Bu₄NF·3H₂O/ml in tetrahydrofuran, dried over molecular sieves Type 4A for 24 hours) was added over five minutes to a stirred, ice-bath cooled, solution of the penem ester (45) (950 mg) in dry tetrahydrofuran (20 ml). The mixture was kept at ice-bath temperature for 30 minutes and then allowed to attain room temperature during a further 30 minutes. The mixture was worked up as for preparation 1(k) to give the hydroxyethylpenem ester (46) (190 mg) as a solid, m.p. 118—119°C (needles ex ethyl acetate/petroleum ether); $\lambda_{\max}$ (EtOH) 263 (ϵ_m 12,720) and 316 nm (9,380); $\nu_{\max}$ (CHCl₃) 3630—3150, 1785, 1710 cm⁻¹; δ ppm (CDCl₃) 0.96 (3H, t, J 7Hz), 1.37 (d, J 6Hz) overlaying 1.3—1.8 (m) together 5H, 2.03 (1H, broad signal) 2.69 and 2.93 (2H, each dt, J 14 and 7Hz), 3.71 (1H, dd, J 1.6 and 6.4Hz), 4.0—4.5 (1H, m, simplifies on irradiation of signal at 2.03 ppm), 5.19 and 5.47 (2H, ABq, J 14Hz), 5.59 (1H, d, J 1.6Hz), 7.62 (2H, d, J 8Hz), 8.22 (2H, d, J 8Hz). (Found: C, 55.1; H, 5.3; N, 7.2. C₁₈H₂₀N₂O₆S requires C, 55.1; H, 5.1; N, 7.1%).

Example 5(a)

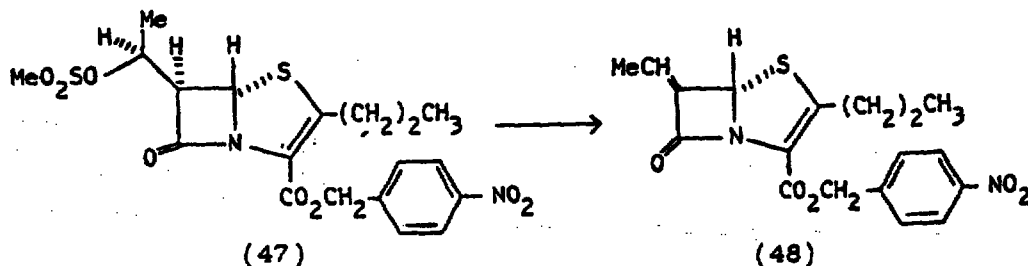
(5RS, 6SR, 8RS)-p-Nitrobenzyl 6-(1-Methylsulphonyloxyethyl)-2-n-propylpenem-3-carboxylate



A solution of methanesulphonyl chloride (88 mg) in dry methylene (1 ml) was added dropwise over 1 minute to a stirred mixture of the hydroxyethylpenem ester (46) (150 mg) and triethylamine (77 mg) in dry methylene chloride (5 ml) with cooling at -10°C. After 20 minutes at -10°C the mixture was diluted with ethyl acetate (20 ml) and washed with brine (3 × 2 ml). The dried (MgSO₄) organic layer was evaporated to give the crude mesylate (47) (181 mg) as a gum, $\nu_{\max}$ (CHCl₃) 1785, 1715 cm⁻¹.

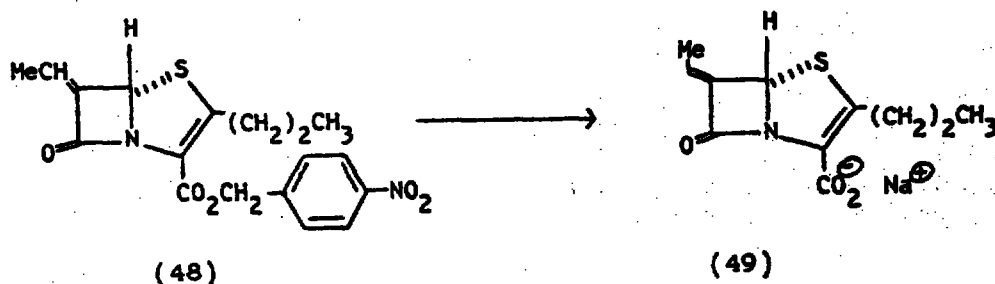
Example 5(b)

(5RS)-p-Nitrobenzyl (Z)-6-Ethylidene-2-n-propylpenem-3-carboxylate



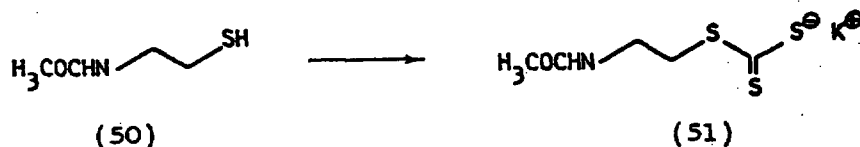
The crude mesylate (47) (181 mg) was dissolved in dry methylene chloride (5 ml), cooled to -10°C , and treated with a solution of 1,8-diazobicyclo-[5.4.0]undec-7-ene (58 mg) in dry methylene chloride (1 ml) dropwise over 1 minute. After stirring at -10°C for 10 minutes the mixture was treated with DBU (23 mg). The mixture was stirred at -10°C for a further 10 minutes, diluted with ethyl acetate (20 ml) and washed with 5% citric acid (2 ml), brine (2 ml), saturated sodium bicarbonate solution (2 ml) and brine (3×2 ml). The dried (MgSO_4) organic layer was evaporated and chromatographed to give the 6-ethylidenepenem ester (48) (116 mg), a mixture of (Z) and (E)-isomers, as a gummy solid. Fractional crystallisation of the mixture from ethyl acetate/petroleum ether gave pure (Z)-isomer (42 mg), m.p. $101-102^{\circ}\text{C}$ (rods), λ_{max} (EtOH) 267 (ϵ_m 12,190) and approximately 296 nm (10,500); ν_{max} (CHCl_3) 1775 and 1710 cm^{-1} ; δ ppm (CDCl_3) 0.92 (3H, t, J 7Hz), 1.35–1.70 (2H, m), 1.79 (3H, d, J 7Hz), 2.50–3.00 (2H, m), 5.16 and 5.44 (2H, ABq, J 14Hz), 6.06 (1H, slightly broadened s), 6.41 (1H, dq, J 7 and approximately 1Hz), 7.60 (2H, d, J 8Hz), 8.19 (2H, d, J 8Hz). (Found: M^+ , 374.0900. $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_5\text{S}$ requires M , 374.0936).

Example 5(c)
(5RS)-Sodium(Z)-6-Ethylidene-2- η -propylpenem-3-carboxylate



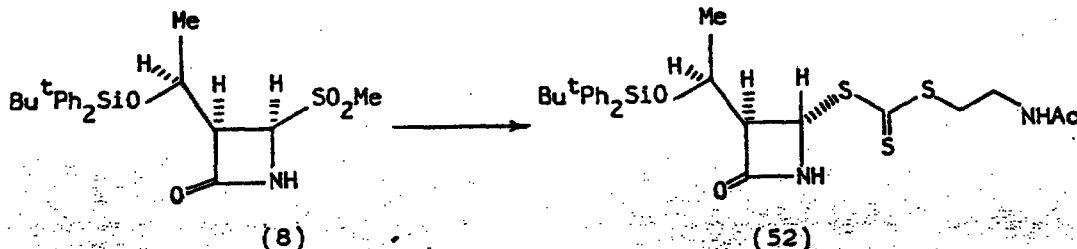
The (Z)-ethylidenepenem ester (48) (40 mg) was dissolved in a mixture of dioxan (8 ml) and water (2 ml) and was hydrogenated over 5% palladium/charcoal catalyst (60 mg) at S.T.P. for 30 minutes. Further catalyst (40 mg) was added and the hydrogenation continued for 30 minutes. A 1% sodium bicarbonate solution (0.90 ml) was added and the mixture worked up as for Example 1(b) to give the sodium salt (49) (4.4 mg) as an amorphous solid, λ_{max} (H_2O) approximately 270 (ϵ_m 5610) and 288 nm (5940).

Preparation 6(a)
Potassium 2-Acetamidoethyltrithiocarbonate



2-Acetamidoethanethiol (50) (3.57 g) was added to a solution of potassium hydroxide (1.62 g) in ethanol (25 ml) at room temperature. After 15 minutes the stirred mixture was cooled in an ice-bath and treated with carbon disulphide (36 ml). After 15 minutes at ice-bath temperature the stirred mixture was allowed to attain room temperature during 30 minutes. The yellow solid which had crystallised was filtered, washed with dry ether, and dried under vacuum to give the trithiocarbonate (51) (4.79 g), ν_{max} (Nujol) 3390, and 1640 cm^{-1} ; δ ppm [$(\text{CD}_3)_2\text{SO}$] 1.82 (3H, s), 3.0–3.4 (4H, m), 8.1 (1H broad signal, exch. D_2O). (Found: C, 25.6; H, 3.4; N, 5.8; S, 41.0. $\text{C}_4\text{H}_8\text{NOS}_3\text{K}$ requires C, 25.8; H, 3.4; N, 6.0; S, 41.2%).

Preparation 6(b)
(3RS, 4SR)-4-(2-Acetamidoethylthiothiocarbonylthio)-3-[1-(SR)-t-butylidiphenylsilyloxyethyl]azetidin-2-one

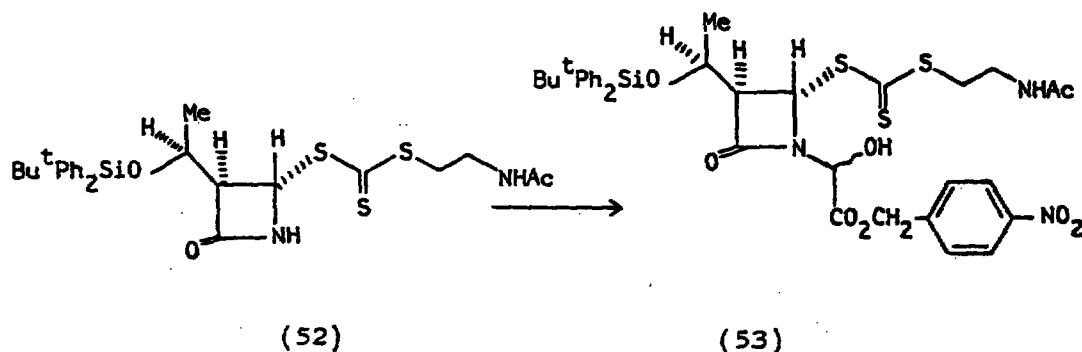


The sulphone (8) (2.05 g) was dissolved in methylene chloride (20 ml) and was treated with a solution of potassium 2-acetamidoethyltrithiocarbonate (51) (2.22 g) in water (4 ml). The mixture was stirred at

room temperature for 4 hours, diluted with methylene chloride (20 ml) and washed with brine (10 ml). The dried (MgSO_4) organic layer was evaporated and the residue chromatographed to give the trithiocarbonate (52) (1.20 g) as an amorphous solid, λ_{max} (CH_3CN) 302 nm (ϵ_m 12,880); ν_{max} (CHCl_3) 3440, 3400, 1775, 1670 cm^{-1} ; δ ppm (CDCl_3) 1.05–1.15 (12H, m), 1.98 (3H, s), 3.21 (1H, dd, J 2.5 and 4.5 Hz), 3.5–3.6 (4H, m), 4.1–4.4 (1H, m), 5.67 (1H, d, J 2.5 Hz), 5.75–6.0 (1H, broad signal, exch. D_2O), 6.70 br (1H, s, exch. D_2O) 7.3–7.8 (10H, m).

Preparation 6(c)

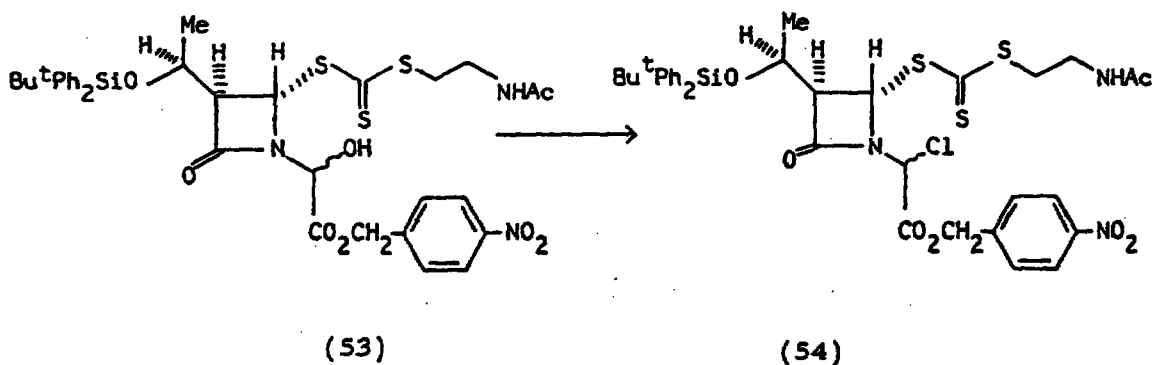
(3RS, 4SR)-4-(2-Acetamidoethylthiothiocarbonylthio)-3-[1-(SR)-t-butyldiphenylsilyloxyethyl]-1-(1-hydroxy-1-p-nitrobenzyloxycarbonylmethyl)azetidin-2-one



The trithiocarbonate (52) (1.26 g) and p-nitrobenzyl glyoxylate monohydrate (1.05 g) were heated in refluxing benzene (25 ml) under argon for 24 hours with provision for removal of water. The mixture was evaporated and chromatographed to give the hydroxyester (53) (1.04 g), a mixture of stereoisomers, as an amorphous solid, ν_{max} (CHCl_3) 3600–3000, 1775, 1755 slight shoulder, 1670 cm^{-1} .

Preparation 6(d)

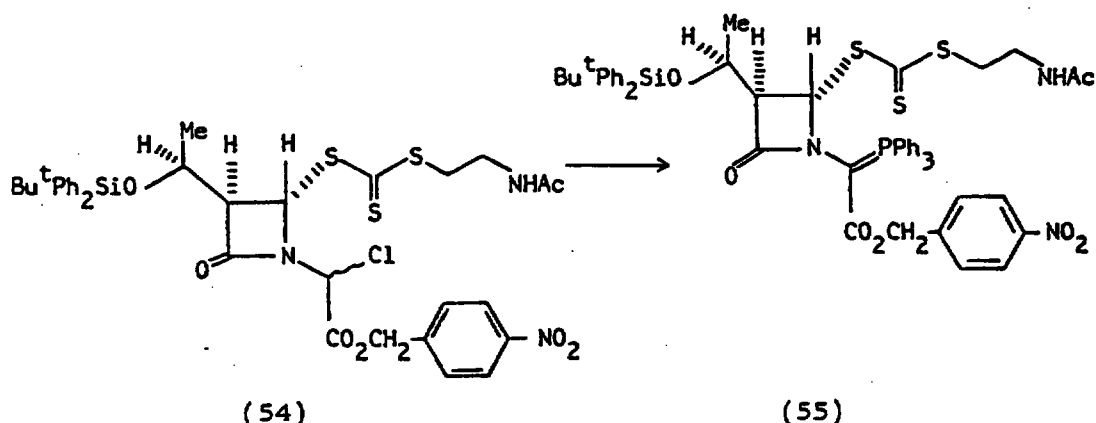
(3RS, 4SR)-4-(2-Acetamidoethylthiothiocarbonylthio)-3-[1-(SR)-t-butyldiphenylsilyloxyethyl]-1-(1-chloro-1-p-nitrobenzyloxycarbonylmethyl)azetidin-2-one



A solution of thionyl chloride (246 mg) in dry tetrahydrofuran (5 ml) was added, dropwise in 5 minutes, to a stirred mixture of the hydroxyester (53) (1.04 g) and 2,6-lutidine (221 mg) in dry tetrahydrofuran (20 ml) at -10°C . After stirring at -10°C for 15 minutes the mixture was filtered and the filtrate evaporated. The residue was re-evaporated from dry toluene (2×5 ml) to give the chloroester (54) (1.04 g) as an amorphous solid, ν_{max} (CHCl_3) 3430, 1785, 1760 slight shoulder, 1670 cm^{-1} .

Preparation 6(e)

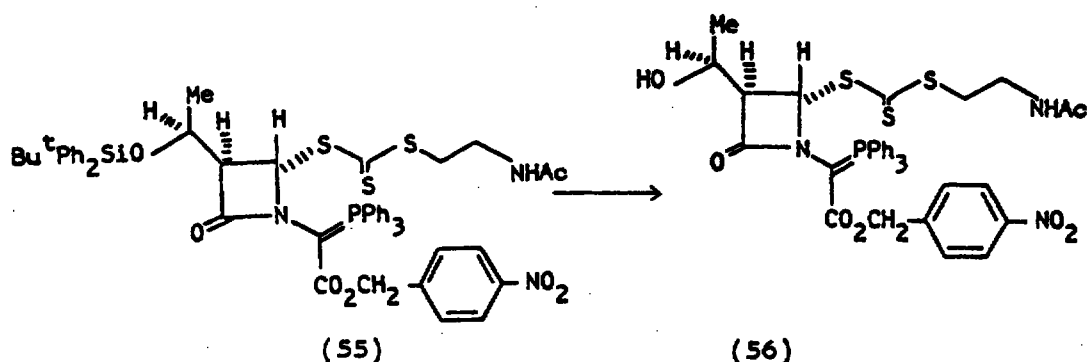
(3RS, 4SR)-4-(2-Acetamidoethylthiothiocarbonylthio)-3-[1-(SR)-t-butylidiphenylsilyloxyethyl]-1-(1-p-nitrobenzyloxycarbonyl-1-triphenylphosphoranylidene)azetidin-2-one



A mixture of the chloroester (54) (1.04 g), triphenylphosphine (1.44 g) and 2,6-lutidine (177 mg) was heated in dry dioxan (20 ml) at 60°C under dry argon for 32 hours. The mixture was worked up as for preparation 1(i) to give the phosphorane (55) (662 mg) as an amorphous solid, $\nu_{\max}$ (CHCl₃) 3430, 1755, 1670, 1620, 1605 shoulder cm^{-1} . Also obtained was recovered chloroester (54) (245 mg) which was recycled to give the phosphorane (55) (195 mg).

Preparation 6(f)

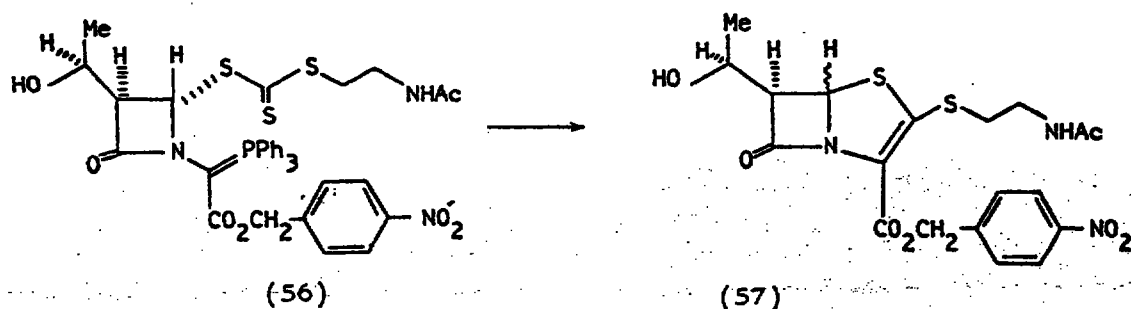
(3RS, 4SR)-4-(2-Acetamidoethylthiothiocarbonylthio)-3-[1-(SR)-hydroxyethyl]-1-(1-p-nitrobenzyloxycarbonyl-1-triphenylphosphoranylidene)azetidin-2-one



The phosphorane (55) (800 mg) was dissolved in methanolic hydrogen chloride (15% w/v HCl, 20 ml) and the mixture kept at room temperature for 7 hours. The mixture was diluted with ethyl acetate and neutralised with saturated sodium bicarbonate solution. The organic layer was separated and washed with brine. The dried (MgSO₄) organic layer was evaporated and chromatographed to give the phosphorane (56) (397 mg) as an amorphous solid, $\nu_{\max}$ (CHCl₃) 3600—3100, 1755, 1670, 1625, 1610 shoulder cm^{-1} .

Preparation 6(g)

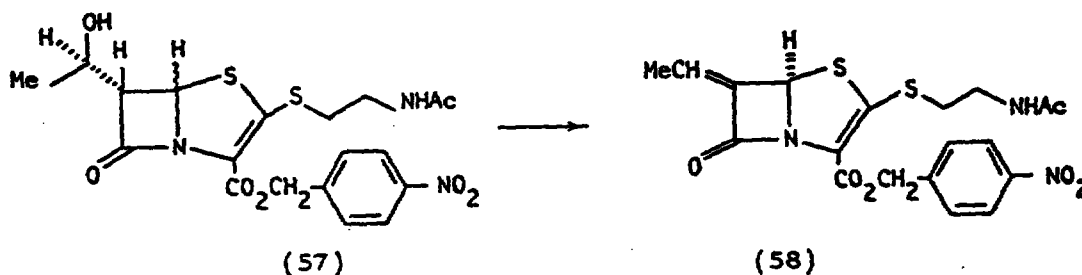
(5RS, 6SR, 8RS) and (5RS, 6RS, 8SR)-p-Nitrobenzyl-2-(2-Acetamidoethylthio)-(1-hydroxyethyl)penem-3-carboxylate



The phosphorane (56) (375 mg) was heated in refluxing xylene (375 ml) under dry argon for 5 hours. The mixture was evaporated and the residue chromatographed to give a mixture of the *cis* and *trans* isomers of the hydroxyethylpenem (57) (150 mg). Fractional crystallisation of the mixture from methanol gave the pure (5RS, 6SR, 8RS) isomer of the penem ester (57) (50 mg) as needles, m.p. 199–202°C; $\lambda_{\max}$ (EtOH) 261 (ϵ_m 12,360) and 338 nm (7,760); $\nu_{\max}$ (Nujol) 3520, 3290, 1800, 1670 and 1635 cm^{-1} ; δ ppm [(CD₃)₂SO] 1.17 (3H, d, J 6Hz), 1.80 (3H, s), 2.95–3.17 (2H, m), 3.26–3.36 (2H, m), 3.86 (1H, dd, J 1.5 and 5.5Hz), 3.92–4.06 (1H, m, collapsing to dq, J 5.5 and 6Hz on ech. D₂O), 5.2–5.5 (3H, m, 1H exch. D₂O leaving 5.28 and 5.33, 2H, ABq, J 14Hz), 5.74 (1H, d, J 1.5Hz), 7.68 (2H, d, J 8Hz), 8.15 (1H, t, J 5Hz, exch. D₂O), 8.23 (2H, d, J 8Hz). (Found: C, 48.6; H, 4.4; N, 8.7. C₁₉H₂₁N₃O₇S₂ requires C, 48.8; H, 4.5; N, 9.0%). Evaporation and rechromatography of the mother liquors gave the impure (5RS, 6RS, 8SR) isomer (57) (53 mg), δ ppm [(CD₃)₂CO] (inter alia) 1.51 (3H, d, J 6Hz), 2.01 (3H, s), 4.12 (1H, dd, J 4.0 and 10.5Hz), 4.28–4.45 (1H, m), 4.54 (1H, d, J 5.5Hz), 5.98 (1H, d, J 4.0Hz).

Example 6(a)

(5RS)-p-Nitrobenzyl 2-(2-Acetamidoethylthio)-6-ethylidenepenem-3-carboxylate

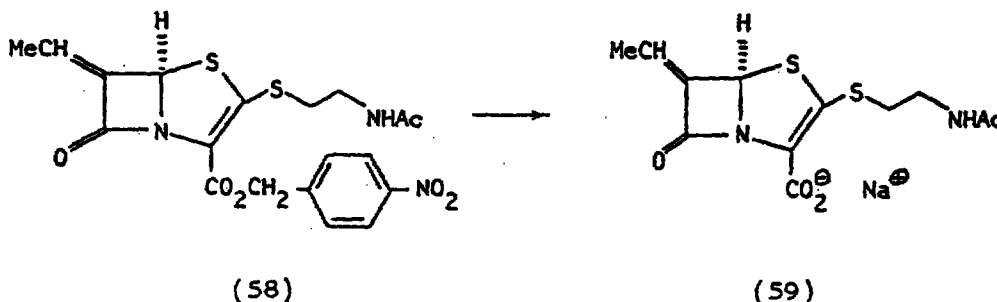


The (5RS, 6SR, 8RS) isomer of the penem ester (57) (40 mg) was suspended in dry dioxan (10 ml), cooled in an ice-water bath, and treated with triethylamine (17 mg) and methanesulphonyl chloride (20 mg). After stirring at room temperature for 30 minutes the mixture was treated with a further 1 equivalent of each reagent. The mixture was stirred for a further 30 minutes, cooled in an ice-water bath and treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (39 mg). The mixture was allowed to attain room temperature, stirred for 10 minutes, and treated with further DBU (26 mg). After stirring at room temperature for 20 minutes the mixture was evaporated to low volume, diluted with ethyl acetate (20 ml) and washed successively with 5% citric acid (4 ml), brine (4 ml), saturated NaHCO₃ solution (4 ml) and brine (3 × 4 ml). The dried (MgSO₄) organic layer was evaporated and chromatographed to give the ethylidenepenem ester (58) (26 mg), a 2:1 mixture of (E) and (Z) isomers, as an amorphous solid, $\lambda_{\max}$ (EtOH) 265 and 318 nm; $\nu_{\max}$ (CHCl₃) 3440, 1780 and 1675 cm^{-1} ; δ ppm (CDCl₃) 1.84 and 2.10 (3H, each d, J 7Hz), 1.94 (3H, s), 2.95–3.65 (4H, m), 5.19 and 5.49 (2H, ABq, J 13Hz), 6.02 (½H, q, J 7Hz), 6.13 and 6.17 (1H, each s), 6.46 (½H, q, J 7Hz), 7.4–7.8 (3H, broad signal plus d, J 9Hz), 8.21 (2H, d J 9Hz).

Similar treatment of the impure (5RS, 6RS, 8SR) isomer of the penem ester (57) (40 mg) gave a 4:1 mixture of the (E) and (Z) isomers of the ethylidenepenem ester (58) (18 mg).

Example 6(b)

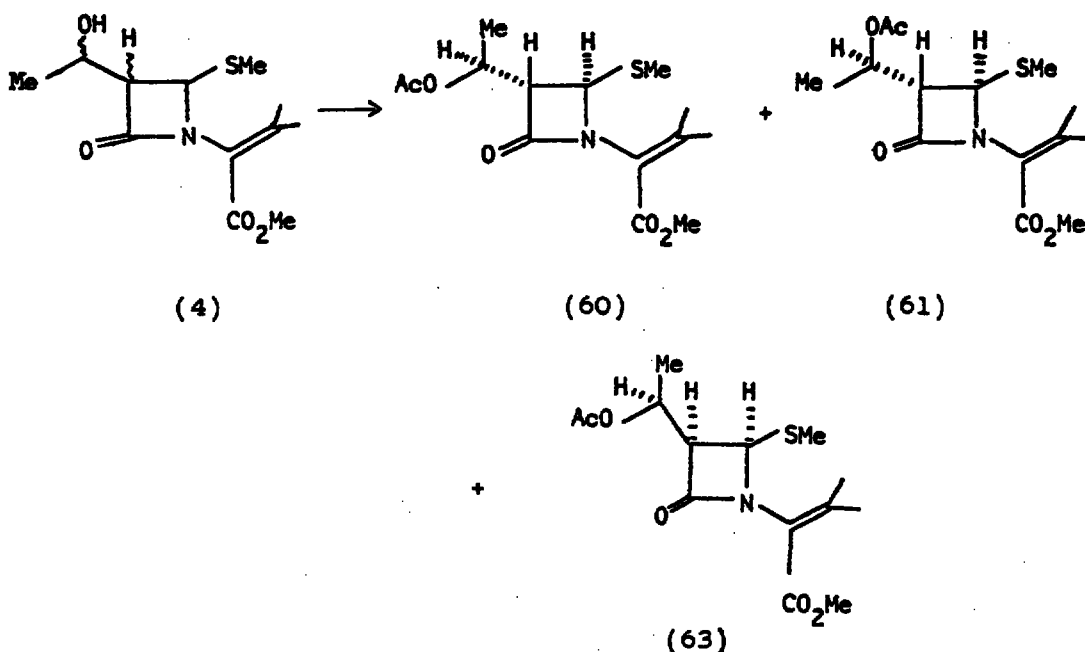
(5RS)-Sodium 2-(2-Acetamidoethylthio)-6-ethylidene-penem-3-carboxylate



The ethylidenepenem ester (58) (40 mg) was dissolved in a mixture of dioxan (8 ml) and water (2 ml) and hydrogenated over 5% palladium/charcoal catalyst (60 mg) at S.T.P. for 40 minutes. Further catalyst (40 mg) was added and the hydrogenation continued for 30 minutes. A 1% sodium bicarbonate solution (0.75 ml) was added and the mixture worked up as for Example 1(b) to give the sodium salt (59) (9.9 mg), a 2:1 mixture of (E) and (Z) isomers, as an amorphous solid, $\lambda_{\max}$ (H₂O) 302 nm; δ ppm (D₂O) 1.83 (½ CH, d, J 7Hz), 1.98 (3H, s), 2.04 (½ CH₃, d, J 7Hz), 2.87–3.20 (2H, m), 3.35–3.55 (2H, m), 6.18 (½H, s), 6.20 (½H q, J 7Hz), 6.27 (½H, s), 6.54 (½H, q, J 7Hz).

Preparation 7(a)

3-(1-Acetoxyethyl)-1-(1-methoxycarbonyl-2-methylprop-1-enyl)-4-methylthioazetidin-2-one.

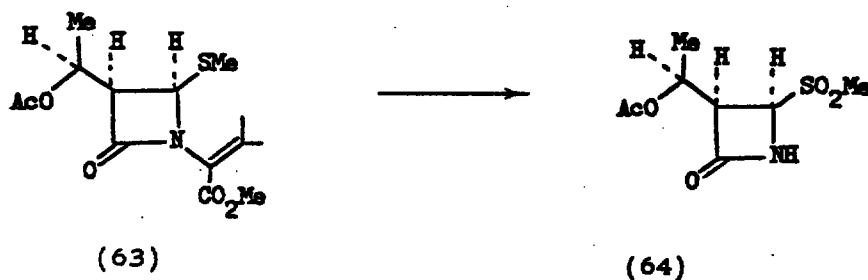


A solution of acetic anhydride (292 mg) in dry methylene chloride (2 ml) was added dropwise over 30 minutes to a stirred, ice-bath cooled, mixture of the hydroxyethylazetidinones (4) (650 mg), triethylamine (288 mg) and 4-dimethylaminopyridine (26 mg) in dry methylene chloride (10 ml). After 45 minutes at ice-bath temperature the mixture was evaporated to low volume, diluted with ethyl acetate, and washed with dilute hydrochloric acid, brine, sodium bicarbonate solution, and brine. The dried (MgSO_4) organic layer was evaporated and chromatographed to give two fractions. The less polar fraction, the (3RS,4SR)-3-[1-(SR)-acetoxyethyl]azetidinone (60), contaminated with approximately 25% of the (3RS,4SR)-3-[1-(SR)-acetoxyethyl]azetidinone (61), was obtained as a gum (204 mg), ν_{max} (CHCl_3) 1760, 1730 sh. cm^{-1} ; δ ppm (CDCl_3) 1.41 and 1.43 (3H, each d, J 7 Hz), 1.98–2.23 (12H, m), 3.18–3.37 (1H, m), 3.76 (3H, s), 4.91 (0.75 H, d, J 2 Hz), 4.99 (0.25 H, d, J 2 Hz), 5.15–5.50 (1H, m).

The more polar fraction the (3RS,4RS)-3-[1-(SR)-acetoxyethyl]azetidinone (63) (502 mg) was obtained 40 as a waxy solid, m.p. 73–5°C (cubes ex ethyl acetate/petroleum ether), ν_{max} (CHCl_3) 1760, 1750 sh. cm^{-1} ; δ ppm (CDCl_3) 1.47 (3H, d, J 6.5 Hz), 1.99, 2.03 and 2.24 (12H, each s), 3.63 (1H, dd, J 5 and 9 Hz), 3.76 (3H, s), 5.07 (1H, d, J 5 Hz), 5.29 (1H, dq, J 6.5 and 9 Hz). (Found: C, 53.3; H, 6.7; N, 4.4; S, 10.5; M^+ , 315.1149. $\text{C}_{15}\text{H}_{21}\text{NO}_5\text{S}$ requires C, 53.3; H, 6.7; N, 4.4; S, 10.2%; M^+ , 315.1137).

Preparation 7(b)

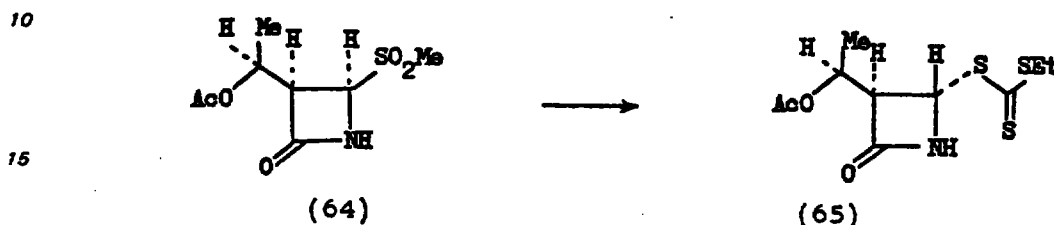
(3RS,4RS)-3-[1-(SR)-Acetoxyethyl]-4-methylsulphonylazetidin-2-one



A solution of m-chloroperbenzoic acid (307 mg) in ethyl acetate (5 ml) was added dropwise over 30 minutes to a stirred, ice-bath cooled, solution of the (3RS,4RS) azetidinone (63) (255 mg) in ethyl acetate (10 ml). The mixture was allowed to attain room temperature during 45 minutes and was washed with saturated sodium bicarbonate solution (2×5 ml) and brine (3×5 ml). The dried (MgSO_4) organic layer was diluted with ethyl acetate (25 ml), cooled to -20°C , and ozonised oxygen passed until the starting material had been consumed (t.l.c.). The excess ozone was removed by passage of argon and the mixture was 65 treated with methanol (20 ml). After stirring at room temperature for 20 hours the mixture was evaporated

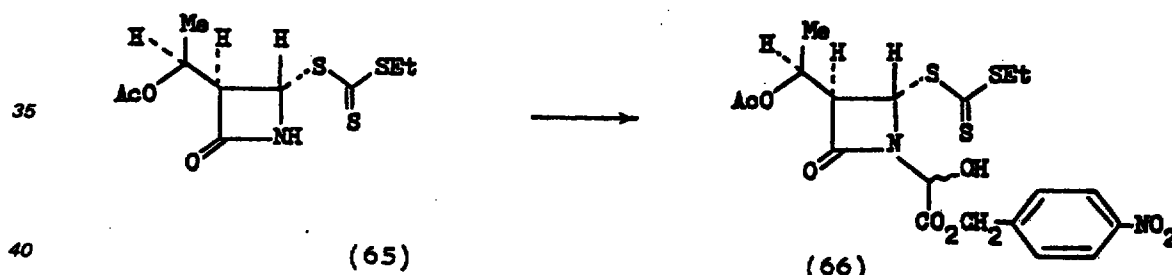
and the residue triturated with ether to give the sulphone (64) (137 mg) as a solid, m.p. 139—141°C (plates ex chloroform/ether); $\nu_{\max}$ (CHCl_3) 3400, 3340, 1790, 1735 cm^{-1} ; δ ppm [CDCl_3 + $(\text{CD}_3)_2\text{CO}$] 1.44 (3H, d, J 6Hz), 2.01 (3H, s), 2.97 (3H, s), 3.86 (1H, dd, J 5 and 10Hz with further slight coupling to the NH proton as revealed by a decoupling experiment), 4.83 (1H, d, J 5Hz), 5.65 (1H, dq, J 6 and 10Hz), 7.99 (1H, broad s signal). (Found: C, 41.2; H, 5.6; N, 5.9; S, 13.7. $\text{C}_8\text{H}_{13}\text{NO}_5\text{S}$ requires, C, 40.9; H 5.5; N, 6.0; S, 13.6%).

Preparation 7(c)
(3RS,4SR)-3-[1-(SR)-Acetoxyethyl]-6-ethylthiothiocarbonylthioazetidin-2-one



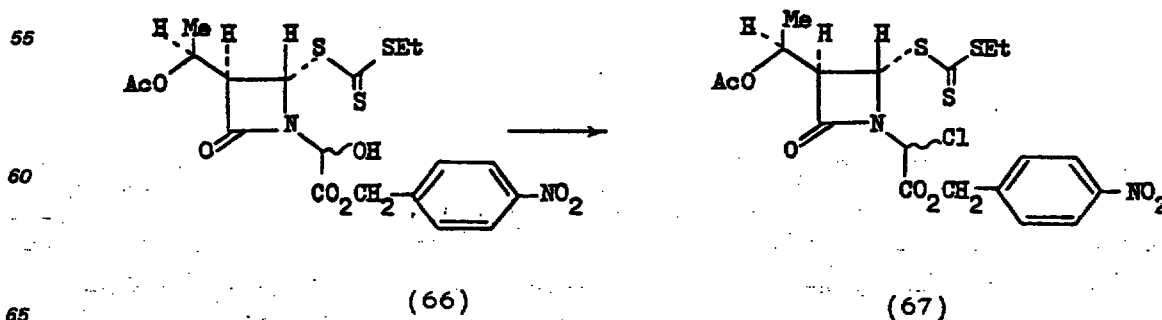
Potassium ethyltrithiocarbonate (82 mg) was added to a stirred, ice-bath cooled, mixture of the sulphone (64) (100 mg), methylene chloride (8 ml) and water (2 ml). After 10 minutes the stirred mixture was allowed to attain room temperature during 30 minutes. The mixture was worked up as for preparation 1(f) to give, after chromatography, the trithiocarbonate (65) (100 mg) as a yellow solid, m.p. 101—5°C (ethyl acetate/petroleum ether); $\lambda_{\max}$ (EtOH) 300 (ϵ_m 13,700) and 236 nm (3,700); $\nu_{\max}$ (CHCl_3) 3420, 1780, 1740 cm^{-1} ; δ ppm 1.36 (t, J 7Hz) and 1.37 (d, J 6Hz) together 6H, 2.03 (3H, s), 3.35 (q, J 7Hz) superimposed on m, together 3H, 5.30 (1H, dq, J 6 and 6Hz), 5.58 (1H, d, J 2.5Hz), 6.80 (1H, broad signal). (Found: C, 41.3; H, 5.2; N, 4.7; S, 33.2. $\text{C}_{10}\text{H}_{15}\text{NO}_3\text{S}_3$ requires C, 41.0; H, 5.1; N, 4.8; S, 32.8%).

Preparation 7(d)
(3RS,4SR)-3-[1-(SR)-Acetoxyethyl]-4-ethylthiothiocarbonylthio-1-(1-hydroxy-1-p-nitrobenzyloxycarbonylmethyl)azetidin-2-one



The trithiocarbonate (65) (100 mg) and *p*-nitrobenzyl glyoxylate monohydrate (116 mg) were heated in refluxing benzene (5 ml) under argon for 26 hours with provision for removal of water. The mixture was evaporated and chromatographed to give the hydroxyester (66) (112 mg), a 1:1 mixture of stereoisomers, as a gum, $\nu_{\max}$ (CHCl_3) 3600—3000, 1780, 1750 cm^{-1} ; δ ppm (CDCl_3) 1.25—1.45 (6H, m), 2.00 (3H, s), 3.22—3.60 (3H, m, plus q, 7Hz), 3.90 (1H, d, J 8Hz, exch. D_2O), 4.04 (1H, d, J 9Hz, exch. D_2O), 5.25—5.45 (3H, m), 5.56 (1H, d, J 9Hz, collapses to s on exch. D_2O), 6.08 (1H, d, J 2.5Hz), 6.11 (1H, d, J 2.5Hz), 7.54 and 7.56 (2H, each d, J 8Hz), 8.24 (2H, d, J 8Hz).

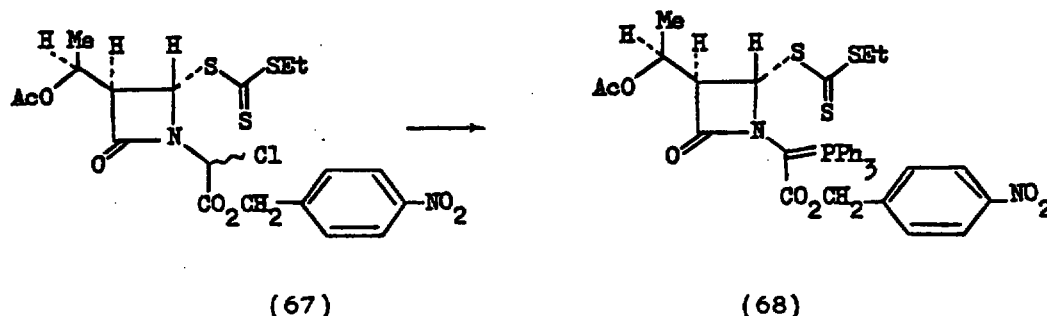
Preparation 7(e)
(3RS,4SR)-3-[1-(SR)-Acetoxyethyl]-1-(1-chloro-1-p-nitrobenzyloxycarbonylmethyl)-4-ethylthiothiocarbonylthioazetidin-2-one



A solution of thionyl chloride (39 mg) in dry tetrahydrofuran (0.5 ml) was added dropwise to a stirred mixture of the hydroxyester (66) (110 mg) and 2,6-lutidine (35 mg) in dry tetrahydrofuran (5 ml) at -10°C . The mixture was stirred at -10°C for 10 minutes, filtered, and evaporated. The residue was re-evaporated from dry toluene (2×3 ml) to give the chloroester (67) (114 mg) as a gum, ν_{max} (CHCl_3) $1790, 1745\text{ cm}^{-1}$.

Preparation 7(f)

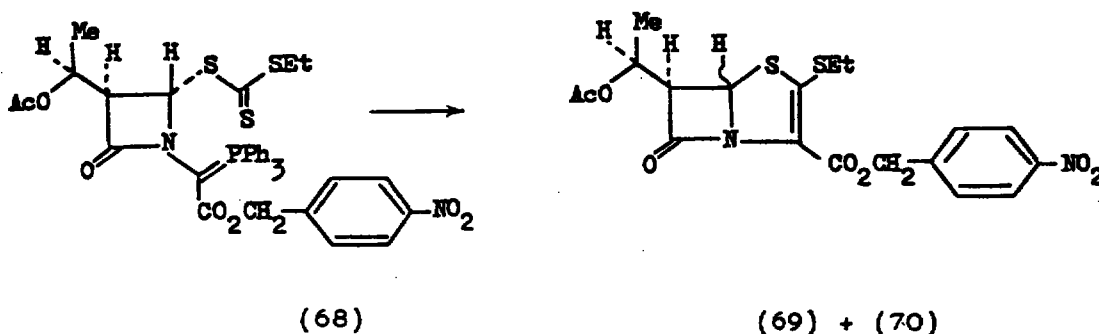
(3RS,4SR)-3-[1-(SR)-Acetoxyethyl]-4-ethylthiothiocarbonylthio-1-(1-p-nitrobenzyloxycarbonyl-1-triphenylphosphoranylidene)azetidin-2-one



A mixture containing the chloroester (67) (114 mg), triphenylphosphine (115 mg) and 2,6-lutidine (28 mg) in dry dioxan (5 ml) was stirred at 60°C under dry argon for 26 hours. The mixture was worked up for preparation 1(i) to give, after chromatography, the phosphorane (68) (77 mg) as an amorphous solid, ν_{max} (CHCl_3) $1760, 1620, 1605$ shoulder cm^{-1} .

Preparation 7(g)

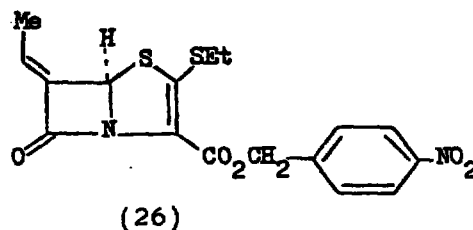
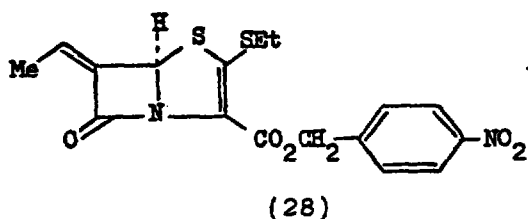
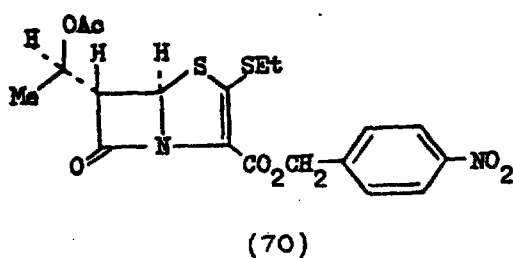
(5RS,6SR,8RS) and (5RS,6RS,8SR)-p-Nitrobenzyl-6-(1-Acetoxyethyl)-2-ethylthiopentem-3-carboxylate



A solution of the phosphorane (68) (1.0 g) in xylene (1000 ml) was refluxed under argon for 10 hours. The mixture was evaporated and chromatographed to give two products. The less polar product, the (5RS,6RS,8SR) penem ester (69) (120 mg) was obtained as a solid, m.p. $131-133^{\circ}\text{C}$ (needles ex ethylacetate/petroleum ether), λ_{max} (EtOH) 260 (ϵ_m 16,200) and 334 n.m. (11,000); ν_{max} (CHCl_3) $1795, 1730$ and 1695 cm^{-1} ; δ ppm (CDCl_3) 1.37 (3H, t, J 7.7 Hz), 1.54 (3H, d, J 6.3 Hz), 2.04 (3H, s), 2.76-3.26 (2H, m), 4.00 (1H, dd, J 4.0 and 9.9 Hz), 5.18 and 5.48 (ABq, J 14 Hz) overlaying a m, together 3H, 5.73 (1H, d, J 4.0 Hz), 7.60 (2H, d, J 8 Hz), 8.21 (2H, d, J 8 Hz). (Found: C, 50.5; H, 4.2; N, 6.1; S, 13.8; M^+ , 452.0729. $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_7\text{S}_2$ requires C, 50.5; H, 4.4; N, 6.2; S, 14.2%; M , 452.0712). The more polar product, the (5RS,6SR,8RS) penem ester (70) (221 mg), was obtained as a solid, m.p. $131-132^{\circ}\text{C}$ (needles ex ethyl acetate/petroleum ether), λ_{max} (EtOH) 261 (ϵ_m 16,500) and 339 n.m. (11,000); ν_{max} (CHCl_3) $1795, 1740$, and 1695 cm^{-1} ; δ ppm (CDCl_3) 1.29-1.46 (6H, m), 2.05 (3H, s), 2.70-3.16 (2H, m), 3.84 (1H, dd, J 1.6 and 7.7 Hz), 5.21 and 5.47 (ABq, J 14 Hz) overlaying a m, together 3H, 5.62 (1H, d, J 1.6 Hz), 7.62 (2H, d, J 8 Hz), 8.21 (2H, d, J 8 Hz). (Found: C, 50.4; H, 4.2; N, 6.1; S, 13.9; M^+ , 452.0707. $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_7\text{S}_2$ requires C, 50.5; H, 4.4; N, 6.2; S, 14.2%; M , 452.0712).

Example 7

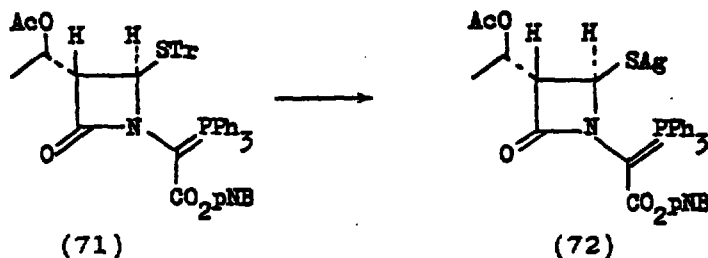
(5RS)-p-Nitrobenzyl 6-Ethylidene-2-ethylthiopene-3-carboxylate



An ice-bath cooled solution of the penem ester (70) (45 mg) in dry methylene chloride (1 ml) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.1 ml of a solution containing 166 mg DBU/ml methylene chloride). After stirring at ice-bath temperature for 15 minutes the mixture was diluted with ethyl acetate (10 ml) and washed with 5% citric acid (2 ml), brine (2 ml), saturated sodium bicarbonate solution (2 ml) and brine (3 × 2 ml). The dried (MgSO₄) organic layer was evaporated and the residue chromatographed on silica gel eluting with methylene chloride to give the E-ethylidenepenem ester (28) (7 mg) and the Z-ethylidenepenem ester (26) (14 mg).

Preparation 8(a)

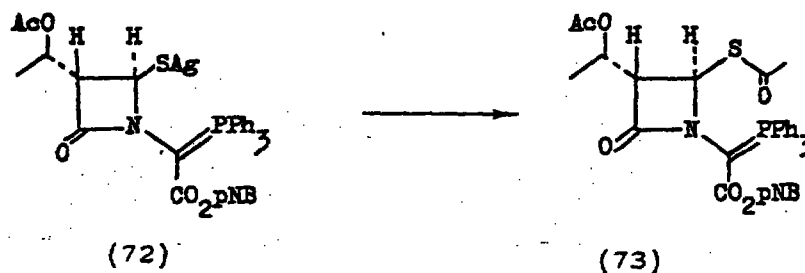
Silver (3RS,4SR)-3-[1-(SR)-Acetoxyethyl]-1-p-nitrobenzyloxycarbonyl-1-triphenylphosphoranylidene-methyl)azetidin-2-one-4-thiolate (72)



A solution of the phosphorane (71) (GB 2 042 515 A) (230 mg, 0.26 mmol) was dissolved in dry dichloromethane (3 ml) and diluted with hot (50°) methanol (8 ml). The mixture was sequentially treated with pyridine (25 µl, 0.31 mmol) and a hot (50°) 0.15M methanolic solution of silver nitrate (2.08 ml, 0.31 mmol). The mixture was then stirred at room temperature for one hour and a further hour at 0°. The reaction mixture was concentrated, then filtered and the solid washed with ice-cold methanol and ether, then dried to give the silver thiolate (72) (100 mg, 51%) as a light brown solid, $\nu_{\max}$ (Nujol) 1760, 1745 cm⁻¹.

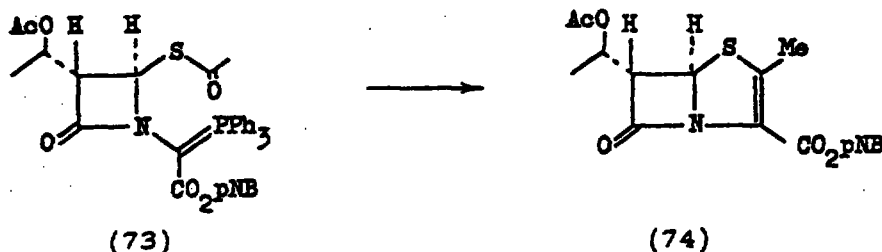
Preparation 8(b)

(3RS,4SR)-3-[1-(SR)-Acetoxyethyl]-4-acetylthio-1-(1-p-nitrobenzyloxycarbonyl-1-triphenylphosphoranylidene-methyl)azetidin-2-one (73)



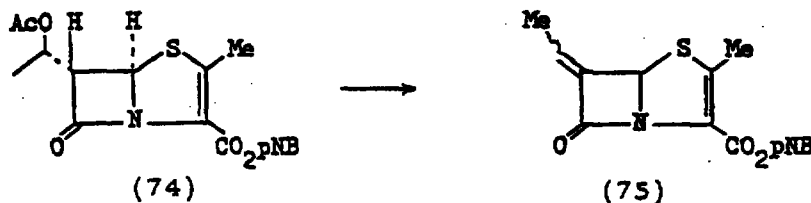
A solution of the silver thiolate (72) (100 mg, 0.13 mmol) in dry dichloromethane (6 ml) under argon at 0° was sequentially treated with pyridine (40 μ l, 0.49 mmol) and acetyl chloride (30 μ l, 0.42 mmol). The mixture was stirred at 0° for 30 minutes and the solid was filtered and washed with dichloromethane. The organic solution was washed with dilute hydrochloric acid solution, dilute sodium bicarbonate solution and brine. The dried organic phase was evaporated and the residue was chromatographed on silica eluting with ethyl acetate/petroleum ether mixtures to give the thioester (73) (50 mg, 55%) as a light yellow amorphous solid, $\nu_{\max}$ (CH_2Cl_2) 1760, 1740 (sh), 1690, 1620 cm^{-1} .

Preparation 8(c)
(5RS,6SR,8RS)-p-Nitrobenzyl-6-(1-Acetoxyethyl)-2-methylpenem-3-carboxylate (74)



A solution of the thioester (73) (50 mg, 0.073 mmol) in toluene (50 ml) was heated at reflux under argon for 6 hours. The reaction mixture was evaporated and chromatographed on silica eluting with ethyl acetate/petroleum ether mixtures to give the penem (74) as a white solid after trituration with ether (24 mg, 81%), m.p. 115–6° (needles ex ethyl acetate/petroleum ether), $\lambda_{\max}$ (EtOH) 311 n.m. (ϵ_m 9,325), 264 (12,700) $\nu_{\max}$ (CHCl_3) 1790, 1760, 1710, 1590 cm^{-1} ; δ (CDCl_3) 1.39 (3H, d, J 7Hz), 2.04 (3H, s), 2.35 (3H, s), 3.81 (1H, dd, J 2, 8Hz), 5.20 and 5.45 (ABq, J 14Hz) overlaying 5.26 (dd, J 7, 8Hz) (together 3Hz), 5.53 (1H, d, J 2Hz), 7.60 (2H, d, J 8Hz), 8.22 (2H, d, J 8Hz); Found: M^+ 406.0844. $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_7\text{S}$ requires M , 406.0833).

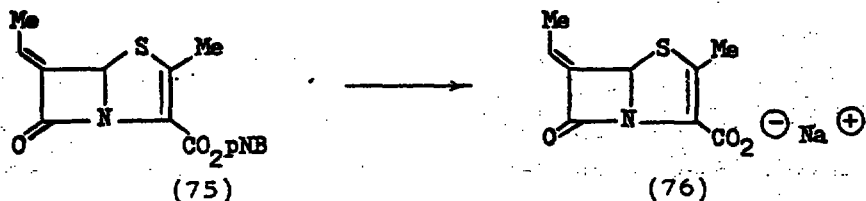
Example 8(a)
(5RS)-p-Nitrobenzyl-6-Ethylidene-2-methylpenem-3-carboxylate (75)



A solution of the acetate (74) (22 mg, 0.054 mmol) in dry dichloromethane (2 ml) at –20° under argon was treated with a solution of 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU) (10.1 mg, 0.067 mmol) in dichloromethane (0.1 ml). After 45 minutes the reaction mixture was treated with more DBU (0.24 equivalents). After a further 30 minutes at –20° the reaction mixture was poured into dichloromethane, washed with 5% citric acid solution, brine, dilute sodium bicarbonate solution and brine, then dried and evaporated. The residue was dissolved in 25% dichloromethane/petroleum ether and chromatographed on silica eluting with dichloromethane/petroleum ether mixtures to give a separable mixture of *E* and *Z* ethylidenepenems (75). The less polar, *E* isomer (2 mg, 11%), was obtained as a gum, $\nu_{\max}$ (CH_2Cl_2) 1780, 1715, 1590 cm^{-1} ; δ (CDCl_3) 2.15 (3H, d, J 7.5Hz), 2.39 (3H, s), 5.23 and 5.48 (2H, ABq, J 13.5Hz), 6.00 (1H, q, J 7.5Hz), 6.09 (1H, s), 7.65 (2H, d, J 9Hz), 8.25 (2H, d, J 9Hz).

The more polar, *Z* isomer (15 mg, 80%), was obtained as light yellow needles, m.p. 139–140° (ex ethyl acetate/petroleum ether), $\lambda_{\max}$ (EtOH) 267 n.m. (ϵ_m 10,015), approx. 280 (inflection) $\nu_{\max}$ (CH_2Cl_2) 1780, 1715, 1590 cm^{-1} ; δ (CDCl_3) 1.85 (3H, d, J 7.5Hz), 2.40 (3H, s), 5.25 and 5.48 (2H, ABq, J 15Hz), 6.12 (1H, s, $\frac{1}{2}$ 3Hz), 6.45 (1H, q, with further fine coupling, J 7.5Hz), 7.66 (2H, d, J 9Hz), 8.24 (2H, d, J 9Hz). (Found: M^+ 346.0612. $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_5\text{S}$ requires M , 346.0602).

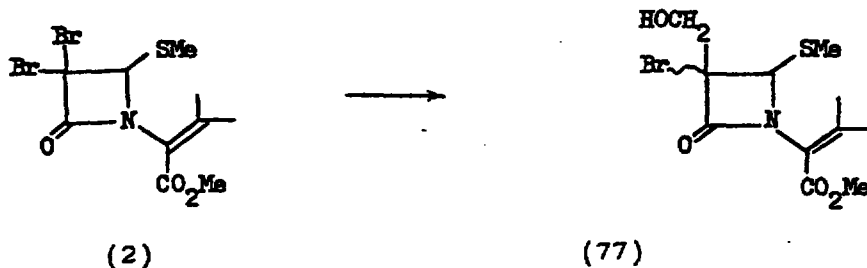
Example 8(b)
(5RS)-Sodium (*Z*)-Ethylidene-2-methylpenem-3-carboxylate



A solution of the (Z)-ethylidenepenenem ester (75) (15 mg) in dioxane (2.5 ml) and water (0.5 ml) was hydrogenated over 5% palladium/charcoal catalyst (23 mg) at S.T.P. for 45 minutes. A further amount of catalyst (15 mg) was added and the hydrogenation continued for 30 minutes. A 1% sodium bicarbonate solution (0.36 ml) was added and the mixture worked up as for Example 1(b) to give the sodium salt (76) (2 mg) as an amorphous solid, $v_{\max}$ (H_2O) 291, 257 n.m., δ (D_2O) 1.82 (3H, d, J 7.5Hz), 2.32 (3H, s), 6.25 (1H, s), 6.57 (1H, q, J 7.5Hz).

Preparation 9(a)

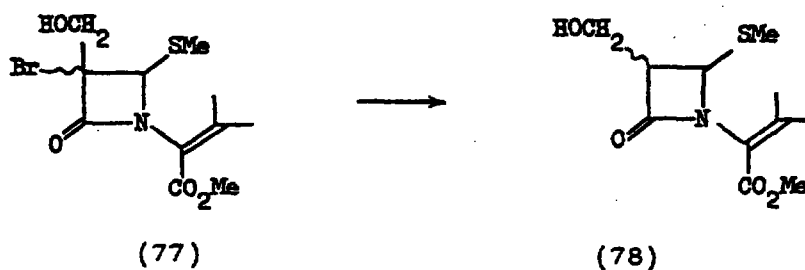
(3,4RS)-3-Bromo-3-hydroxymethyl-1-(1-methoxycarbonyl-2-methylprop-1-enyl)-4-methylthioazetidin-2-one



A solution of methyl magnesium bromide (2M in diethyl ether, 0.7 ml) was added dropwise to a stirred solution of the dibromosecopenicillanate (2) (0.5 g) in dry tetrahydrofuran (10 ml) at $-76^\circ C$. After stirring at $-76^\circ C$ for 10 minutes a stream of argon was passed, first over dry paraformaldehyde (0.5 g) heated at $150^\circ C$ and then over the surface of the vigorously stirred reaction mixture. [During a 10 minutes reaction time approximately 0.2 g of formaldehyde was generated]. The argon/formaldehyde stream was then interrupted, stirring was maintained for 5 minutes, then a saturated aqueous solution of ammonium chloride (1 ml) was added and the stirred mixture was allowed to reach room temperature. The mixture was then diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$) and evaporated to give a crude gum. Chromatography of the crude product on silica gel eluting with ethyl acetate/petroleum ether mixtures gave the bromohydrin (77) (0.23 g, 53%) as a clear gum, $v_{\max}$ ($CHCl_3$) 3570, 3350 (b), 1765, 1720, 1625 (w) cm^{-1} . δ ($CDCl_3$) 2.03 (3H, s), 2.14 (3H, s), 2.26 (3H, s), 2.86 (1H, t, J 7Hz exch. D_2O) 3.78 (s) 4.1 (m, collapses to ABq, centres 3.92 and 4.17, J 12Hz with D_2O) two signals together 4H, 5.39 (1H, s).

Preparation 9(b)

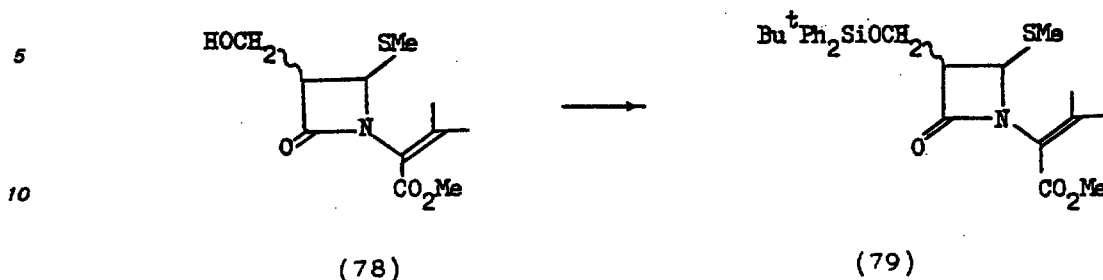
(3RS,4RS) and (3RS,4SR)-3-Hydroxymethyl-1-(1-methoxycarbonyl-2-methylprop-1-enyl)-4-methylthioazetidin-2-one



The bromohydrin (77) (100 mg) in tetrahydrofuran (1 ml) cooled in ice/salt mixture was stirred with zinc dust (200 mg) and N/1 aqueous ammonium acetate solution (0.2 ml). After 10 minutes in the cold and 10 minutes at room temperature the reaction mixture was filtered, diluted with ethyl acetate and washed with N/10 aqueous hydrochloric acid then brine. The solution was dried ($MgSO_4$) and evaporated to an oil. Chromatography on silica gel eluting with ethyl acetate/petroleum ether mixture gave an 85:15 mixture of the *cis* and *trans*-hydroxymethylazetidinones (78) (54 mg, 70%) $v_{\max}$ ($CHCl_3$) 3450 (b), 1760, 1725, 1630 cm^{-1} . δ ($CDCl_3$) 2.0 (3H, s), 2.14 (3H, s), 2.24 (3H, s), 2.4–2.8 (1H, m, exch. D_2O), 3.2–3.7 (1H, m), 3.75 (3H, s), 3.9–4.1 (2H, m), 5.03 (d, J 3Hz), 5.10 (d, J 5Hz) together 1H.

Preparation 9(c)

3-t-Butyldiphenylsilyloxymethyl-1-(1-methoxycarbonyl-2-methylprop-1-enyl-4-methylthioazetidinone

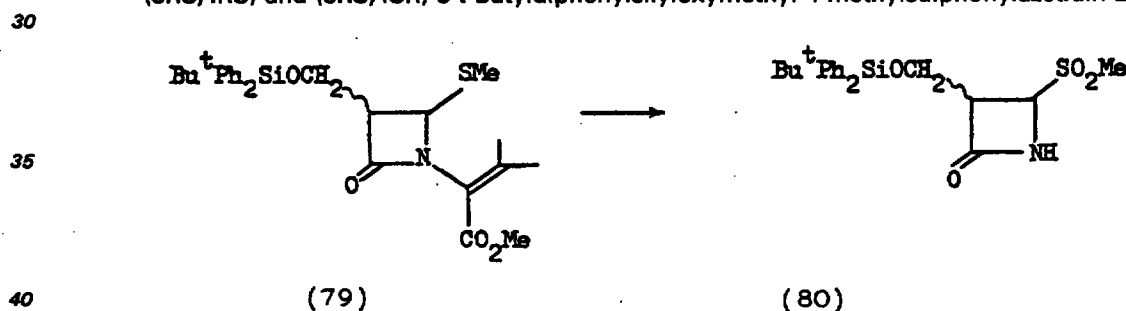


15 The mixture of *cis* and *trans*-hydroxymethylazetidinones (78) (0.650 g) in dry dimethylformamide (20 ml) was treated with t-butyldiphenylsilyl chloride (1.25 g) and imidazole (0.34 g) at room temperature for 2½ hours. Most of the solvent was evaporated off *in vacuo* and the residue was partitioned between ethyl acetate and water. The solvent layer was then separated, dried (MgSO₄) and evaporated. The residue was chromatographed on silica gel eluting with ethylacetate/petroleum ether mixtures. First to be eluted was the fraction containing the *trans* isomer (240 mg), then a mixed *cis/trans* fraction (45 mg) and finally the *cis* isomer (825 mg). The less polar fraction, the (3*RS*,4*SR*)-3-t-butyldiphenylsilyloxymethylazetidin-2-one was obtained as a gum, $\nu_{\max}$ (CHCl₃) 1755, 1725, 1630 cm⁻¹; δ (CDCl₃) 1.12 (9H, s), 2.05 (3H, s), 2.15 (3H, s), 2.15 (3H, s), 2.30 (3H, s), 3.2—3.55 (1H, m), 3.77 (3H, s), 4.08 (2H, b.d., J 4Hz), 5.25 (1H, d, J 3Hz), 7.35—8.0 (10H, m). The more polar fraction, the (3*RS*,4*SR*)-3-t-butyldiphenylsilyloxymethylazetidin-2-one was obtained as a gum, $\nu_{\max}$ (CHCl₃) 1755, 1725, 1630 cm⁻¹; δ (CDCl₃) 1.10 (9H, s), 2.08 (3H, s), 2.17 (3H, s), 2.28 (3H, s), 3.79 (3H, s), 4.0—4.45 (3H, m), 5.23 (1H, d, J 6Hz), 7.1—8.1 (10H, m).

20

25

Preparation 9(d)

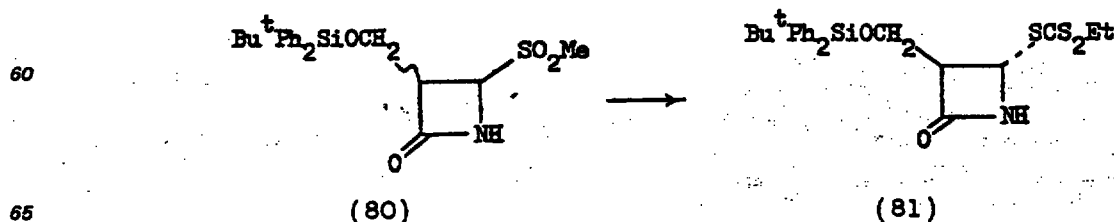
(3*RS*,4*RS*) and (3*RS*,4*SR*)-3-t-Butyldiphenylsilyloxymethyl-4-methylsulphonylazetidin-2-one

A solution of m-chloroperbenzoic acid (0.85 g) in ethyl acetate (10 ml) was added dropwise over ten minutes to a stirred, ice-cooled solution of the azetidinone (79) (*cis/trans* mixture) in ethyl acetate (30 ml). After 10 minutes the temperature was raised to room temperature for half an hour. The reaction mixture was washed with saturated aqueous sodium bicarbonate, water and brine. The dried (MgSO₄) organic layer was evaporated. The white amorphous residue was redissolved in methylene dichloride, cooled to -20°C, and ozonised oxygen was passed for 45 minutes. Methanol (50 ml) and 2,6-lutidine (10 drops) were then added and the mixture was kept at room temperature for 1 hour then evaporated to give a gum. This was redissolved in ethyl acetate, washed with 5% aqueous citric acid, then brine, dried (MgSO₄) and evaporated. The residual gum was chromatographed on silica gel eluting with ethyl acetate/petroleum ether mixtures to give the sulphone (80) as a gummy mixture of *cis/trans* isomers (500 mg), $\nu_{\max}$ (CHCl₃) 3400, 1790, 1320, 1150 cm⁻¹; δ (CDCl₃) 1.1 (9H, s), 3.1 (3H, s), 3.65—4.65 (m, CH₂OSi, C-3-H and C-4-H *trans*), 4.78 (d, J 4Hz, C-4-H *cis*) together 4H, 7.2—7.9 (11H, one H exch. D₂O).

45

50

Preparation 9(e)

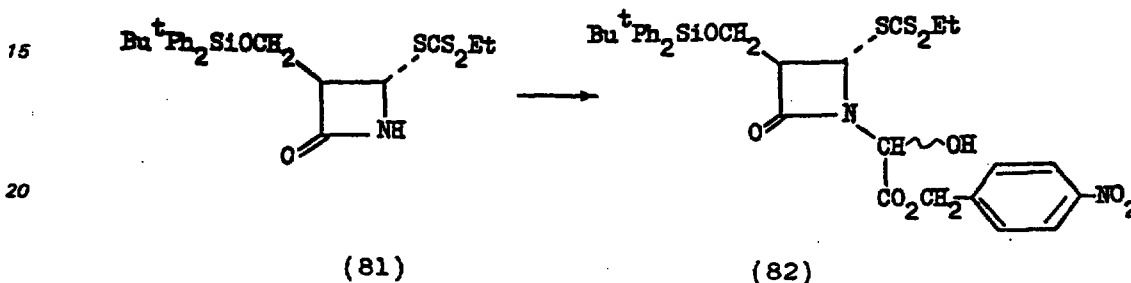
(3*RS*,4*SR*)-3-(t-Butyldiphenylsilyloxymethyl)-4-ethylthiothiocarbonylthioazetidin-2-one

A mixture of the sulphone (80) (*cis/trans* mixture, 1.8 g) in methylene chloride (50 ml) and potassium ethyl trithiocarbonate (1.52 g) in water (50 ml) was stirred vigorously at room temperature. After 6 hours the solvent layer was separated, washed with water, dried (MgSO_4) and evaporated. The residue was a yellow crystalline mass which was washed with a little toluene/petroleum ether mixture (1.22 g). Recrystallisation from ethyl acetate/petroleum ether gave the pure *trans* azetidinone (81) as yellow needles, m.p. 142°, v_{max} (CHCl_3) 3420, 1780 cm^{-1} , δ (CDCl_3) 1.06 (9H, s), 1.38 (3H, t, J 8Hz), 3.40 (q, J 8Hz) overlaying (m), together 3H, 3.95–4.15 (2H, m), 5.76 (1H, d, J 2Hz), 6.78 (1H, b.s.), 7.25–7.9 (10H, m). (Found: C, 57.8; H, 6.0; N, 2.9; S, 20.3. $\text{C}_{23}\text{H}_{29}\text{NO}_2\text{S}_3\text{Si}$ requires C, 58.1; H, 6.1; N, 3.0; S, 20.2%).

10

Preparation 9(f)

(*RS,4SR*)-3-*t*-Butyldiphenylsilyloxymethyl-4-ethylthiothiocarbonylthio-1-(1-hydroxy-1-*p*-nitrobenzyloxycarbonylmethyl)azetidin-2-one

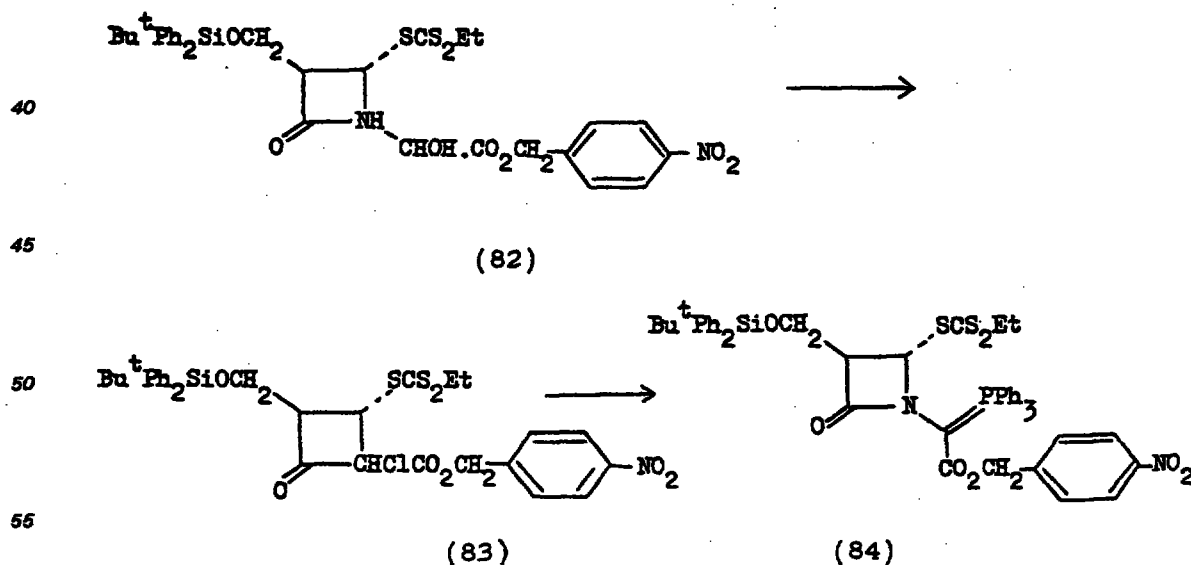


25 The trithiocarbonate (81) (310 mg) and *p*-nitrobenzyl glyoxylate monohydrate (300 mg) were refluxed in benzene (20 ml) under argon for 24 hours with provision for removal of water. The mixture was evaporated and the residual gum chromatographed on silica gel eluting with ethyl acetate/petroleum ether mixtures to give the hydroxy-ester (82) as a mixture of diastereoisomers (420 mg), a yellow amorphous solid. v_{max} (CHCl_3) 3500, 1780, 1760 cm^{-1} . δ (CDCl_3) 1.06 (9H, s), 1.45 (3H, t, J 8Hz), 3.40 (q, J 8Hz), 3.52 (b.d. J 2Hz) together 3H, 4.1 (2H, b.s.), 4.34 and 4.4 (1H, 2 d. J 8Hz, exch. D_2O) 5.35 (s) 5.47 and 5.73 (2 d, J 8Hz) together 3H, 6.3 and 6.44 (1H, 2 d, J 2Hz), 7.3–8.5 (14H, m).

30

Preparation 9(g)

35 (*3RS,4SR*)-3-*t*-Butyldiphenylsilyloxymethyl-4-ethylthiothiocarbonylthio-1-(1-*p*-nitrobenzyloxycarbonyl-1-triphenylphosphoranylideneethyl)azetidin-2-one



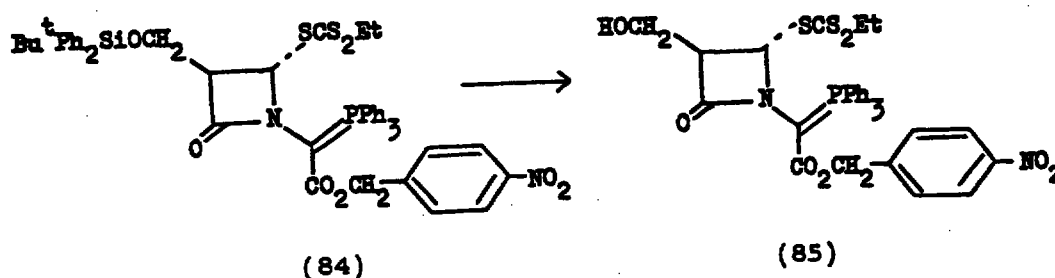
The hydroxy-ester (82) (420 mg) in tetrahydrofuran (20 ml) at -20°C was treated with 2,6-lutidine (99 mg) and thionyl chloride (0.07 ml) and allowed to reach room temperature over 0.5 hours. The solution was then filtered and evaporated under high vacuum to give the crude chloro-ester (83). This was redissolved in dioxan (20 ml) then 2,6-lutidine (29 mg) and triphenylphosphine (320 mg) were added. The stirred mixture was kept at 60°C under argon for 7 days and was then evaporated to dryness *in vacuo*. The residue was dissolved in ethyl acetate and washed successively with 1% aqueous citric acid solution, sodium bicarbonate solution and brine. The dried (MgSO_4) organic layer was evaporated the residue chromato-

65

graphed on silica gel eluting with ethyl acetate/petroleum ether mixtures to give the phosphorane (84) as an amorphous yellow solid (370 mg) $\nu_{\max}$ (CHCl_3) 1750, 1615, 1605 cm^{-1} .

Preparation 9(h)

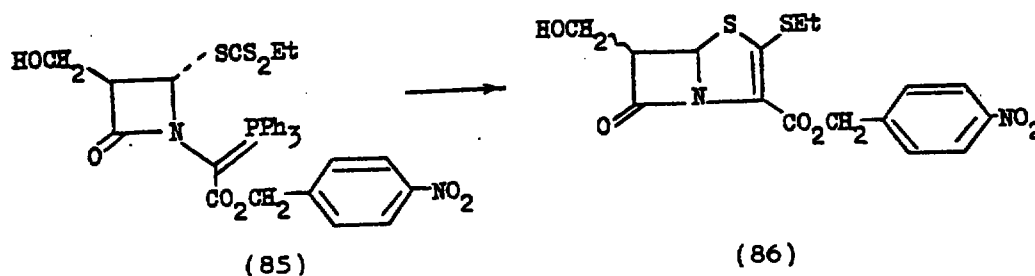
(3RS,4SR)-3-Hydroxymethyl-4-ethylthiiothiocarbonylthio-1-(1-p-nitrobenzyloxycarbonyl)-1-triphenylphosphoranylideneazetidin-2-one



A solution of the phosphorane (84) (1.75 g) in 15% methanolic hydrogen chloride (30 ml) was kept for 1 hour at room temperature. It was then neutralised with aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The solvent layer was dried (MgSO_4) and evaporated then the residue was chromatographed on silica gel eluting with ethyl acetate—petroleum ether mixtures. The pure product (85) was isolated as a yellow amorphous solid (1.09 g), $\nu_{\max}$ (CHCl_3) 3400 (b), 1760, 1620, 1610 cm^{-1} .

Preparation 9(i)

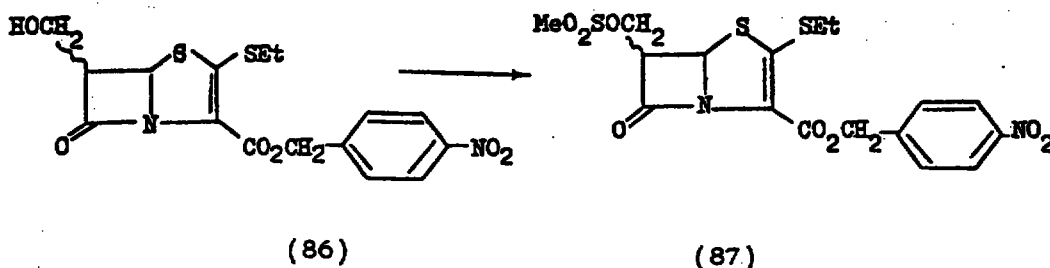
(6RS,5SR) and (6RS,4RS)-p-Nitrobenzyl 6-Hydroxymethyl-2-ethylthiopenem-3-carboxylate



A solution of the phosphorane (85) (547 mg) was refluxed in xylene (150 ml) under argon for 10 hours. The mixture was evaporated and the residue chromatographed on silica gel eluting with ethyl acetate/petroleum ether mixtures to give the *cis* and *trans* penems (86) 260 mg *trans/cis* 7/3. Careful re-chromatography allowed pure samples of the *trans* and *cis* isomers to be separated. The more polar *trans* isomer was a cream crystalline solid, m.p. 162—163° (from ethyl acetate/petroleum ether) $\lambda_{\max}$ (EtOH) 338 n.m. (ϵ_m 10,025) 261 (13,050) $\nu_{\max}$ 3600, 3400 (b), 1790, 1695, 1610 cm^{-1} . δ (250 m.c. (CDCl_3)) 1.35 (3H, t, J 7Hz), 2.90—3.20 (2H, m), 3.94—4.10 (3H, m), 4.38 (1H, t, J 5Hz, exch. D_2O), 5.28 and 5.53 (2H, ABq, J 14Hz), 5.81 (1H, d, J 1.5Hz) 7.78 (2H, d, J 7Hz) 8.26 (2H, d, J 7Hz). (Found: M^+ , 396.480. $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_6\text{S}_2$ requires 396.0446). The less polar *cis* isomer was also a cream solid, m.p. 150—155°, $\nu_{\max}$ (CHCl_3) 3600, 3400 (b), 1790, 1690 cm^{-1} . δ (CDCl_3) 1.37 (3H, t, J 7Hz), 3.06 (2H, q, with fine coupling, J 7Hz), 2.75 (1H, s, exch. D_2O), [4.03 and 4.05 (2H, q, J 7 and 9Hz), 4.34 (1H, ddd, J 9, 7, 4Hz) these signals described with D_2O exch.], 5.27 and 5.50 (2H, ABq, J 14Hz), 5.90 (1H, d, J 4Hz), 7.75 (2H, d, J 7Hz), 8.24 (2H, d, J 7Hz). (Found: M^+ , 396.0480, $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_6\text{S}_2$ requires 396.0446).

Example 9

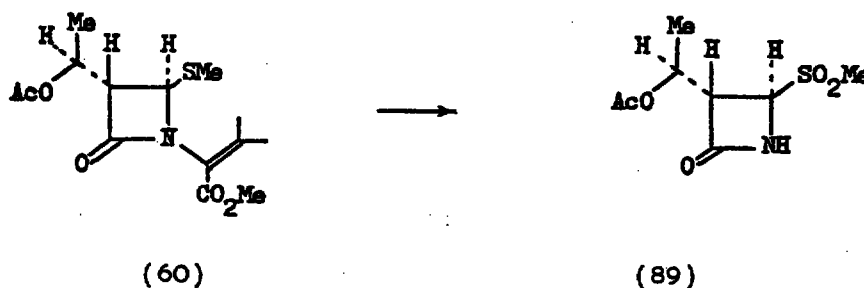
5(RS)-p-Nitrobenzyl 6-Methylene-2-ethylthiopentem-3-carboxylate



The hydroxymethylpenem (86) (102 mg) in methylene chloride (15 ml) at 0°C was treated with triethylamine (33 mg) followed by methanesulphonyl chloride (33 mg). The mixture was kept at room temperature for 0.5 hours, evaporated to dryness and redissolved in ethyl acetate. The solution was washed with brine, dried (MgSO₄) and again evaporated to give the crude methanesulphonate (87). This was dissolved in methylene chloride (10 ml) cooled to 0°C and treated with DBU (43 mg). The mixture was then kept at room temperature for 0.5 hours. This was then evaporated and chromatographed on silica gel eluting with ethyl acetate/petroleum ether mixtures to give the methylene penem (88) (47 mg) as a yellow crystalline solid, m.p. 146–147°C (from ethyl acetate), $\lambda_{\max}$ (EtOH) 267 n.m. (ϵ_n 18,500) 302 n.m. (infl.) (11,500) 343 n.m. (infl.) (5,400), δ (CDCl₃) 1.38 (3H, t, J 7Hz), 2.96 and 2.98 (2H, 2 d, J 7Hz), 5.20 and 5.48 (2H, ABq, J 14Hz), 5.48 (1H, dd, J 2.4 and 0.7Hz), 5.98 (1H, dd, J 2.4 and 1.3Hz), 6.19 (1H, dd, J 1.3 and 0.7Hz), 7.63 and 8.20 (4H, 2 d, J 8Hz). (Found: M⁺ 378.0333. C₁₆H₁₄N₂O₅S₂ requires M, 378.0342).

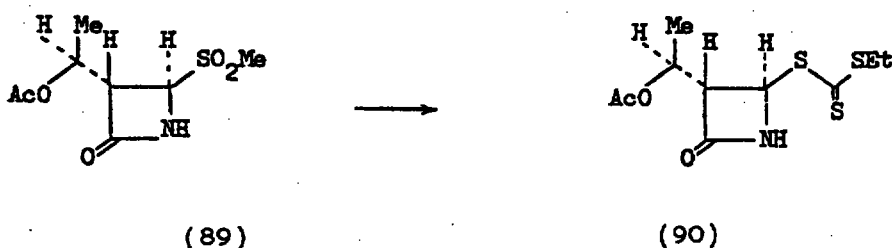
Preparation 10(a)

(3RS,4SR)-3-[1-(RS)-Acetoxyethyl]-4-methylsulphonylazetidin-2-one



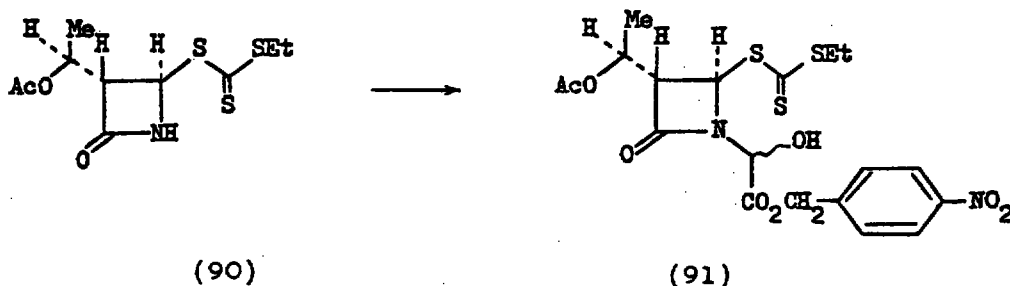
A solution of m-chloroperbenzoic acid (241 mg) in ethyl acetate (3 ml) was added dropwise over 2 minutes to a stirred, ice-bath cooled, solution of the impure azetidinone (60) (200 mg) in ethyl acetate (10 ml). The stirred mixture was allowed to attain room temperature during 45 minutes and was washed with saturated sodium bicarbonate solution (2 × 5 ml) and brine (3 × 5 ml). The dried (MgSO₄) organic layer was diluted with ethyl acetate (15 ml) and treated with ozonised oxygen and methanol as in preparation 1(e) to give, after chromatography, the sulphone (89) (137 mg) contaminated with approximately 25% of the (3RS,4SR)-3-[1-(SR)-acetoxyethyl] isomer as a gum, $\nu_{\max}$ (CHCl₃) 3550 br, 3410, 3300 br, 1795, 1745 cm⁻¹; δ ppm (CDCl₃) 1.41 and 1.43 (3H, each d, J 6.5Hz), 2.03 and 2.08 (3H, each s), 2.95 (3H, s), 3.68 (dd, J 2 and 7Hz) and 3.79 (dd, J 2 and 5Hz) together 1H, 4.53 (2H, d, J 2Hz), 4.73 (2H, d, J 2Hz), 5.14–5.45 (1H, m), 7.05 (1H, br. signal).

Preparation 10(b)
 (3RS,4SR)-3-[1-(RS)-Acetoxyethyl]-4-ethylthiothiocarbonylthioazetidin-2-one



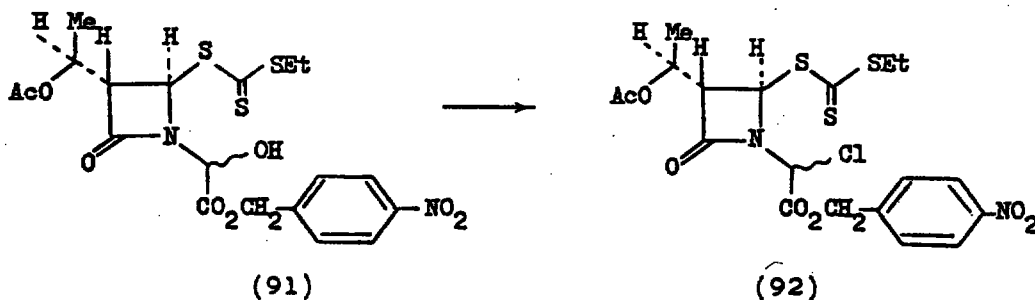
A solution of the impure sulphone (89) (110 mg) in methylene chloride (5 ml) was cooled in an ice-bath and treated with a solution of potassium ethyltrithiocarbonate (91 mg) in water (1 ml). After 10 minutes at ice-bath temperature the stirred mixture was allowed to attain room temperature during 30 minutes. The mixture was worked up as for preparation 1(f) to give, after chromatography, the (3RS,4SR)-3-[1-(RS)-acetoxyethyl]azetidinone (90) (97 mg) containing approximately 20% of the (3RS,4SR)-3-[1-(SR)-acetoxyethyl] isomer as impurity, $\nu_{\max}$ (CHCl_3) 3610, 3410, 1780, 1740 cm^{-1} ; δ ppm (CDCl_3) 1.35 (t, J 7Hz), 1.37 (d, J 6Hz) and 1.41 (d, J 6.5Hz) together 6H, 2.03 and 2.07 (3H, each s), 3.2—3.5 (3H, m), 5.17—5.5 (1H, m), 5.43, 0.8H, d, J 2Hz), 5.58 (0.2H, d, J 2Hz), 6.5—6.8 br (1H).

Preparation 10(c)
 (3RS,4SR)-3-[1-(RS)-Acetoxyethyl]-4-ethylthiothiocarbonylthio-1-(1-hydroxy-1-p-nitrobenzyloxycarbonylmethyl)azetidin-2-one



The impure azetidinone (90) (1.0 g) and *P*-nitrobenzyl glyoxylate monohydrate (1.55 g) were heated in refluxing benzene (40 ml) under argon with provision for removal of water for 22 hours. The mixture was evaporated and chromatographed to give the hydroxyester (91) (1.51 g), a mixture of stereoisomers, as a gum, $\nu_{\max}$ (CHCl_3) 3600—3100, 1780, 1745 cm^{-1} .

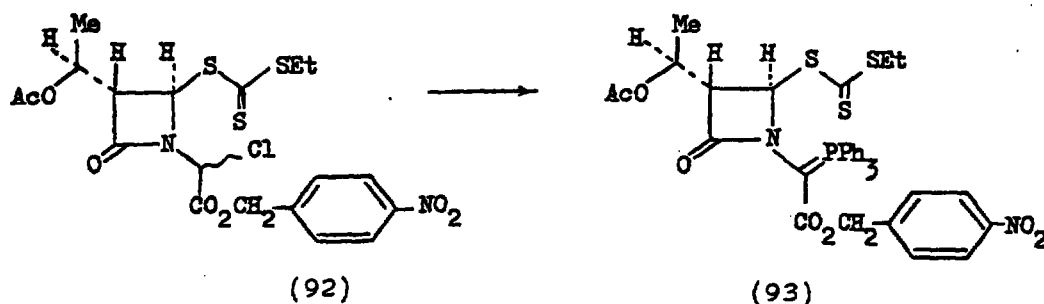
Preparation 10(d)
 (3RS,4SR)-3-[1-(RS)-Acetoxyethyl]-1-(1-chloro-1-p-nitrobenzyloxycarbonylmethyl)-4-ethylthiothiocarbonylthioazetidin-2-one



A solution of thionyl chloride (537 mg) in dry tetrahydrofuran (5 ml) was added dropwise over 10 minutes to a stirred mixture of the hydroxyester (91) (1.51 g) and 2,6 lutidine (483 mg) in dry tetrahydrofuran (30 ml) at -10°C . The mixture was stirred at -10°C for 10 minutes, filtered and evaporated. The residual gum was re-evaporated from dry toluene (2×3 ml) to give the chloroester (92) (1.57 g) as a gum, $\nu_{\max}$ (CHCl_3) 1790 and 1745 cm^{-1} .

Preparation 10(e)

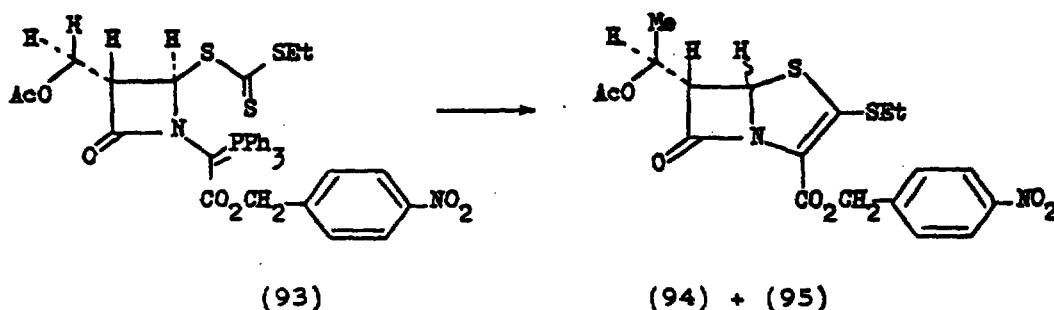
(3RS,4SR)-3-[1-(RS)-Acetoxyethyl]-4-ethylthiobenzothiazolidine-2-one-1-(1-p-nitrobenzyloxycarbonyl-1-triphenylphosphoranylidene)azetidin-2-one



A mixture containing the chloroester (92) (1.57 g), triphenylphosphine (1.58 g) and 2,6-lutidine (387 mg) in dry dioxan (30 ml) was stirred at 60°C under dry argon for 24 hours. The mixture was worked up as for preparation 1(i) to give the phosphorane (93) (1.12 g) as an amorphous solid, $\nu_{\max}$ (CHCl₃) 1760, 1625 cm⁻¹.

Preparation 10(f)

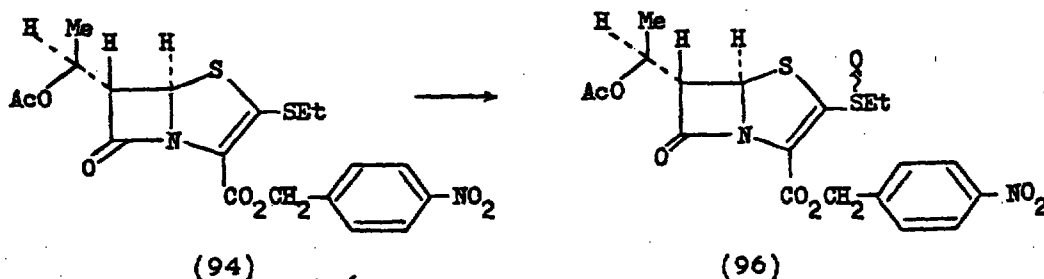
(5RS,6SR,8SR) and (5RS,6RS,8RS)-p-Nitrobenzyl 6-(1-Acetoxyethyl)-2-ethylthiopenem-3-carboxylate



The phosphorane (93) (1.04 g) was heated in refluxing xylene (1000 ml) under dry argon for 10 hours. The mixture was evaporated and chromatographed to give two products. The less polar product, the (5RS,6SR,8SR) penem ester (94) (262 mg) was obtained as a solid, m.p. 143–144°C (needles ex ethyl acetate/petroleum ether); $\lambda_{\max}$ (EtOH) 339 (ϵ_m 9,600) and 261 n.m. (14,400); $\nu_{\max}$ (CHCl₃) 1785, 1740, 1695 cm⁻¹; δ ppm (CDCl₃) 1.37 (3H, t, J 7.4 Hz), 1.44 (3H, d, J 6.4 Hz), 2.09 (3H, s), 2.84–3.13 (2H, m), 3.96 (1H, dd, J 1.6 and 4.0 Hz), 5.1–5.5 (3H, m), 5.54 (1H, d, J 1.6 Hz), 7.62 (2H, d, J 8.6 Hz), 8.22 (2H, d, J 8.6 Hz). (Found: C, 50.5; H, 4.4; N, 6.2; S, 14.0; M⁺, 452.0721. C₁₉H₂₀N₂O₇S₂ requires C, 50.5; H, 4.4; N, 6.2; S, 14.2%; M, 452.0712). The more polar product, the (5RS,6RS,8RS) penem ester (95) (15 mg) was also obtained as a solid, m.p. 179–181°C (needles ex ethyl acetate/petroleum ether); $\lambda_{\max}$ (EtOH) 336 (ϵ_m 10,300) and 261 n.m. (15,500); $\nu_{\max}$ (CHCl₃) 1795, 1735, 1690 cm⁻¹; δ ppm (CDCl₃) 1.21–1.39 (6H, m), 2.09 (3H, s), 2.87–3.14 (2H, m), 4.04 (1H, dd, J 4.1 and 7.8 Hz), 5.09–5.55 (3H, m), 5.73 (1H, d, J 4.1 Hz), 7.61 (2H, d, J 8.7 Hz), 8.22 (2H, d, J 8.7 Hz). (Found: M⁺, 452.0692. C₁₉H₂₀N₂O₇S₂ requires 452.0712).

Preparation 10(g)

(5RS,6SR,8SR)-p-Nitrobenzyl 6-(1-Acetoxyethyl)-2-ethylsulphonylpenem-3-carboxylate

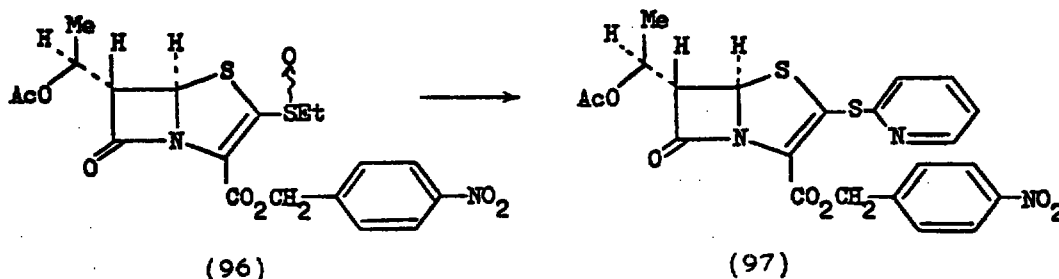


A solution of *m*-chloroperbenzoic acid (45 mg) in methylene chloride (1 ml) was added, in one portion, to a vigorously stirred, ice-bath cooled, mixture of the penem ester (94) (90 mg), methylene chloride (5 ml) and saturated sodium bicarbonate solution (5 ml). The mixture was stirred at ice-bath temperature for 10

minutes and diluted with methylene chloride (10 ml). The organic layer was separated and washed with brine (3 x 2 ml), dried (MgSO₄), evaporated and chromatographed to give the sulfoxide (96) (53 mg), and approximately 1:1 mixture of isomers, as an amorphous solid, $\nu_{\max}$ (CHCl₃) 1805, 1740 and 1710 cm⁻¹; δ ppm (CDCl₃) 1.32—1.50 (6H, m), 2.10 (3H, s), 2.9—3.3 (2H, m), 4.11 (1H, dd, J 2 and 4Hz), 5.23 and 5.46 (ABq, J 14Hz) plus 5.1—5.5 (m) together 3H, 5.59 (1H, d, J 2Hz), 5.70 (1H, d, J 2Hz), 7.59 and 7.60 (2H, each d J 8Hz), 8.25 (2H, d, J 8Hz).

Preparation 10(h)

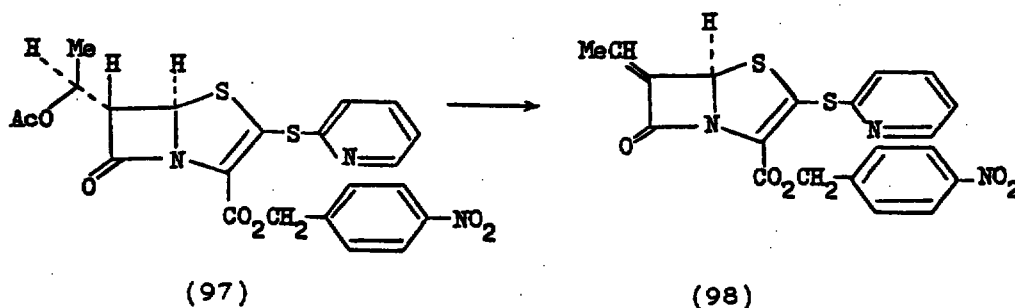
(5RS,6SR,8SR)-p-Nitrobenzyl 6-(1-Acetoxyethyl)-2-(2-pyridylthio)penem-3-carboxylate



A stirred, ice-bath cooled, mixture of the penem sulfoxide (96) (50 mg) methylene chloride (5 ml), and water (2 ml) was treated with sodium 2-mercaptopyridine (16 mg) followed by benzyldimethyl-n-hexadecyl-ammonium chloride (47 mg) portionwise over 5 minutes. The cooled mixture was stirred for a further 5 minutes, diluted with methylene chloride (10 ml) and washed successively with 5% citric acid (2 ml), brine (2 ml), saturated sodium bicarbonate solution (2 ml) and brine (3 x 2 ml). The dried (MgSO₄) organic layer was evaporated and chromatographed to give the penem ester (97) (22 mg) as a solid, m.p. 140—142°C (needles ex ethyl acetate/petroleum ether); $\lambda_{\max}$ (EtOH) 262 (ϵ_m 17,790) and 339 n.m. (12,090); $\nu_{\max}$ (CHCl₃) 1790, 1735, 1700 cm⁻¹; δ ppm (CDCl₃) 1.43 (3H, d, J 7Hz), 2.10 (3H, s), 3.96 (1H, dd, J 1.7 and 3.9Hz), 5.22—5.32 (1H, m), 5.30 and 5.50 (2H, ABq, J 14Hz), 5.44 (1H, d, J 1.7Hz), 7.25—7.34 (1H, m), 7.54—7.74 (4H, m), 8.20—8.27 (2H, m), 8.58—8.62 (1H, m). (Found: C, 52.8; H, 4.0; N, 8.2; S, 12.5. C₂₂H₁₉N₃O₇S requires C, 52.7; H, 3.8; N, 8.4; S, 12.8%).

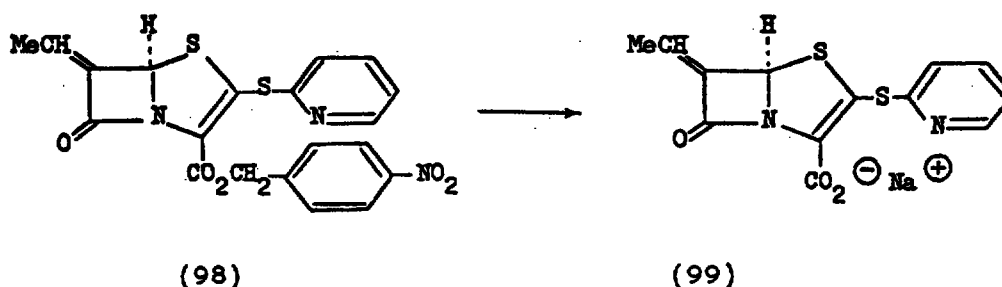
Example 10(a)

(5RS,6SR)-p-Nitrobenzyl 6-Ethylidene-2-(2-pyridylthio)penem-3-carboxylate



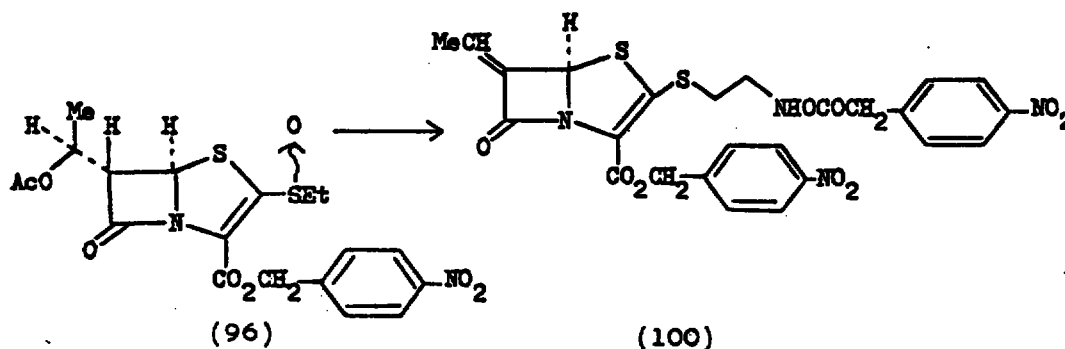
A solution of the penem ester (97) (55 mg) in dry methylene chloride (2 ml) was cooled to -20°C and treated with a solution of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) (20 mg) in dry methylene chloride (1.2 ml). After stirring at -20°C for 10 minutes the mixture was treated with DBU (5 mg) in dry methylene chloride (0.3 ml). After a further 10 minutes at -20°C the mixture was diluted with ethyl acetate (15 ml) and washed with 5% citric acid (2 ml), brine (2 ml), saturated sodium bicarbonate solution (2 ml), and brine (3 x 2 ml). The dried (MgSO₄) organic layer was evaporated and chromatographed to give the 6-ethylidenepenem ester (98) (26 mg), an approximately 2:1 mixture of Z and E isomers, as a solid, $\lambda_{\max}$ (EtOH) 261 (16,860) and approximately 316 n.m. (inflection); $\nu_{\max}$ (CHCl₃) 1780 and 1700 cm⁻¹; δ ppm (CDCl₃) 1.76 (3H, d, J 7Hz), 2.08 (3H, d, J 7Hz), 5.25 and 5.51 (2H, ABq, J 14Hz), 5.95 (q, J 7Hz) plus 6.03 and 6.08 (each s) together 1 1/2 H, 6.44 (1/2 H, q, J 7Hz), 7.2—7.4 (1H, m), 7.5—7.75 (4H, m), 8.21 (2H, d, J 8Hz), 8.5—8.7 (1H, m). Found: M⁺, 441.0461. C₂₀H₁₅N₃O₅S requires 441.0452).

Example 10(b)
(5RS)-Sodium 6-Ethylidene-2-(2-pyridylthio)penem-3-carboxylate



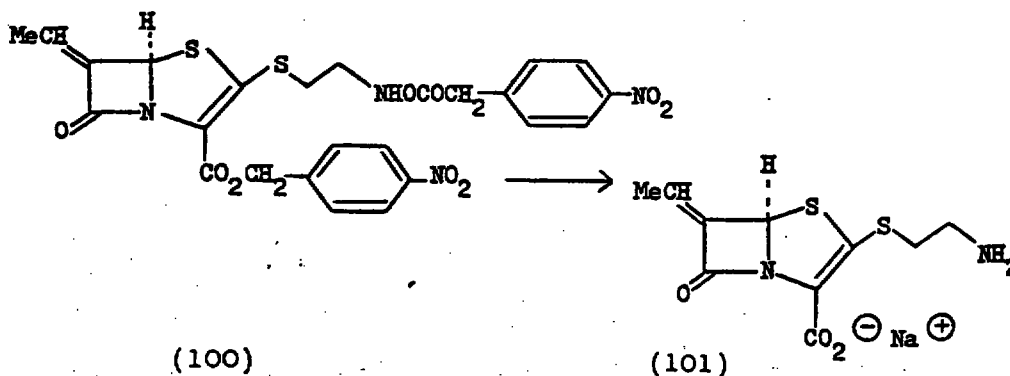
The 6-ethylidenepenem ester (98) (24 mg) was dissolved in a mixture of dioxan (8 ml) and water (2 ml) and hydrogenated over 5% palladium/charcoal catalyst (36 mg) at S.T.P. for 40 minutes. Further catalyst (24 mg) was added and the hydrogenation continued for 40 minutes. A 1% sodium bicarbonate solution (0.46 ml) was added and the mixture was worked up as for Example 1(b) to give the sodium salt (99) (8.2 mg) as a yellow amorphous solid, $\lambda_{\max}$ (H₂O) 294 n.m. (6960).

Example 11(a)
(5RS)-p-Nitrobenzyl 6-Ethylidene-2-(2-p-nitrobenzyloxycarbonylaminoethylthio)penem-3-carboxylate



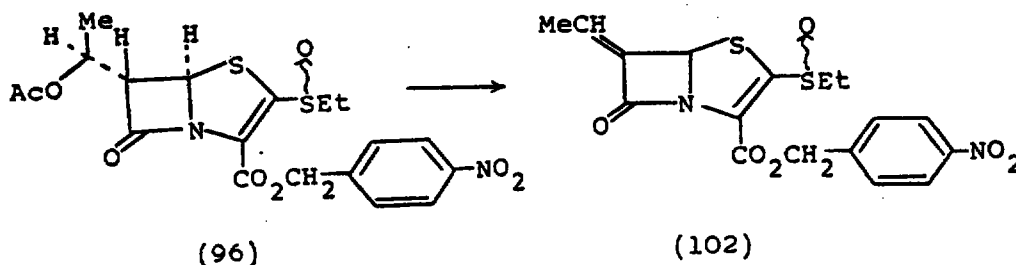
2-p-Nitrobenzyloxycarbonylaminoethanethiol (49 mg) was dissolved in 0.1N sodium hydroxide solution (1.9 ml), cooled in an ice-bath, and treated with a solution of the sulfoxide (96) (79 mg) in methylene chloride (5 ml). The stirred, ice-bath cooled, mixture was treated, portionwise over 5 minutes, with benzyldimethyl-n-hexadecylammonium chloride (75 mg). The cooled mixture was stirred for a further 10 minutes, diluted with methylene chloride (10 ml), and washed with 5% citric acid (2 ml), brine (2 ml), saturated sodium bicarbonate (2 ml), and brine (3 x 2 ml). The dried (MgSO₄) organic layer was evaporated and chromatographed to give the 6-ethylidenepenem ester (100) (46 mg), an approximately 2:1 mixture of *E* and *Z* isomers, as an amorphous solid, $\lambda_{\max}$ (EtOH) 262 (ϵ_m 23,600) and approximately 314 n.m. (inflection); $\nu_{\max}$ (CHCl₃) 3450, 1785, 1730, 1705 slight shoulder cm⁻¹; δ ppm (CDCl₃) 1.81 (½ CH₃, d, J 7Hz), 2.10 (½ CH₃, d, J 7Hz), 2.95—3.20 (2H, m), 3.35—3.65 (2H, m), 5.18 (s) plus 5.19 and 5.49 (ABq, J 14Hz) plus 5.1—5.5 (m) together 5H, 6.02 (½H, q, J 7Hz), 6.13 and 6.18 (1H, each s), 6.47 (½ H, q, J 7Hz), 7.48 and 7.62 (4H, each d, J 8Hz), 8.19 (4H, d, J 8Hz).

Example 11(b)
(5RS)-Sodium 2-(2-aminoethylthio)-6-ethylidenepenem-3-carboxylate



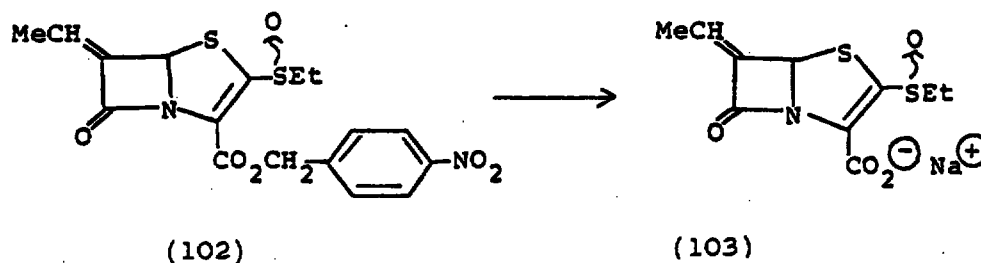
The 6-ethylidenepenem ester (100) (42 mg) was dissolved in a mixture of dioxan (8 ml), water (2 ml), and a 1% sodium bicarbonate solution (0.60 ml) and was hydrogenated over 5% palladium/charcoal catalyst (63 mg) at S.T.P. for 30 minutes. Further catalyst (42 mg) was added and the hydrogenation continued for 15 minutes. The mixture was filtered through Kieselguhr and worked up as for Example 1(b) to give the sodium salt (101) (1.6 mg), a 1:1 mixture of *E* and *Z* isomers, as an amorphous solid, δ ppm (D_2O) 1.85 ($\frac{1}{2} CH_3$, d, J 7Hz), 2.06 ($\frac{1}{2} CH_3$, d J 7Hz), 3.00–3.34 (4H, m), 6.22 (q, J 7Hz) and 6.24 (s) together 1H, 6.33 ($\frac{1}{2}H$, s), 6.58 ($\frac{1}{2}H$, q, J 7Hz).

Example 12(a)
(5*RS*)-*p*-Nitrobenzyl 6-Ethylidene-2-ethylsulphinylnem-3-carboxylate



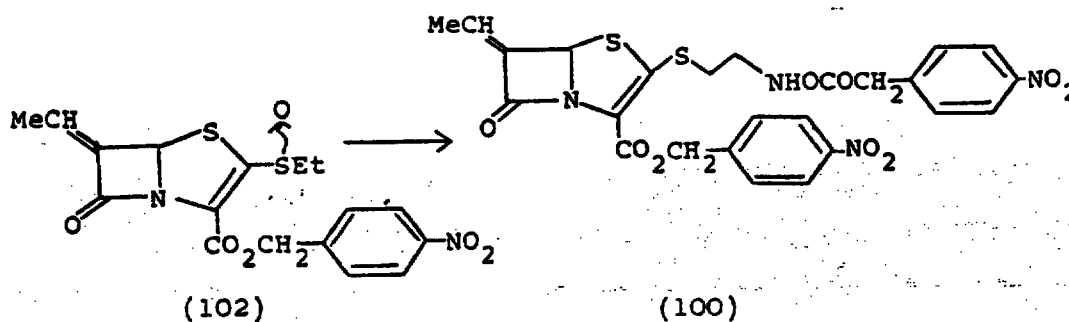
A solution of the penem sulfoxide (96) (60 mg) in dry methylene chloride (3 ml) was cooled to $-20^\circ C$ and treated, dropwise, over 3 minutes, with a solution of 1,8-diazabicyclo [5.4.0] undec-7-ene (27 mg) in dry methylene chloride (4.2 ml). The mixture was stirred at $-20^\circ C$ for 10 minutes and worked up as for Example 7 to give, after chromatography, the 6-alkylidenepenem sulfoxide ester (102) (30 mg) as an amorphous solid λ_{max} (EtOH) 213 (ϵ_m 22,380), 261 (13,570) and 356 n.m. (5,420); ν_{max} ($CHCl_3$) 1790 and 1705 cm^{-1} ; δ ppm ($CDCl_3$) 1.35–1.50 (3H, m), 1.87 and 1.89 ($\frac{1}{2} CH_3$), each d, J 7Hz), 2.16 and 2.18 ($\frac{1}{2} CH_3$, each d, J 7Hz), 3.03–3.24 (2H, m), 5.21–5.32 (1H, m), 5.41–5.52 (1H, m), 6.12 and 6.17 ($\frac{1}{2} H$, each dq, J 7 and 0.8Hz), 6.23 and 6.25 ($\frac{1}{2} H$, each broadened s), 6.38 ($\frac{1}{2} H$, broadened s), 6.57 and 6.61 ($\frac{1}{2} H$, each dq, J 7 and 1.2Hz), 7.60–7.68 (2H, m), 8.23–8.29 (2H, m). (Found: M^+ , 408.0410. $C_{17}H_{16}N_2O_6S$ requires M , 408.0447).

Example 12(b)
(5*RS*)-Sodium 6-Ethylidene-2-ethylsulphinylnem-3-carboxylate



The 6-ethylidenepenem sulfoxide ester (102) (26 mg) was dissolved in a mixture of dioxan (8 ml) and water (2 ml) and hydrogenated over 5% palladium/charcoal catalyst (39 mg) at S.T.P. for 40 minutes. A 1% sodium bicarbonate solution (0.54 ml) was added and the mixture was worked up as for Example 1(b) to give the sodium salt (103) (12.2 mg) as an amorphous solid, λ_{max} (H_2O) 222 (ϵ_m 13,490), 306 (3390) and approximately 335 n.m. (inflection); ν_{max} (KBr) 3700–3000, 1765, 1700, 1610, 1550 cm^{-1} .

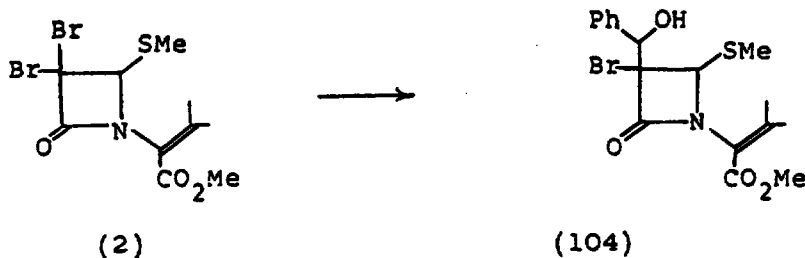
Example 13
(5*RS*)-*p*-Nitrobenzyl 6-Ethylidene-2-(2-*p*-nitrobenzoyloxycarbonylaminoethylthio)penem-3-carboxylate



2-*p*-Nitrobenzyloxycarbonylaminoethanethiol (5.6 mg) was dissolved in 0.1 N sodium hydroxide solution (0.22 ml), cooled in an ice-bath, and treated with a solution of the penem sulphoxide (9 mg) in methylene chloride (1 ml). The stirred, ice-bath cooled, mixture was treated, portionwise over 1 minute, with benzyldimethyl-*n*-hexadecylammonium chloride (8.7 mg). The mixture was stirred at ice-bath temperature for 10 minutes and worked up as for Example 11(a) to give the 6-ethylidenepenem ester (100) (5 mg), an approximately 1:1 mixture of *E* and *Z* isomers, as a gum (infra-red and n.m.r. data consistent with those obtained in Example 11a).

Preparation 14(a)

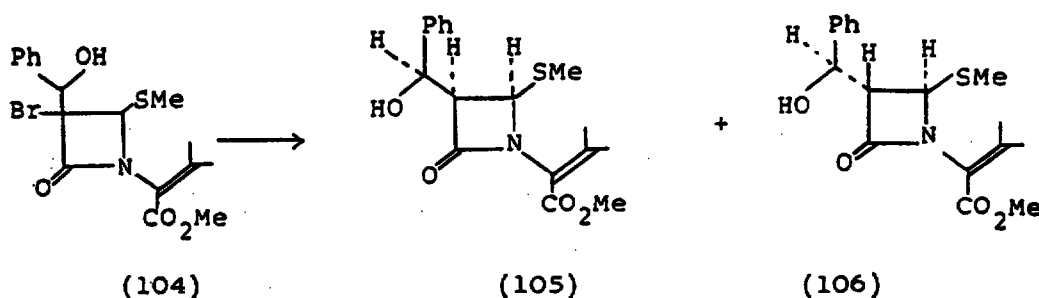
(3,4*RS*)-3-Bromo-3-[1-()-hydroxy-1-phenylmethyl]-1-(1-methoxycarbonyl-2-methylprop-1-enyl)-4-methylthioazetidin-2-one



A solution of methyl magnesium bromide (2M in diethyl ether, 17.1 ml) was added, dropwise over 15 minutes, to a stirred solution of the dibromosecopenicillanate (2) (12.0 g) in dry tetrahydrofuran (120 ml) at -76°C . After stirring at -76°C for a further 20 minutes a solution of redistilled benzaldehyde (3.96 g) in dry tetrahydrofuran (10 l) was added dropwise over 10 minutes. The mixture was stirred at -76°C for a further 10 minutes, treated with saturated ammonium chloride solution (60 ml) and allowed to attain room temperature. The mixture was diluted with ethyl acetate and the organic layer was separated. After washing with brine the dried (MgSO_4) organic layer was evaporated to give, after trituration with ether, the bromohydrin (104) (11.7 g as a solid, m.p. $111-112^{\circ}\text{C}$ (plates ex ethyl acetate/hexane) ν_{max} (CHCl_3) $3600-3100$, 1765 , 1720 cm^{-1} ; δ ppm (CDCl_3) 1.85 (3H, s), 2.02 (3H, s), 2.19 (3H, s), 2.88 (1H, d, J 3Hz), 3.49 (3H, s), 5.18 (1H, s), 5.25 (1H, d, J 3Hz), $7.2-7.7$ (5H, m). (Found: C, 49.5; H, 4.8; N, 3.6; S, 7.6. $\text{C}_{17}\text{H}_{20}\text{NBrO}_4\text{S}$ requires C, 49.3; H, 4.8; N, 3.4; S, 7.7%).

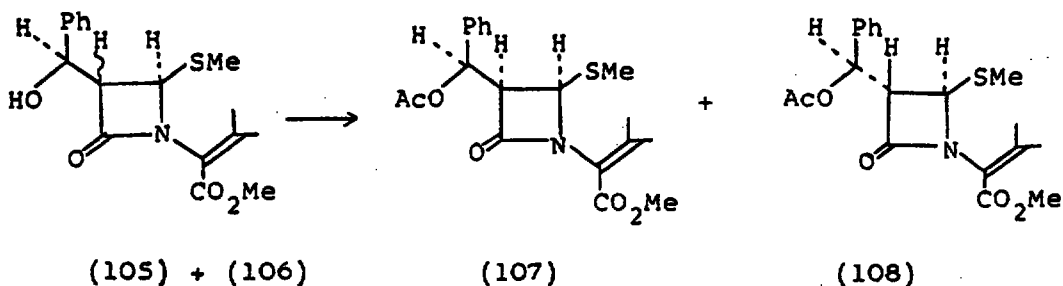
Preparation 14(b)

(3*RS*,4*RS*)-3-[1-(*RS*)-Hydroxy-1-phenylmethyl] and (3*RS*,4*SR*)-3-[1-(*SR*)-hydroxy-1-phenylmethyl]-1-(1-methoxycarbonyl-2-methylprop-1-enyl)-4-methylthioazetidin-2-ones



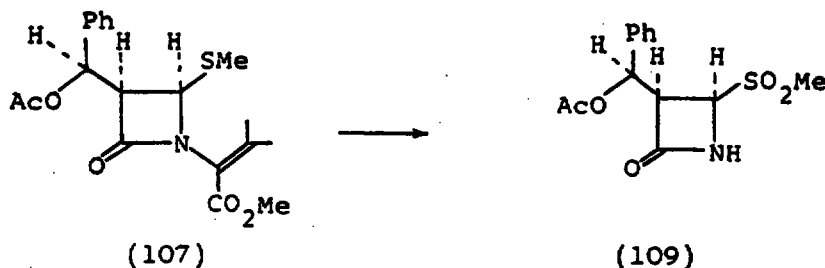
A stirred, ice-bath cooled, mixture of the bromohydrin (104) (11.7 g), tetrahydrofuran (120 ml) and aqueous ammonium acetate solution (1M, 24 ml) was treated with zinc powder (23.4 g). After stirring at ice-bath temperature for 30 minutes the mixture was treated with a further portion of zinc powder (2 g). The mixture was stirred at ice-bath temperature for a further 10 minutes and filtered through Kieselguhr, the residual zinc being washed with a little tetrahydrofuran. The combined filtrates were evaporated to low volume, diluted with ethyl acetate (300 ml) and washed successively with 1N hydrochloric acid (20 ml), brine (20 ml), saturated sodium bicarbonate solution (20 ml) and brine (3×20 ml). The dried (MgSO_4) organic layer was evaporated and chromatographed to give an approximately 1:1 mixture of the (3*RS*,4*RS*)-3-[1-(*RS*)-hydroxy-1-phenylmethyl] and (3*RS*,4*SR*)-3-[1-(*SR*)-hydroxy-1-phenylmethyl] azetidinones (105) and (106) (8.60 g) ν_{max} (CHCl_3) $3600-3200$, 1760 , 1725 cm^{-1} ; δ ppm (CDCl_3) 1.92 (3H, s), 2.01 (3H, s), 2.19 ($\frac{1}{2}\text{CH}_3$, s), 2.24 ($\frac{1}{2}\text{CH}_3$, s), $2.5-3.3$ (1H, broad signal, exch. D_2O), 3.49 ($\frac{1}{2}\text{H}$, dd, J 3 and $6\frac{1}{2}\text{Hz}$), 3.68 ($\frac{1}{2}\text{CH}_3$, s), 3.73 ($\frac{1}{2}\text{CH}_3$, s), 3.91 ($\frac{1}{2}\text{H}$, dd, J 5 and $7\frac{1}{2}\text{Hz}$), 4.82 ($\frac{1}{2}\text{H}$, d, J 3Hz), $4.95-5.35$ ($\frac{1}{2}\text{H}$, m, collapses on exch. D_2O to 5.07 (d, J $6\frac{1}{2}\text{Hz}$), 5.09 (d, J 5Hz), and 5.21 (d, J $7\frac{1}{2}\text{Hz}$), $7.2-7.6$ (5H, m).

Preparation 14(c)
 (3RS,4RS)-3-[1-(RS)-Acetoxy-1-phenylmethyl] and (3RS,4SR)-3-[1-(SR)-Acetoxy-1-phenylmethyl]-1-(1-methoxycarbonyl-2-methylprop-1-enyl)-4-methylthioazetidin-2-ones



Acetic anhydride (3.14 g) was added dropwise over 5 minutes to a stirred, ice-bath-cooled, mixture of the azetidinones (105) and (106) (a 1:1 mixture, 8.60 g), triethylamine (3.11 g) and 4-dimethylaminopyridine (282 mg) in dry methylene chloride (100 ml). The mixture was stirred at room temperature for 1 hour and washed successively with 5% citric acid (30 ml), brine (30 ml), saturated sodium bicarbonate solution (30 ml) and brine (3 x 30 ml). The dried (MgSO₄) organic layer was evaporated and chromatographed to give two fractions. The less polar product, the (3RS,4SR)-3-[1-(SR)-acetoxy-1-phenylmethyl]azetidinone (108) (4.20 g) was obtained as a solid, m.p. 102–104°C (cubes ex ethyl acetate/hexane); $\nu_{\max}$ (CHCl₃) 1760 and 1725 cm⁻¹; δ ppm (CDCl₃) 1.89 (3H, s), 1.99 (3H, s), 2.11 (3H, s), 2.19 (3H, s), 3.55–3.75 (4H, m), 4.82 (1H, d, J 2½ Hz), 6.20 (1H, d, J 5 Hz), 7.2–7.6 (5H, m). (Found: C, 60.6; H, 6.1; N, 3.6; S, 8.3. C₁₉H₂₃NO₅S requires C, 60.5; H, 6.1; N, 3.7; S, 8.5%). The more polar product, the (3RS,4RS)-3-[1-(RS)-acetoxy-1-phenylmethyl]azetidinone (107) (3.64 g) was obtained as a solid, m.p. 96–97°C (needles ex ethyl acetate/hexane); $\nu_{\max}$ (CHCl₃) 1765, and 1725 cm⁻¹; δ ppm (CDCl₃) 1.96 (3H, s), 2.05 and 2.07 (6H, each s), 2.21 (3H, s), 3.71 (3H, s), 4.03 (1H, dd, J 5 and 9 Hz), 5.13 (1H, d, J 5 Hz), 6.16 (1H, d, J 9 Hz), 7.2–7.6 (5H, m). (Found: C, 60.9; H, 6.1; N, 3.6; S, 8.4. C₁₉H₂₃NO₅S requires C, 60.5; H, 6.1; N, 3.7; S, 8.5%).

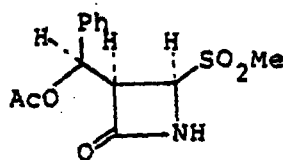
Preparation 14(d)
 (3RS,4RS)-3-[1-(RS)-Acetoxy-1-phenylmethyl]-4-methylsulphonyl-azetidin-2-one



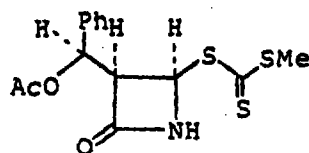
A solution of *m*-chloroperbenzoic acid (3.53 g) in ethyl acetate (20 ml) was added dropwise over 15 minutes to a stirred, ice-bath-cooled, solution of the *cis*-azetidinone (107) (3.50 g) in ethyl acetate (70 ml). The mixture was stirred at room temperature for 1 hour when a solid precipitated. The mixture was diluted with methylene chloride (100 ml) and the resulting solution was washed with saturated sodium bicarbonate solution (2 x 50 ml) and brine (3 x 50 ml). The dried (MgSO₄) organic layer was cooled to -20°C and treated with ozonised oxygen for 1 hour. The excess ozone was removed by passage of argon and the mixture evaporated. The residue was dissolved in a mixture of methanol (100 ml) and methylene chloride (400 ml) and treated with 2,6-lutidine (40 drops). The mixture was stirred at room temperature for 10 minutes and evaporated to give, after trituration with ether, the sulphone (109) (2.44 g), as a solid, m.p. 178–82°C (fine needles ex acetone/ether); $\nu_{\max}$ (Nujol) 3370, 1795, 1730 cm⁻¹; δ ppm [(CD₃)₂CO] 3.03 (3H, s), 4.38 (1H, dd, J 5 and 12 Hz with further fine coupling which collapsed on exch. D₂O), 5.10 (1H, d, J 5 Hz), 6.43 (1H, d, J 12 Hz), 7.2–7.5 (5H, m), 8.1–8.4 (1H, broad signal, exch. D₂O). (Found: C, 52.7; H, 5.1; N, 4.6; S, 10.7. C₁₃H₁₅NO₅S requires C, 52.5; H, 5.1; N, 4.7; S, 10.8%).

Preparation 14(e)

(3RS,4SR)-3-[1-(RS)-Acetoxy-1-phenylmethyl]-4-ethylthiothiocarbonylthioazetidin-2-one



(109)

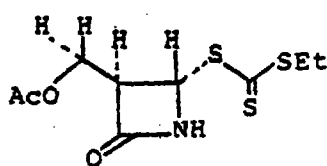


(110)

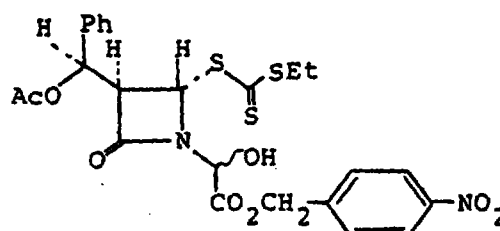
Potassium ethyltrithiocarbonate (1.50 g) was added to an ice-bath cooled mixture of the sulphone (109) (2.30 g), methylene chloride (200 ml) and water (40 ml). The mixture was stirred at room temperature for 1½ hours and worked up as for preparation 1(f) to give the trithiocarbonate (110) (2.01 g) as a yellow gum, $v_{\max}$ (CHCl₃) 3410, 1785, 1750 shoulder cm^{-1} ; δ ppm (CDCl₃) 1.34 (3H, t, J 7Hz), 2.10 (3H, s), 3.32 (2H, q, J 7Hz), 3.66 (1H, dd, J 2 and 5Hz), 5.65 (1H, d, J 2Hz), 6.19 (1H, d, J 5Hz), 6.62 br (1H, s, exch. D₂O), 7.32 (5H, s).

Preparation 14(f)

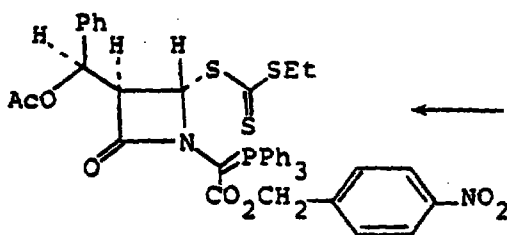
(3RS,4SR)-3-[1-(RS)-Acetoxy-1-phenylmethyl]-4-ethylthiothiocarbonylthio-1-(1-p-nitrobenzyloxycarbonyl-1-triphenylphosphoranylideneethyl)azetidin-2-one



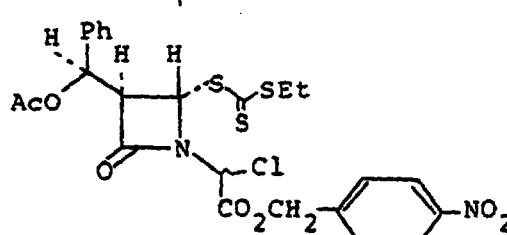
(110)



(111)



(113)



(112)

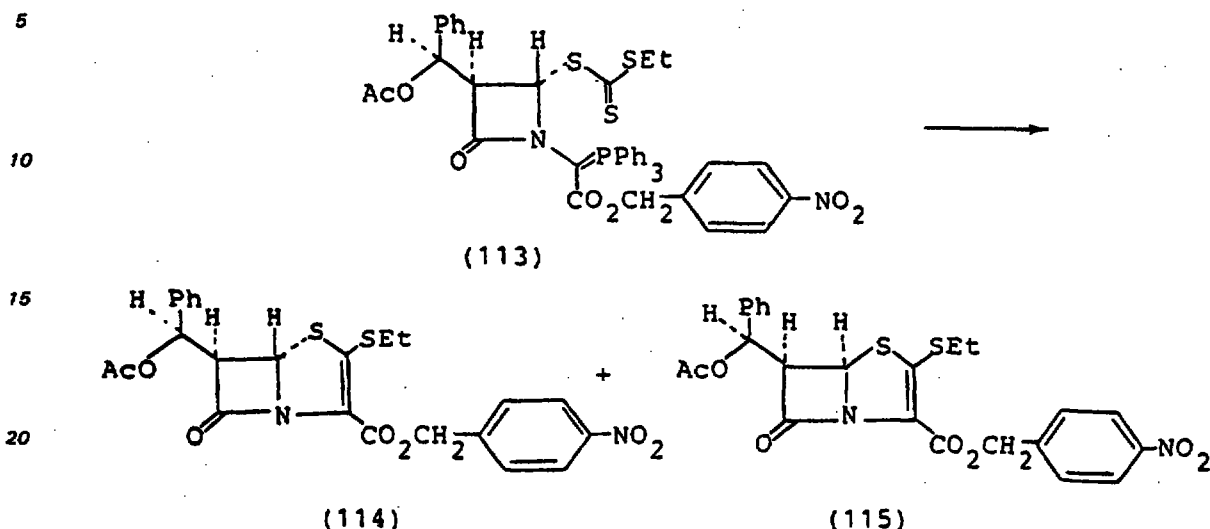
A mixture of the trithiocarbonate (110) (2.01 g) and *p*-nitrobenzyl glyoxylate monohydrate (1.42 g) was heated in refluxing benzene (100 ml) in a Dean and Stark apparatus containing molecular sieves (type 4A). After 1 hour the mixture was cooled and treated with triethylamine (57 mg). The mixture was kept at room temperature for 15 minutes and evaporated to give the crude hydroxyester (111), $v_{\max}$ (CHCl₃) 3700—3100, 1785, 1755 cm^{-1} .

A solution of thionyl chloride (1.01 g) in dry tetrahydrofuran (5 ml) was added, dropwise over 5 minutes, to a stirred solution of the crude hydroxyester (111) and 2,6-lutidine (910 mg) in dry tetrahydrofuran (60 ml) at -10°C . The mixture was stirred at -10°C for 10 minutes, filtered and evaporated. The residue was re-evaporated from dry toluene (2×10 ml) to give the crude chloroester (112) as a gum, $v_{\max}$ (CHCl₃) 1795, 1760 cm^{-1} .

A mixture containing the crude chloroester (112), triphenylphosphine (2.97 g) and 2,6-lutidine (727 mg) in dry dioxan (60 ml) was stirred at 60°C under dry argon for 36 hours. The mixture was worked up as for preparation 1(i) to give, after chromatography, the phosphorane (113) (3.17 g) as an amorphous solid, $v_{\max}$ (CHCl₃) 1765, 1620, 1610 shoulder cm^{-1} .

Preparation 14(g)

(5RS,6SR,8SR)- and (5RS,6RS,8RS)-p-Nitrobenzyl-6-(1-Acetoxy-1-phenylmethyl)-2-ethylthiopenem-3-carboxylate



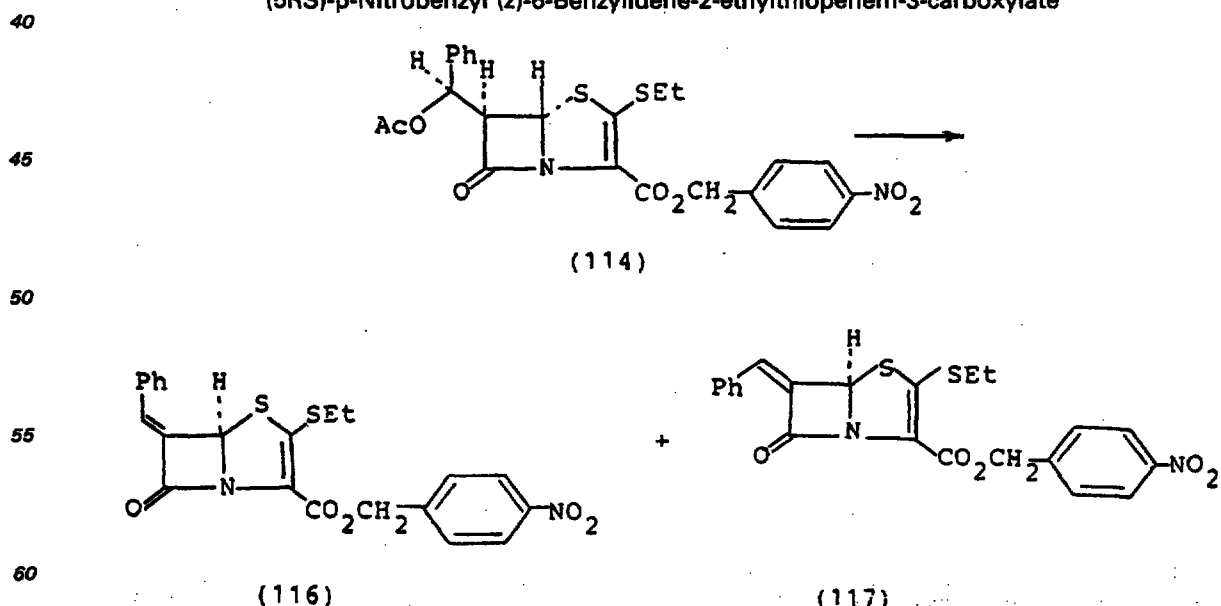
25 A solution of the phosphorane (113) (2.97 g) in xylene (1500 ml) was refluxed under argon for 8½ hours. The mixture was evaporated and chromatographed to give two products. The less polar product, the (5RS,6RS,8RS) penem ester (115) (195 mg), was obtained as a pale yellow solid, m.p. 176–178°C (plates ex ethyl acetate/hexane); λ_{max} (EtOH) 260 (ϵ_m 15,860) and 335 n.m. (10,650); ν_{max} (CHCl₃) 1795, 1745, 1690 cm⁻¹; δ ppm (CDCl₃) 1.39 (3H, t, J 7Hz), 2.06 (3H, s), 2.9–3.2 (2H, m), 4.42 (1H, dd, J 4 and 10Hz), 5.12 and 5.40 (2H, ABq, J 14Hz), 5.78 (1H, d, J 4Hz), 6.11 (1H, d, J 10Hz), 7.38 (5H, s), 7.52 (2H, d, J 9Hz), 8.14 (2H, d, J 9Hz). (Found: C, 56.1; H, 4.4; N, 5.4. C₂₄H₂₂N₂O₇S₂ requires C, 56.0; H, 4.3; N, 5.4%).

30 The more polar product, the (5RS,6SR,8SR) penem ester (114) (740 mg), was obtained as pale yellow solid, m.p. 157–159°C (plates ex ethyl acetate/hexane; λ_{max} (EtOH) 261 (ϵ_m 15,930) and 339 n.m. (9840); ν_{max} (CHCl₃) 1795, 1740, 1690 cm⁻¹; δ ppm (CDCl₃) 1.34 (3H, t, J 7Hz), 2.10 (3H, s), 2.78–3.12 (2H, m), 4.18 (1H, dd, J 1.7 and 6Hz), 5.19 and 5.42 (2H, ABq, J 14Hz), 5.64 (1H, d, J 1.7Hz), 6.18 (1H, d, J 6Hz), 7.33 (5H, s), 7.58 (2H, d, J 9Hz), 8.19 (2H, d, J 9Hz). (Found: C, 56.3; H, 4.4; N, 5.5. C₂₄H₂₂N₂O₇S₂ requires C, 56.0; H, 4.3; N, 5.4%).

35

Example 14(a)

(5RS)-p-Nitrobenzyl (z)-6-Benzylidene-2-ethylthiopenem-3-carboxylate

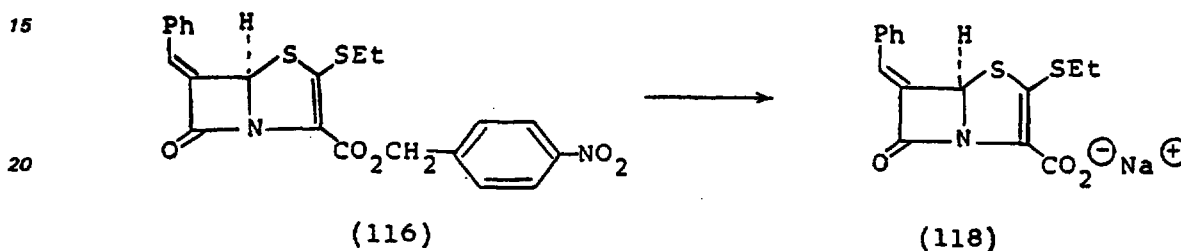


A solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (44 mg) in dry methylene chloride (1 ml) was added, dropwise over 1 minute, to a stirred solution of the *trans*-penem ester (114) (100 mg) in dry methylene chloride (4 ml) at -40°C. After stirring at -40°C for 10 minutes the mixture was diluted with methylene

65

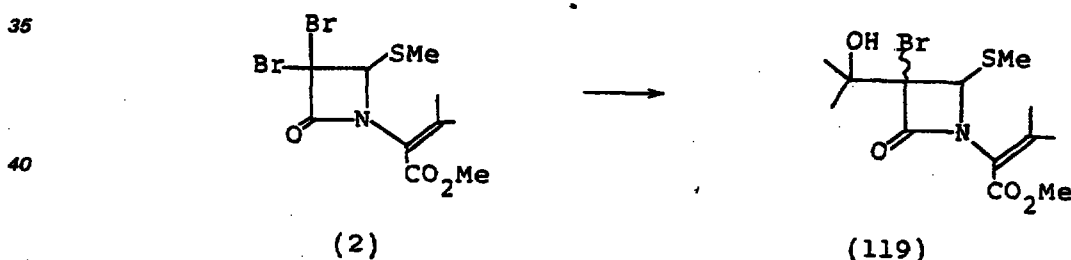
chloride (10 ml) and washed with 5% citric acid (2 ml), brine (2 ml), saturated sodium bicarbonate solution (2 ml) and brine (3 × 2 ml). The dried (MgSO₄) organic layer was evaporated and chromatographed to give two fractions. The less polar product, the (E)-benzylidenepenem ester (117) (12 mg) was obtained as a yellow solid, $\nu_{\max}$ (CHCl₃) 1770, 1690 cm⁻¹; δ ppm (CDCl₃) 1.37 (3H, t, J 7Hz), 2.73–3.25 (2H, m), 5.23 and 5.51 (2H, ABq, J 14Hz), 6.29 (1H, s), 6.61 (1H, s), 7.3–7.5 (3H, m), 7.67 (2H, d, J 9Hz) 7.85–8.05 (2H, m), 8.23 (2H, d, J 9Hz). The more polar product, the (Z)-benzylidenepenem ester (116) (64 mg) was obtained as a yellow solid, m.p. 178–179°C (fine needles ex ethyl acetate/hexane); $\lambda_{\max}$ (EtOH) 286 (ϵ_m 31,450) and approximately 328 nm (inflection); $\nu_{\max}$ (CHCl₃) 1780, 1690 cm⁻¹; δ ppm (CDCl₃) 1.35 (3H, t, J 7Hz), 2.65–3.25 (2H, m), 5.22 and 5.49 (2H, ABq, J 14Hz), 6.49 (1H, s), 7.12 (1H, s), 7.2–7.5 (5H, m), 7.65 (2H, d, J 9Hz), 8.20 (2H, d, J 9Hz). (Found: M⁺ 454.0686. C₂₂H₁₈N₂O₅S₂ requires 454.0654).

Example 14(b)
(5RS)-Sodium (Z)-6-Benzylidene-2-ethylthiopenem-3-carboxylate



The (Z)-benzylidenepenem ester (116) (50 mg) was dissolved in a mixture of dioxan (8 ml) and water (25 ml) and hydrogenated over 5% palladium/charcoal catalyst at S.T.P. for 40 minutes. Further catalyst (50 mg) was added and the hydrogenation continued for 40 minutes. A 1% sodium bicarbonate solution (0.93 ml) was added and the mixture worked up as for Example 1(b) to give the sodium salt (118) (12.6 mg) as a yellow-orange amorphous solid, $\lambda_{\max}$ (H₂O) 291 (ϵ_m 21,870) and 380 n.m. (2.140); δ ppm (D₂O) 1.27 (3H, t J 7Hz), 2.68–2.98 (2H, m), 6.49 (1H, s), 7.10 (1H, s), 7.32–7.56 (5H, m).

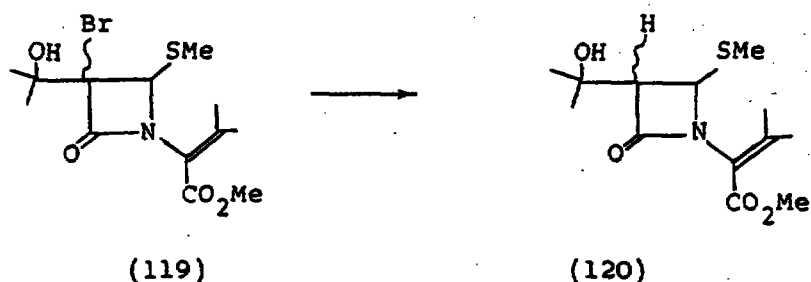
Preparation 15(a)
(3,4RS)-3-Bromo-3(2-hydroxyprop-2-yl)-1(1-methoxycarbonyl-2-methylprop-1-enyl)-4-methylthioazetidin-2-one



45 A solution of methyl magnesium bromide (2M in diethyl ether, 20 ml) was added, dropwise over five minutes, to a stirred solution of the dibromosecopenicillanate (2) (13.6 g) in dry tetrahydrofuran (250 ml) at -76°C. After stirring at -76°C for further ten minutes a mixture of dry acetone (5.2 ml) and tetrahydrofuran (10 ml) was added dropwise over five minutes. The mixture was stirred at -76°C for a further twenty minutes, treated with a saturated aqueous solution of ammonium chloride (10 ml) and allowed to attain room temperature. Excess of tetrahydrofuran was evaporated *in vacuo* and the residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried (MgSO₄) and evaporated to give a pale cream crystalline solid. This was recrystallised from ethyl acetate/petroleum ether to give colourless rhombs, m.p. 130–131.5°C (8.0 g). (Chromatography of the mother liquors gave a further portion (1.2 g) of product). $\nu_{\max}$ (CHCl₃) 3550, 3400 (b), 1760, 1720, 1625 (w) cm⁻¹; δ ppm (CDCl₃) 1.45 (3H, s) 1.57 (3H, s) 2.04 (3H, s) 2.16 (3H, s) 2.26 (4H, s, 1H, exchangeable with D₂O), 3.77 (3H, s), 5.46 (1H, s). (Found: C, 42.5; H, 5.5; N, 3.8; S, 8.7; Br, 21.9. C₁₃H₂₀NO₄SBr requires C, 42.6; H, 5.5; N, 3.8; S, 8.7; Br, 21.9%).

Preparation 15(b)

(3RS,4RS) and (3RS,4SR)-3(2-Hydroxyprop-2-yl)-1-(1-methoxycarbonyl-2-methylprop-1-enyl)-4-methylthioazetidin-2-one



The bromohydrin (119) (7 g) in tetrahydrofuran (100 ml) at room temperature was stirred vigorously with zinc dust (14 g) and N aqueous ammonium acetate solution (14 ml) for 30 minutes. The mixture was filtered and after evaporation *in vacuo* of most of the solvent the residue was partitioned between ethyl acetate and water. The organic layer was washed with N/10 hydrochloric acid, sodium bicarbonate solution then brine. The dried (MgSO_4) organic layer was evaporated and the product was chromatographed on silica gel eluting with ethyl acetate/petroleum ether mixtures to give a 2:1 mixture of the *trans* and *cis*-hydroxyisopropylazetidinones (120) as a gum (5.2 g) ν_{max} 3600, 3500 (b), 1750, 1720, 1630 cm^{-1} ; δ ppm (CDCl_3) 1.35 (s), 1.42 (s), 1.46 (s), 1.50 (s) (together 6H), 2.00 (s), 2.04 (s), 2.12 (s), 2.15 (s), 2.22 (s), 2.26 (s) (together 9H) overlaying ($\frac{1}{2}$ H, exchangeable with D_2O) 2.71 ($\frac{1}{2}$ H, exchangeable with D_2O) 3.16 ($\frac{1}{2}$ H, d, J 3Hz), 3.54 ($\frac{1}{2}$ H, d, J 5Hz) 3.76 (3H, s), 5.04 (d, J 3Hz) and 5.07 (d, J 5Hz) (together 1H).

Preparation 15(c)

(3RS,4RS)-3(2-Hydroxyprop-2-yl)-4-methylsulphonylazetidin-2-one

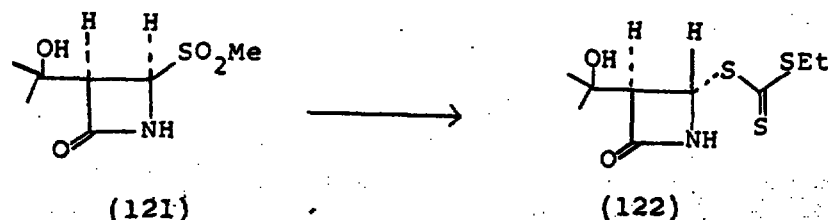


A solution of *m*-chloroperbenzoic acid (6.4 g) in dichloromethane (50 ml) was added over five minutes to an ice-cooled solution of azetidinone (120) (*cis/trans* mixture) (4.55 g) in dichloromethane (50 ml). The mixture was kept at room temperature for 30 minutes and was then washed twice with saturated solution, twice with dilute sodium bicarbonate solution, then dried (MgSO_4).

The solution was then diluted to 100 ml with dichloromethane, cooled to -60°C and ozonised oxygen was passed for 2 h with the temperature gradually rising to -10°C . Argon was passed through the solution for five minutes then methanol (100 ml) and 2,6-lutidine (10 drops) were added. After one hour the mixture was concentrated to low volume and white crystals were filtered off (1.63 g) white rhombs $205-208^\circ$ (from ethyl acetate) ν_{max} (CHCl_3) 3500, 3300 (b), 1785 cm^{-1} ; δ ppm (CD_3COCD_3) 1.52 (6H, s), 3.18 (3H, s), 4.04 (1H, dd, J 6, 1Hz) 4.22 (1H, s, exchangeable with D_2O) 5.14 (1H, d, J 6Hz) 8.0-8.5 (1H, m, exchangeable with D_2O) (Found: C, 40.5; H, 6.3; N, 6.6; S, 15.1. $\text{C}_7\text{H}_{13}\text{NO}_4\text{S}$ requires C, 40.6; H, 6.2; N, 6.8; S, 15.5%).

Preparation 15(d)

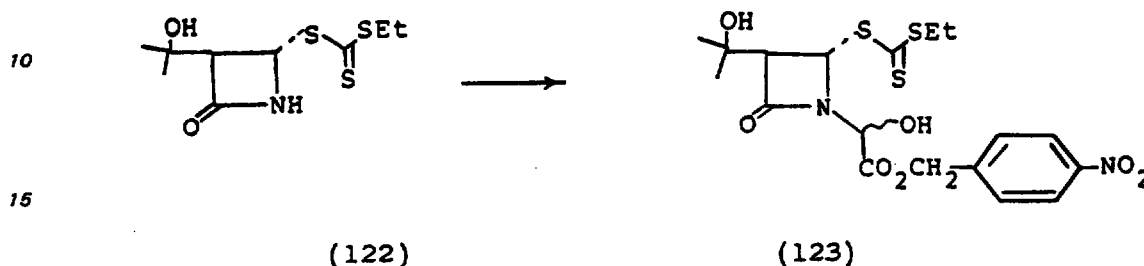
(3RS,4SR)-3(2-Hydroxyprop-2-yl)-4-ethylthiothiocarbonylthioazetidin-2-one



The sulphone (121) (1.38 g) in dichloromethane (15 ml) was vigorously stirred with a solution of potassium ethyltrithiocarbonate (1.25 g) in water (15 ml) at room temperature for 20 minutes. The solvent layer was separated, washed with water, dried (MgSO_4) and evaporated to give the trithiocarbonate (122)

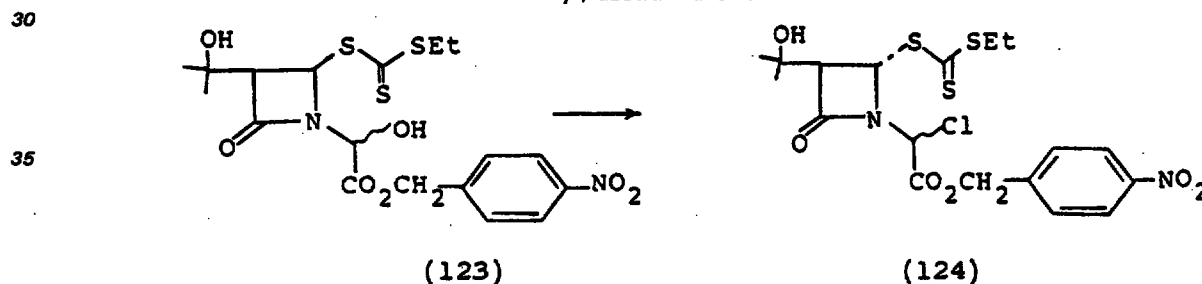
(1.25 g) as a yellow solid; $\nu_{\max}$ (CHCl_3) 3600, 3420, 1770, cm^{-1} ; δ ppm (CDCl_3) 1.29 (s), 1.36 (t, J 7Hz) 1.43 (s), together 9H, 2.00 (1H, s, exchangeable with D_2O) 3.22 (d, J 2Hz) 3.55 (q, J 7Hz) together 3H, 5.62 (1H, d, J 2Hz) 6.64 (1H, b.s., exchangeable with D_2O). (Found: M, 265.0269. $\text{C}_9\text{H}_{15}\text{NO}_2\text{S}_3$ requires M, 265.0265).

5 Preparation 15(e)
(3RS,4SR)-4-Ethylthiothiocarbonylthio-1-(1-hydroxy-1-p-nitrobenzyloxycarbonylmethyl)-3(2-hydroxyprop-2-yl)azetidin-2-one



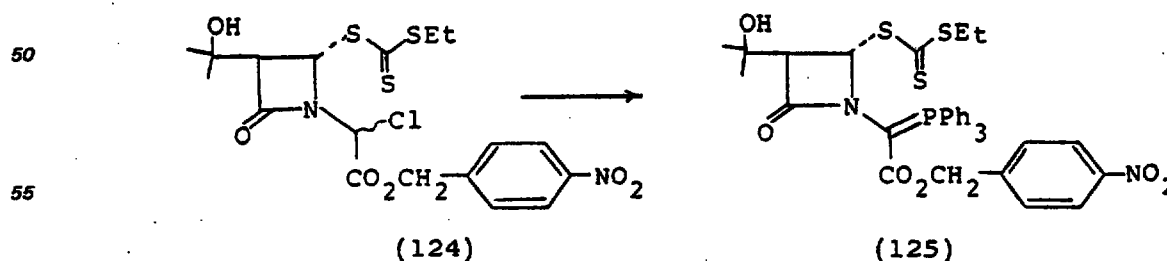
The trithiocarbonate (122) (1.14 g) and *p*-nitrobenzyl glyoxylate monohydrate (1.95 g) were refluxed in benzene (100 ml) for three hours with constant removal of water. The mixture was then evaporated and chromatographed on silica gel eluting with ethyl acetate/petroleum ether mixtures to give the hydroxy-ester (123) (1.6 g) as a mixture of stereoisomers — a gum, $\nu_{\max}$ (CHCl_3) 3600—3200, 1775, 1760 cm^{-1} ; δ ppm (CDCl_3) 1.40 (s), 1.47 (t, J 7Hz) 1.56 (s) (together 9H), 2.9 (1H, b.s., exchangeable with D_2O) 3.5 (q, J 7Hz) overlaying 3.5 (d, J 2Hz) (together 3H), 4.85 (1H, d, J 8Hz exchangeable with D_2O) 5.4 and 5.5 (2H, 2s) 5.77 (1H, d, J 8Hz) 6.3, 6.37 (1H, 2d, J 2Hz) 7.7 and 8.3 (4H, 2d, J 8Hz).

Preparation 15(f)
(3RS,4SR)-1-(1-Chloro-1-p-nitrobenzyloxycarbonylmethyl)-4-ethylthiothiocarbonylthio-3-(2-hydroxyprop-2-yl)-azetidin-2-one



The hydroxy-ester (123) (mixed stereoisomers) (464 mg) in dry tetrahydrofuran (20 ml) at -15°C was treated with 2,6-lutidine (115 mg) followed by thionyl chloride (0.08 ml) for 10 minutes. The mixture was filtered and the filtrate was evaporated to give the chloro-ester (124) as a yellow gum.

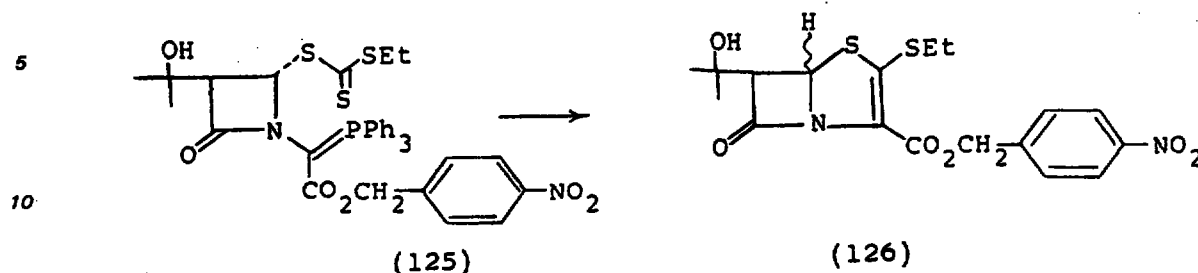
Preparation 15(g)
(3RS,4SR)-4-Ethylthiothiocarbonylthio-3-(2-hydroxyprop-2-yl)-1-(1-p-nitrobenzyloxycarbonyl-1-triphenylphosphoranylidene)methylazetidin-2-one



The total chloro-ester (124) from preparation 15(f) in dioxan (40 ml) was heated with triphenylphosphine (510 mg) and lutidine (45 mg) at 60° for 24 hours. The mixture was then evaporated *in vacuo* and the residue partitioned between ethyl acetate and dilute aqueous citric acid. The organic layer was then separated and washed with water, aqueous sodium bicarbonate then brine. The solution was dried (MgSO_4) and evaporated then the residual gum was chromatographed on silica gel eluting with ethyl acetate/petroleum ether mixtures to give the phosphorane (125) (250 mg) as a yellow amorphous solid, $\nu_{\max}$ (CHCl_3) 3600, 3450 (b), 1755, 1620 cm^{-1} .

Preparation 15(h)

(5RS,6SR) and (5RS,6RS)-p-Nitrobenzyl 2-Ethylthio-6-(2-hydroxyprop-2-yl)penem-3-carboxylate



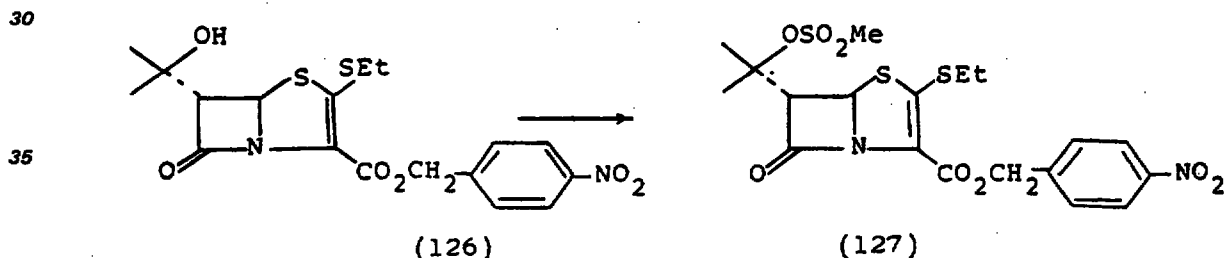
15 The phosphorane (125) (1.05 g) was refluxed in dry xylene (300 ml) for 12 hours, finally evaporating to dryness *in vacuo*. The residue was chromatographed on silica gel eluting with ethyl acetate/petroleum ether mixtures giving a fraction consisting of a mixture of *cis* and *trans* isomers of the penem (126) and a less mobile fraction of unchanged phosphorane which was recovered (143 mg). Rechromatography of the penem fraction on silica gel eluting with diethyl ether/dichloromethane 1:9 gave the pure *trans* isomer of (126) (274 mg) preceded by a 1:1 mixture of *cis* and *trans* penems (126) (20 mg). The pure *trans* isomer was an off-white solid, needles m.p. 156°. $\lambda_{\max}$ (EtOH) 340 n.m. (ϵ_m 10,680) 261 n.m. (16,430) $\nu_{\max}$ 3600, 3500 (b) 1790, 1690, 1610 cm^{-1} ; δ ppm (CDCl_3) 1.34 (s) 1.35 (t, J 7Hz) 1.43 (s) (together 9H) 1.94 (1H, s, exchangeable with D_2O) 2.96 (2H, q, J 7Hz with fine coupling) 3.76 (1H, d, J 1½ Hz), 5.18 and 5.48 (2H, ABq, J 14Hz) 5.64 (1H, d, J 1½ Hz) 7.60 and 8.19 (4H, 2d, J 8Hz). (Found: M^+ , 424.0740, $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_6\text{S}_2$ requires M, 424.0718). The *cis/trans* mixture showed the following n.m.r. signals characteristic of the *cis* compound: δ ppm (CDCl_3) 2.34 (s, exchangeable with D_2O) 4.01 (d, J 4Hz), 5.74 (d, J 4Hz).

20

25

Example 15(a)

(5RS,6SR)-p-Nitrobenzyl 2-Ethylthio-6-(2-methylsulphoxyprop-2-yl)-penem-3-carboxylate

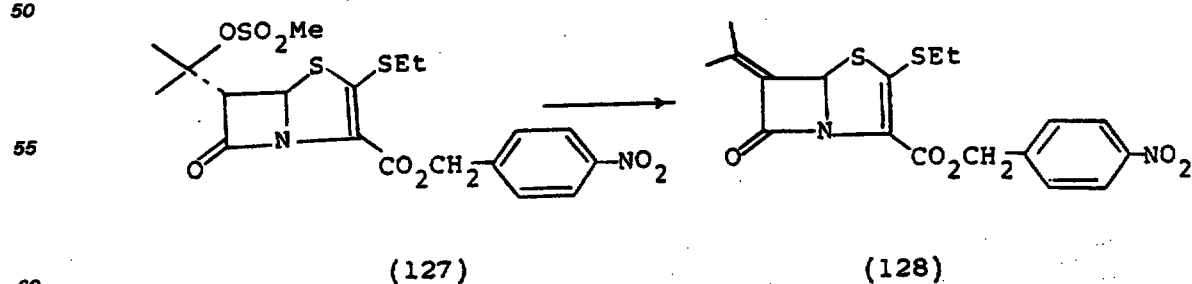


40 To a solution of the hydroxy-penem (126) (69 mg) in dry tetrahydrofuran at -76°C under Ar was added a solution prepared by adding butyl lithium solution in n-hexane (1.6 N, 0.2 ml) to diisopropylamine (20 mg) in tetrahydrofuran (5 ml) at -76°C . After 4 minutes methylsulphonyl chloride (3 drops) was added and stirring was continued at low temperature for five minutes then the mixture was allowed to reach room temperature. Chromatography on silica gel eluting with ethyl acetate/petroleum ether mixtures gave first mesyloxypenem (127) (26 mg) as a gum, $\nu_{\max}$ (CHCl_3) 1790, 1697 cm^{-1} followed by some recovered hydroxypenem (126) (21 mg) (identified by t.l.c. and infra-red spectrum).

45

Example 15(b)

(5RS) p-Nitrobenzyl 2-Ethylthio-6-isopropylidenepenem-3-carboxylate

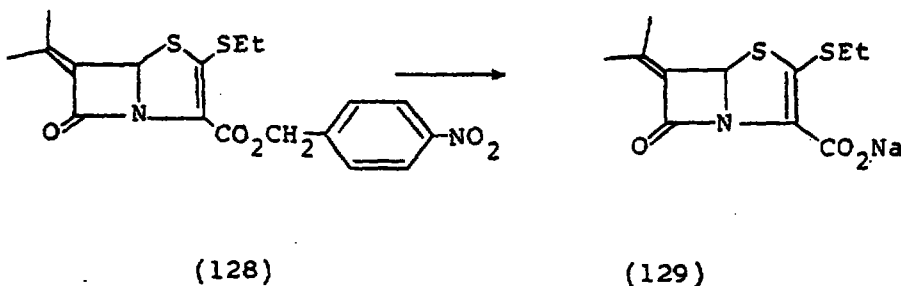


The mesylate (127) (26 mg) in chloroform (2 ml) was treated at room temperature with 1,8-diazabicyclo [5.4.0]undec-7-ene (1 drop). After 10 minutes the mixture was diluted with ethyl acetate, washed with dilute aqueous citric acid then with brine, dried (MgSO_4) and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with ethyl acetate/n-hexane 3:7 mixture. The product zone

65

crystallised on standing (8 mg) m.p. 175—176° from ethyl acetate/n-hexane. $\lambda_{\max}$ (EtOH) 322 nm (ϵ_m 8,100) 256 (16,070), $\nu_{\max}$ (KBr) 1762, 1720, 1675, 1600 cm^{-1} ; δ ppm (CDCl_3) 1.38 (3H, t, J 7.4Hz) 1.83 (3H, s) 2.14 (3H, s) 2.96 (2H, q, J 7.4Hz) 5.22 and 5.50 (2H, ABq, J 14Hz) 6.15 (1H, s) 7.66 and 8.24 (4H, 2d, J 9Hz). (Found: M^+ : 406.0634, $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_5\text{S}_2$ requires M , 406.0657).

Example 15(c)
(5RS)-Sodium 2-Ethylthio-6-isopropylidenepenem-3-carboxylate



A solution of isopropylidene-penem ester (128) (5 mg) in dioxan (4 ml) and water (1 ml) was hydrogenated at atmospheric pressure over 5% palladium on carbon catalyst (5 mg) for 30 minutes. A further portion of catalyst (5 mg) was added and hydrogenation was continued at room temperature for 30 minutes longer. The mixture was filtered through Kieselguhr. Sodium bicarbonate (1.2 mg) in water (0.12 ml) was then added and the mixture was evaporated *in vacuo*. The residue was worked up as in Example 1(b) to give the sodium salt (129) as an amorphous solid (2 mg) $\lambda_{\max}$ (H_2O) 290 n.m.

Biological Data

1. Antibacterial activity

The antibacterial activity of a number of compounds described in the foregoing Examples against a number of organisms is shown in tables 1 and 10.

2. β -Lactamase inhibitory activity

The β -lactamase inhibitory activity of the compound of Example 1 is demonstrated by the synergistic properties shown in tables 2—5. These tables show the MIC values of amoxycillin, cephaloridine, ticarcillin and apalcillin against a number of β -lactamase producing organisms. In each case, the addition of the compound of Example 1 shows a marked decrease in the MIC.

Similar data for the compound of Example 2 are given in tables 6 to 8.

Data demonstrating the β -lactamase inhibitory activity of further compounds of the Examples in combination with amoxycillin are given in tables 9 and 11.

Table 1 Broth MIC Values (g/ml) for 6-Ethylidenepipem. Compound number - see Examples

Organism	(27)	(29)	(40)	(49)	(59)	(76)	(99)	(101)	(103)
<i>C. freundii</i> E 8	31	62	125	125	25	100	100	100	100
<i>E. cloacae</i> N 1	31	31	125	62	25	100	25	100	100
<i>E. coli</i> O111	31	31	62	125	25	100	100	100	100
<i>E. coli</i> JT 39 R ⁺	16	31	62	62	12.5	100	50	100	100
<i>E. coli</i> ESS	16	2	16	1	3.1	6.2	3.1	12.5	100
<i>K. aerogenes</i> A	16	16	62	31	12.5	100	50	100	100
<i>P. mirabilis</i> 977	31	125	250	62	25	100	100	100	100
<i>P. morganii</i> I 580	31	31	250	31	25	100	50	100	100
<i>P. rettgeri</i> WM 16	62	62	125	62	25	100	25	100	100
<i>P. vulgaris</i> WO 91	31	62	250	62	25	100	50	100	100
<i>P. aeruginosa</i> A	500	500	250	250	100	100	100	100	100
<i>S. typhimurium</i> CT 10	16	62	62	62	12.5	100	50	100	100
<i>S. marcescens</i> US 20	62	62	250	125	25	100	50	100	100
<i>S. sonnei</i> MB 11967	31	62	62	62	25	100	50	100	100
<i>B. subtilis</i> A	-	2	31	1	3.1	25	6.2	12.5	25
<i>S. aureus</i> Oxford	2	2	8	1	3.1	12.5	12.5	3.1	50
<i>S. aureus</i> Russell	4	-	16	2	3.1	6.2	6.2	3.1	100
<i>S. aureus</i> 1517	16	16	125	62	100	50	100	100	100
<i>S. faecalis</i> I	250	250	250	125	100	100	100	100	100
<i>S. pneumoniae</i> CN 33	2	1	31	0.2	0.2	-	-	-	25
<i>S. pyogenes</i> CN 10	4	4	8	-	0.1	-	1.6	3.1	12.5

Table 2 Activity of Amoxycillin Alone or in Combination with Compound of Example 1

MIC ($\mu\text{g/ml}$)

Organism	Amoxycillin Alone	Amoxycillin + compound of Example 1	
		(5.0 $\mu\text{g/ml}$)	(1.0 $\mu\text{g/ml}$)
<i>E. coli</i> 0111	10	5.0	5.0
<i>E. coli</i> JT410 C ₊	250	250	500
<i>E. coli</i> JT39R ₊	>1000	5.0	25
<i>E. coli</i> JT20R ₊	>1000	25	100
<i>K. aerogenes</i> A	100	0.5	1.0
<i>K. aerogenes</i> 1112	500	2.5	2.5
<i>K. aerogenes</i> Ba95R ₊	>1000	50	250
<i>P. mirabilis</i> 977	2.5	2.5	2.5
<i>P. mirabilis</i> 889	>1000	100	500
<i>P. morganii</i> 1580	1000	50	250
<i>P. rettgeri</i> WM16	1000	50	250
<i>P. vulgaris</i> W091	>1000	1.0	2.5
<i>E. cloacae</i> N1	500	25	50
<i>S. marcescens</i> US20	50	50	50
<i>C. freundii</i> E8	250	100	250
<i>C. freundii</i> B10R ₊	>1000	500	>1000
<i>P. aeruginosa</i> A	>1000	>1000	>1000
<i>P. aeruginosa</i> Dalglish	>1000	>1000	>1000
<i>S. aureus</i> Russell	100	$\leq 0.2^*$	0.5
<i>S. aureus</i> MB9	25	$\leq 0.2^*$	0.5

* Compound alone inhibitory

Table 3 Activity of Cephaloridine alone or in Combination with compound of Example 1

MIC ($\mu\text{g/ml}$)

Organisms	Cephaloridine Alone	Cephaloridine + Compound of Example 1	
		(5.0 $\mu\text{g/ml}$)	(1.0 $\mu\text{g/ml}$)
E. coli O111	2.5	2.5	2.5
E. coli JT41OC ₊	50	50	50
E. coli JT39R ₊	5.0	2.5	2.5
E. coli JT20R ₊	25	2.5	2.5
K. aerogenes A	2.5	1.0	2.5
K. aerogenes 1112	5.0	2.5	2.5
K. aerogenes Ba95R ₊	100	2.5	5.0
P. mirabilis 977	10	10	10
P. mirabilis 889	250	5.0	5.0
P. morganii 1580	1000	10	100
P. rettgeri WM16	1000	5.0	100
P. vulgaris W091	1000	5.0	5.0
E. cloacae N1	500	2.5	5.0
S. marcescens US20	1000	25	100
C. freundii E8	500	25	100
C. freundii B10R ₊	>1000	100	250
P. aeruginosa A	>1000	>1000	>1000
P. aeruginosa Dalglish	>1000	>1000	>1000
S. aureus Russell	0.5	<0.2*	<0.2
S. aureus MB9	<0.2	<0.2*	<0.2

Table 4 Activity of Ticarcillin alone or in Combination with Compound of Example 1

MIC ($\mu\text{g/ml}$)

Organism	Ticarcillin Alone	Ticarcillin + Compound of Example 1	
		(5.0 $\mu\text{g/ml}$)	(1.0 $\mu\text{g/ml}$)
<i>E. coli</i> O111	5.0	5.0	5.0
<i>E. coli</i> JT410 C ₊	10	10	10
<i>E. coli</i> JT39 R ₊	>1000	10	25
<i>E. coli</i> JT20 R ₊	>1000	50	250
<i>K. aerogenes</i> A	100	1.0	1.0
<i>K. aerogenes</i> 1112	500	5.0	5.0
<i>K. aerogenes</i> Ba95R ₊	>1000	100	500
<i>P. mirabilis</i> 977	1.0	11.0	2.5
<i>P. mirabilis</i> 889	>1000	250	1000
<i>P. morganii</i> 1580	250	2.51	2.5
<i>P. rettgeri</i> WM16	25	2.5	5.0
<i>P. vulgaris</i> W091	25	2.5	5.0
<i>E. cloacae</i> N1	2.5	1.0	1.0
<i>S. marcescens</i> US20	5.0	5.0	5.0
<i>C. freundii</i> E8	2.5	5.0	2.5
<i>C. freundii</i> B10R ₊	>1000	500	>1000
<i>P. aeruginosa</i> A	25	25	25
<i>P. aeruginosa</i> Dalglish	>1000	>1000	>1000
<i>S. aureus</i> Russell	25	<0.2*	1.0
<i>S. aureus</i> MB9	10	<0.2*	1.0

* Compound alone inhibitory

Table 5 Activity of Apalcillin alone or in Combination with Compound of Example 1

MIC ($\mu\text{g/ml}$)

Organism	Apalcillin Alone	Apalcillin + Compound of Example 1	
		(5.0 $\mu\text{g/ml}$)	(1.0 $\mu\text{g/ml}$)
<i>E. coli</i> O111	2.5	2.5	2.5
<i>E. coli</i> JT41OC ₊	25	25	25
<i>E. coli</i> JT39R ₊	1000	2.5	2.5
<i>E. coli</i> JT20R ₊	>1000	2.5	5.0
<i>K. aerogenes</i> A	10	<0.2	0.5
<i>K. aerogenes</i> 1112	25	1.0	1.0
<i>K. aerogenes</i> Ba95R ₊	>1000	2.5	10
<i>P. mirabilis</i> 977	2.5	1.0	1.0
<i>P. mirabilis</i> 889	>1000	5.0	25
<i>P. morganii</i> 1580	1000	10	10
<i>P. rettgeri</i> WML6	10	10	10
<i>P. vulgaris</i> WO91	10	1.0	2.5
<i>E. cloacae</i> N1	5.0	5.0	5.0
<i>S. marcescens</i> US20	5.0	5.0	5.0
<i>C. freundii</i> E8	2.5	2.5	5.0
<i>C. freundii</i> BLOR ₊	>1000	5.0	1000
<i>P. aeruginosa</i> A	2.5	2.5	2.5
<i>P. Dalglish</i>	>1000	250	>1000
<i>S. aureus</i> Russell	250	<0.2*	2.5
<i>S. aureus</i> MB9	50	<0.2*	1.0

* Compound alone inhibitory

Table 6 Activity of Amoxycillin Alone and in Combination with Compound of Example 2

Organism	MIC ($\mu\text{g/ml}$)	
	Amoxycillin Alone	Amoxycillin + compound of Example 2 (5.0 $\mu\text{g/ml}$) (1.0 $\mu\text{g/ml}$)
<i>E. coli</i> O111	10	5.0
<i>E. coli</i> JT410 C ₊	500	100
<i>E. coli</i> JT39R ₊	>1000	5.0
<i>E. coli</i> JT20R ₊	>1000	25
<i>P. mirabilis</i> 977	2.5	2.5
<i>P. mirabilis</i> 889	>1000	250
<i>P. morganii</i> 1580	1000	100
<i>P. rettgeri</i> WM16	1000	100
<i>P. vulgaris</i> W091	>1000	1.0
<i>K. aerogenes</i> I112	500	2.5
<i>K. aerogenes</i> Ba95R ₊	>1000	100
<i>E. cloacae</i> N1	500	12.5
<i>S. marcescens</i> US20	100	50
<i>C. freundii</i> E8	250	50
<i>C. freundii</i> B10R ₊	>1000	500
<i>P. aeruginosa</i> A	>1000	>1000
<i>P. aeruginosa</i> Dalglish	>1000	>1000
<i>S. aureus</i> Russell	100	$\leq 0.2^*$
		0.5

Table 7 Activity of Cephaloridine alone and in Combination with Compound of Example 2

MIC ($\mu\text{g/ml}$)

Organisms	Cephaloridine Alone	Cephaloridine + Compound of Example 2	
		(5.0 $\mu\text{g/ml}$)	(1.0 $\mu\text{g/ml}$)
<i>E. coli</i> O111	5.0	2.5	2.5
<i>E. coli</i> Jt410C ₊	100	10	50
<i>E. coli</i> JT39R ₊	10	2.5	2.5
<i>E. coli</i> JT20R ₊	25	2.5	2.5
<i>P. mirabilis</i> 977	5.0	5.0	10
<i>P. mirabilis</i> 889	100	5.0	10
<i>P. morganii</i> 1580	>1000	25	100
<i>P. rettgeri</i> WM16	>1000	10	100
<i>P. vulgaris</i> W091	>1000	2.5	5.0
<i>K. aerogenes</i> I112	5.0	2.5	5.0
<i>K. aerogenes</i> Ba95R ₊	100	2.5	5.0
<i>E. cloacae</i> N1	1000	2.5	10
<i>S. marcescens</i> US20	>1000	50	250
<i>C. freundii</i> E8	500	25	100
<i>C. freundii</i> B10R ₊	>1000	500	1000
<i>P. aeruginosa</i> A	>1000	>1000	>1000
<i>P. aeruginosa</i> Dalglish	>1000	>1000	>1000
<i>S. aureus</i> Russell	< 0.2	< 0.2	< 0.2

Table 8 Activity of Ticarcillin alone and in Combination with Compound of Example 2

Organism	MIC ($\mu\text{g/ml}$)		
	Ticarcillin Alone	Ticarcillin + Compound of Example 2 (5.0 $\mu\text{g/ml}$)	(1.0 $\mu\text{g/ml}$)
<i>E. coli</i> O111	5.0	5.0	5.0
<i>E. coli</i> JT410C ₊	25	10	25
<i>E. coli</i> JT39R ₊	>1000	10	50
<i>E. coli</i> JT20R ₊	>1000	50	500
<i>P. mirabilis</i> 977	1.0	1.0	1.0
<i>P. mirabilis</i> 889	>1000	250	>1000
<i>P. morganii</i> 1580	10	2.5	2.5
<i>P. rettgeri</i> WM16	10	2.5	2.5
<i>P. vulgaris</i> WO91	500	1.0	10
<i>K. aerogenes</i> 1112	250	5.0	25
<i>K. aerogenes</i> Ba95R ₊	>1000	250	>1000
<i>E. cloacae</i> N1	2.5	2.5	2.5
<i>S. marcescens</i> US20	5.0	10	5.0
<i>C. freundii</i> E8	5.0	10	5.0
<i>C. freundii</i> B10R ₊	>1000	>1000	>1000
<i>P. aeruginosa</i> A	25	25	25
<i>P. aeruginosa</i> Dalglish	>1000	>1000	>1000
<i>S. aureus</i> Russell	25	<0.2*	2.5

Table 9

Amoxycillin MIC values ($\mu\text{g/ml}$) in combination
with 6-alkylidenepenems

Organism	Compound Number (concentration)							
	None	(40) (5 $\mu\text{g/ml}$)	(49) (5 $\mu\text{g/ml}$)	(59) (2.5 $\mu\text{g/ml}$)	(76) (2 $\mu\text{g/ml}$)	(99) (5 $\mu\text{g/ml}$)	(101) (2.5 $\mu\text{g/ml}$)	(103) (5 $\mu\text{g/ml}$)
<i>E. coli</i> 0111	5	2.5	5	2.5	2.5	5	5	2.5
<i>E. coli</i> JT 410 C ⁺	500	100	500	100	250	500	250	500
<i>E. coli</i> JT 39 R ⁺	>1000	5	10	1	50	50	50	500
<i>E. coli</i> JT 20 R ⁺	>1000	25	100	10	1000	1000	500	>1000
<i>P. mirabilis</i> C 977	2.5	2.5	2.5	0.5	0.5	1	1	2.5
<i>P. mirabilis</i> C 889	>1000	>1000	100	50	>1000	250	>1000	>1000
<i>P. vulgaris</i> WO 91	1000	5	1	0.5	0.5	1	5	100
<i>P. morgani</i> I 580	>1000	250	100	50	250	250	500	500
<i>P. rettgeri</i> WM 16	1000	250	250	50	250	500	500	500
<i>K. aerogenes</i> A	250	1	1	0.5	1	1	2.5	5
<i>K. aerogenes</i> I 112	500	2.5	5	0.5	10	25	25	25
<i>K. aerogenes</i> Ba 95 R ⁺	>1000	50	100	10	>1000	1000	>1000	>1000
<i>E. cloacae</i> N I	500	250	50	25	500	100	250	100
<i>S. marcescens</i> US 20	1000	250	100	50	10	50	250	100
<i>C. freundii</i> E 8	500	50	100	25	10	250	100	100
<i>C. freundii</i> B 10 R ⁺	>1000	250	>1000	1000	>1000	>1000	>1000	>1000
<i>P. aeruginosa</i> A	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
<i>P. aeruginosa</i> Dalglish	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
<i>S. aureus</i> Russell	100	<0.2	<0.2	<0.2	5	<0.2	<0.2	50
<i>S. aureus</i> MB 9	250	1	-	<0.2	10	<0.2	<0.2	100

0 041 768

Table 10

Broth MIC values (μ /ml) for 6-Alkylideneepenems

Organism	Compound (118)	Compound (129)
<i>C. freundii</i> E 8	100	-
<i>E. cloacae</i> N 1	100	-
<i>E. coli</i> O111	100	-
<i>E. coli</i> JT 39 R ⁺	100	-
<i>E. coli</i> ESS	1.6	12.5
<i>K. aerogenes</i> A	100	-
<i>P. mirabilis</i> 977	100	-
<i>P.morganii</i> I 580	100	-
<i>P. rettgeri</i> WM 16	100	-
<i>P. vulgaris</i> WO 91	100	-
<i>P. aeruginosa</i> A	100	-
<i>S. typhimurium</i> CT 10	100	-
<i>S. marcescens</i> US 20	100	-
<i>S. sonnei</i> MB 11967	100	-
<i>B. subtilis</i> A	12.5	25
<i>S. aureus</i> Oxford	1.6	12.5
<i>S. aureus</i> Russell	3.1	12.5
<i>S. aureus</i> 1517	100	-
<i>S. faecalis</i> I	100	50
<i>S. pneumoniae</i> CN 33	1.6	1.6
<i>S. pyogenes</i> CN 10	1.6	0.4

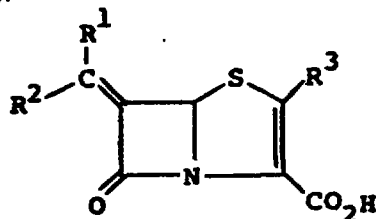
Table 11

Amoxycillin MIC Values ($\mu\text{g/ml}$) in combination
with 6-Benzylidenepenicem (118)

Organism	Amoxycillin alone	Amoxycillin + Compound (118)	
		(5.0 $\mu\text{g/ml}$)	(1.0 $\mu\text{g/ml}$)
E. coli 0111	5.0	2.5	5.0
E. coli JT 410 C ⁺	250	100	250
E. coli JT 39 R ⁺	1000	10	50
E. coli JT 20 R ⁺	>1000	100	500
P. mirabilis C 977	2.5	2.5	2.5
P. mirabilis C 889	>1000	100	250
P. morganii I 580	>1000	100	500
P. rettgeri WM 16	500	100	500
P. vulgaris WO 91	>1000	5.0	25
K. aerogenes A	250	2.5	5.0
K. aerogenes I 112	250	10	50
K. aerogenes Ba 95 R ⁺	>1000	100	500
E. cloacae N 1	500	100	250
E. cloacae T 153	1000	500	1000
S. marcescens US 20	100	25	25
C. freundii E 8	250	25	50
C. freundii B 10 R ⁺	>1000	1000	>1000
P. aeruginosa A	>1000	500	>1000
P. aeruginosa Dalglish	>1000	>1000	>1000
S. aureus Russell	100	≤ 0.2	≤ 0.2
S. aureus MB 9	100	≤ 0.2	≤ 0.2

Claims

1. A compound of formula (II):



(II)

or a pharmaceutically acceptable salt or *in-vivo* hydrolysable ester thereof, in which:

each of R^1 and R^2 , which may be the same or different, denotes a hydrogen atom, a (C_{1-10}) hydrocarbon group optionally substituted by a functional group, or a heterocyclic group; and

R^3 denotes a hydrogen atom or a group of the formula $-R^a$ or $-SR^a$; in which:

R^a denotes a (C_{1-10}) hydrocarbon group (other than an alkyl group), a heterocyclic group, or an unsubstituted or substituted (C_{1-10}) alkyl group in which the optional substituents are selected from hydroxy, halogen, mercapto, carboxy, (C_{1-6}) alkoxy, (C_{1-6}) alkanoyloxy, (C_{1-6}) alkylthio, amino, monoalkylamino, dialkylamino, alkanolylamino, (C_{1-6}) alkoxycarbonyl, and heterocyclythio groups.

2. A compound as claimed in claim 1, wherein each of R^1 and R^2 , which may be the same or different, denotes a hydrogen atom or a (C_{1-10}) hydrocarbon group optionally substituted by a functional group.

3. A compound as claimed in claim 1, wherein each of R^1 and R^2 , which may be the same or different, denotes a hydrogen atom or a (C_{1-10}) hydrocarbon group.

4. A compound as claimed in claim 1, wherein each of R^1 and R^2 , which may be the same or different, denotes a hydrogen atom or an (C_{1-6}) alkyl group.

5. A compound as claimed in claim 1, wherein each of R^1 and R^2 , which may be the same or different, denotes a hydrogen atom, or a methyl, ethyl or phenyl group.

6. A compound as claimed in any one of claims 1 to 5, wherein one of R^1 and R^2 denotes a hydrogen atom.

7. A compound as claimed in any one of claims 1 to 6, wherein R^3 denotes a hydrogen atom, an unsubstituted or substituted (C_{1-10}) alkyl group, or an unsubstituted or substituted (C_{1-10}) alkylthio group, the substituents of said alkyl and alkylthio groups being selected from hydroxy, halogen, mercapto, carboxy, (C_{1-6}) alkoxy, (C_{1-6}) alkanoyloxy, (C_{1-6}) alkylthio, amino, monoalkylamino, dialkylamino, alkanoylamino, and (C_{1-6}) alkoxycarbonyl groups.

8. A compound as claimed in any one of claims 1 to 6, wherein R^3 denotes a hydrogen atom, or an aminomethyl, aminoethyl, methylthio, ethylthio, 2-aminoethylthio, 2-hydroxyethylthio, methyl, ethyl, acetamidoethyl, or pyridylthio group.

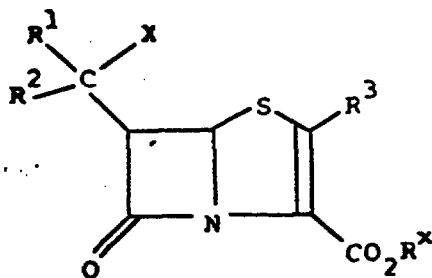
9. A compound as claimed in claim 1, selected from the following or a pharmaceutically acceptable salt thereof:

- 6-(Z)-ethylidene-2-ethylthiopenem-3-carboxylic acid;
- 6-(E)-ethylidene-2-ethylthiopenem-3-carboxylic acid;
- 6-(Z)-ethylidenepenem-3-carboxylic acid;
- 6-(Z)-ethylidene-2-n-propylpenem-3-carboxylic acid;
- 6-ethylidene-2-(2-acetamidoethylthio)penem-3-carboxylic acid;
- 6-(Z)-ethylidene-2-methylpenem-3-carboxylic acid;
- 6-ethylidene-2-(2-pyridylthio)penem-3-carboxylic acid;
- 6-ethylidene-2-(2-aminoethylthio)penem-3-carboxylic acid;
- 6-(Z)-benzylidene-2-ethylthiopenem-3-carboxylic acid; and
- 6-isopropylidene-2-ethylthiopenem-3-carboxylic acid.

10. The compound 6-ethylidene-2-ethylsulphinylpenem-3-carboxylic acid or a pharmaceutically acceptable salt thereof.

11. A process for the preparation of a compound as claimed in claim 1, which process comprises either:

(a) elimination of the elements of a compound of the formula $H-X$ from a compound of formula (III):

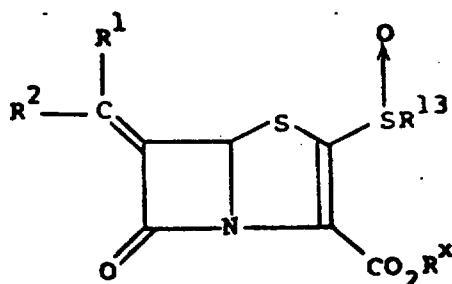


(III)



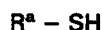
in which R^1 , R^2 and R^3 are as defined in claim 1, X denotes a leaving group, and R^x denotes a hydrogen atom or a carboxyl-blocking group; or

(b) when R^3 denotes a group of the formula $-SR^a$, reaction of a sulfoxide of formula (VIII):



(VIII)

in which R^1 , R^2 and R^x are as defined above, and R^{13} denotes an organic group different from the group R^a (R^a being defined as in claim 1); with a thiol of formula (IX) or a reactive derivative thereof:



(IX)

and, after step (a) or (b), if necessary, carrying out one or more of the following steps:

(i) removal of any carboxyl blocking group R^x ;

(ii) converting the product to a pharmaceutically acceptable salt or *in-vivo* hydrolysable ester.

12. A pharmaceutical composition which comprises a compound as claimed in any one of claims 1 to 10, and a pharmaceutically acceptable carrier.

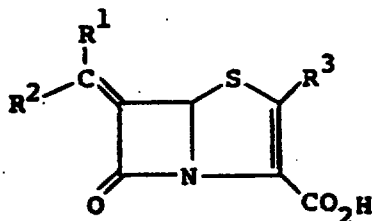
13. A pharmaceutical composition as claimed in claim 12, which additionally comprises a penicillin or cephalosporin.

14. The use of a compound as claimed in any one of claims 1 to 10 for the preparation of a medicament for the treatment of a bacterial infection.

15. The use of a compound as claimed in any one of claims 1 to 10 for the preparation of a medicament having β -lactamase inhibitory activity.

Revendications

1. Composé de formule (II):



(II)

ou un sel ou un ester hydrolysable *in vivo* de celui-ci, acceptable du point de vue pharmaceutique, dans laquelle:

chacun des R^1 et R^2 , qui peuvent être identiques ou différents, est un atome d'hydrogène, un group hydrocarboné en C_{1-10} éventuellement substitué par un groupe fonctionnel, ou un groupe hétérocyclique; et

R^3 est un atome d'hydrogène ou un groupe de formule $-R^a$ ou $-SR^a$; où

R^a est un groupe hydrocarboné en C_{1-10} (autre qu'un groupe alcoyle), un groupe hétérocyclique, ou un groupe alcoyle en C_{1-10} substitué ou non-substitué, dans lequel les substituants éventuels sont choisis parmi un radical hydroxy, un atome d'halogène, un groupe mercapto, carboxy, alcoxy en C_{1-6} , alcanoyloxy en C_{1-6} , alcoylthio en C_{1-6} , amino, monoalcoylamino, dialcoylamino, alcanoylamino, alcoxy(C_{1-6})carbonyle et hétérocyclylthio.

2. Composé suivant la revendication 1, dans lequel chacun des R^1 et R^2 , qui peuvent être identiques ou différents, est un atome d'hydrogène ou un groupe hydrocarboné en C_{1-10} éventuellement substitué par un groupe fonctionnel.

3. Composé suivant la revendication 1, dans lequel chacun des R^1 et R^2 , qui peuvent être identiques ou différents, est un atome d'hydrogène ou un groupe hydrocarboné en C_{1-10} .

4. Composé suivant la revendication 1, dans lequel chacun des R^1 et R^2 qui peuvent être identiques ou différents, est un atome d'hydrogène ou un groupe alcoyle en C_{1-3} .

5. Composé suivant la revendication 1, dans lequel chacun des R^1 et R^2 , qui peuvent être identiques ou différents, est un atome d'hydrogène, ou un groupe méthyle, éthyle ou phényle.



6. Composé suivant l'une quelconque des revendications 1 à 5, dans lequel l'un des R^1 et R^2 est un atome d'hydrogène.

7. Composé suivant l'une quelconque des revendications 1 à 6, dans lequel R^3 est un atome d'hydrogène, un groupe alcoyle en C_{1-10} substitué ou non-substitué, ou un groupe alcoylthio en C_{1-10} substitué ou non-substitué, les substituants de ces groupes alcoyles et alcoylthio étant choisis parmi des groupes hydroxy, halogène, mercapto, carboxy, alcoxy en C_{1-6} , alcanoyloxy en C_{1-6} , alcoylthio en C_{1-6} , amino, monoalcoylamino, dialcoylamino, alcanoylamino et alcoxy(C_{1-6})carbonyle.

8. Composé suivant l'une quelconque des revendications 1 à 6, dans lequel R^3 est un atome d'hydrogène ou un groupe aminométhyle, aminoéthyle, méthylthio, éthylthio, 2-aminoéthylthio, 2-hydroxyéthylthio, méthyle, éthyle, acétamidoéthyle ou pyridylthio.

9. Composé suivant la revendication 1, choisis parmi les acides suivants et leurs sels acceptables du point de vue pharmaceutique:

acide 6-(Z)-éthylidène-2-éthylthiopénèm-3-carboxylique;

acide 6-(E)-éthylidène-2-éthylthiopénèm-3-carboxylique;

15 acide 6-(Z)-éthylidène-pénèm-3-carboxylique;

acide 6-(Z)-éthylidène-2-n-propylpénèm-3-carboxylique;

acide 6-éthylidène-2-(2-acétamidoéthylthio)pénèm-3-carboxylique;

acide 6-(Z)-éthylidène-2-méthylpénèm-3-carboxylique;

acide 6-éthylidène-2-(2-pyridylthio)pénèm-3-carboxylique;

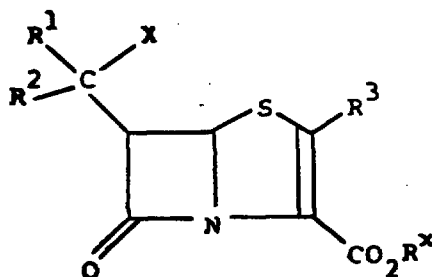
20 acide 6-(Z)-benzylidène-2-éthylthiopénèm-3-carboxylique; et

acide 6-isopropylidène-2-éthylthiopénèm-3-carboxylique.

10. Acide 6-éthylidène-2-éthylsulphinylpénèm-3-carboxylique ou un sel de celui acceptable du point de vue pharmaceutique.

11. Procédé de préparation d'un composé tel que défini dans la revendication 1, lequel procédé comprend soit:

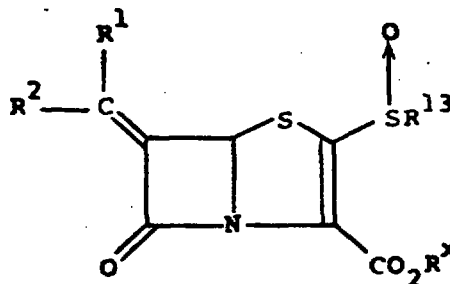
(a) l'élimination des éléments d'un composé de formule $H-X$ à partir d'un composé de formule (III):



(III)

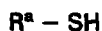
dans laquelle R^1 , R^2 et R^3 sont tels que définis dans la revendication 1, X est un groupe mobile, et R^x est un atome d'hydrogène ou un groupe bloquant la fonction carboxy; soit

(b) lorsque R^3 est un groupe de formule $-SR^a$, la réaction d'un sulfoxyde de formule (VIII):



(VIII)

dans laquelle R^1 , R^2 et R^x sont tels que définis plus haut, et R^{13} est un groupe organique différent du groupe R^a (R^a étant tel que défini dans la revendication 1); avec un thiol de formule (IX) ou un dérivé réactif de celui-ci:



(IX)

et, après l'étape (a) ou (b), si cela est nécessaire, la réalisation d'une ou de plusieurs des étapes suivantes:

(i) l'élimination d'un quelconque groupe R^x bloquant la fonction carboxy;

(ii) la conversion du produit en un sel ou un ester hydrolysable in vivo, acceptable du point de vue pharmaceutique.

12. Composition pharmaceutique qui comprend un composé suivant l'une quelconque des revendications 1 à 10 et un support acceptable du point de vue pharmaceutique.



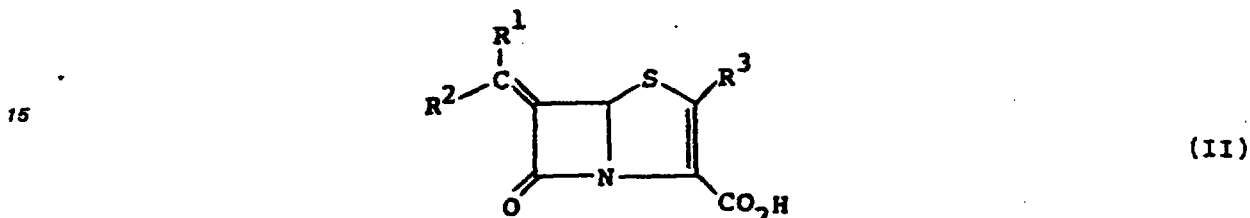
13. Composition pharmaceutique suivant la revendication 12, qui comprend de plus une pénicilline ou une céphalosporine.

14. Utilisation d'un composé suivant l'une quelconque des revendications 1 à 10 pour la préparation d'un médicament pour le traitement d'une infection bactérienne.

5 15. Utilisation d'un composé suivant l'une quelconque des revendications 1 à 10, pour la préparation d'un médicament ayant une activité d'inhibition de la β -lactamase.

Patentansprüche

10 1. Eine Verbindung der Formel (II):



20 oder ein pharmazeutisch verträgliches Salz oder ein in-vivo hydrolysierbarer Ester davon, wobei:

jede der Gruppen R¹ et R², welche gleich oder verschieden sein können, ein Wasserstoffatom darstellt oder eine (C₁₋₁₀)Kohlenwasserstoffgruppe, gegebenenfalls substituiert durch eine funktionelle Gruppe, oder eine heterocyclische Gruppe; und

R³ ein Wasserstoffatom oder eine Gruppe der Formel —R^a oder —SR^a bedeutet, in welcher:

25 R^a eine (C₁₋₁₀)Kohlenwasserstoffgruppe (aber keine Alkylgruppe), eine heterocyclische Gruppe oder eine unsubstituierte oder substituierte (C₁₋₁₀)Alkylgruppe bedeutet, in welcher die fakultativen Substituenten ausgewählt sind aus Hydroxy-, Halogen-, Mercapto-, Carboxy-, (C₁₋₆)Alkoxy-, (C₁₋₆)Alkanoyloxy-, (C₁₋₆)Alkylthio-, Amino-, Monoalkylamino-, Dialkylamino-, Alkanoylamino-, (C₁₋₆)Alkoxy-carbonyl-, und Heterocyclylthiogruppen.

30 2. Eine Verbindung wie in Anspruch 1 beansprucht, in welcher jede der beiden Gruppen R¹ und R², welche gleich oder verschieden sein können, ein Wasserstoffatom oder eine (C₁₋₁₀)Kohlenwasserstoffgruppe gegebenenfalls substituiert durch eine funktionelle Gruppe, darstellt.

3. Eine Verbindung wie in Anspruch 1 beansprucht, in welcher jede der Gruppen R¹ und R², welche gleich oder verschieden sein können, ein Wasserstoffatom oder ein (C₁₋₁₀)Kohlenwasserstoffgruppe

35 darstellt.

4. Eine Verbindung wie in Anspruch 1 beansprucht, in welcher jede der Gruppen R¹ und R², welche gleich oder verschieden sein können, ein Wasserstoffatom oder eine (C₁₋₆)Alkylgruppe darstellt.

5. Eine Verbindung wie in Anspruch 1 beansprucht, in welcher jede der Gruppen R¹ und R², welche gleich oder verschieden sein können, ein Wasserstoffatom oder ein Methyl-, Äthyl-, oder Phenylgruppe

40 darstellt.

6. Eine Verbindung wie in einem der Ansprüche 1 bis 5 beansprucht, in welcher eine der beiden Gruppen R¹ und R² ein Wasserstoffatom darstellt.

7. Eine Verbindung wie in einem der Ansprüche 1 bis 6 beansprucht, in welcher R³ ein Wasserstoffatom, eine unsubstituierte oder substituierte (C₁₋₁₀)Alkylgruppe oder eine unsubstituierte oder

45 substituierte (C₁₋₁₀)Alkylthiogruppe darstellt, wobei die Substituenten der genannten Alkyl- und Alkylthiogruppen ausgewählt sind aus Hydroxy-, Halogen-, Mercapto-, Carboxy-, (C₁₋₆)Alkoxy-, (C₁₋₆)Alkanoyloxy-, (C₁₋₆)Alkylthio-, Amino-, Monoalkylamino-, Dialkylamino-, Alkanoylamino und (C₁₋₆)Alkoxy-carbonylgruppen.

8. Eine Verbindung wie in einem der Ansprüche 1 bis 6 beansprucht, in welcher R³ ein

50 Wasserstoffatom, oder eine Aminomethyl-, Aminoäthyl-, Methylthio-, Äthylthio-, 2-Aminoäthylthio-, 2-Hydroxyäthylthio-, Methyl-, Äthyl-, Acetamidoäthyl- oder Pyridylthiogruppe darstellt.

9. Eine Verbindung wie in Anspruch 1 beansprucht, ausgewählt aus den folgenden Verbindungen oder

ein pharmazeutisch verträgliches Salz davon.

6-(Z)-Äthyliden-2-äthylthiopentem-3-carbonsäure;

55 6-(E)-Äthyliden-2-äthylthiopentem-3-carbonsäure;

6-(Z)-Äthylidenpentem-3-carbonsäure;

6-(Z)-Äthyliden-2-n-propylpentem-3-carbonsäure;

6-Äthyliden-2-(2-acetamidoäthylthio)pentem-3-carbonsäure;

6-(Z)-Äthyliden-2-methylpentem-3-carbonsäure;

60 6-Äthyliden-2-(2-pyridylthio)pentem-3-carbonsäure;

6-Äthyliden-2-(2-aminoäthylthio)pentem-3-carbonsäure;

6-(Z)-Benzyliden-2-äthylthiopentem-3-carbonsäure; und

6-Isopropyliden-2-äthylthiopentem-3-carbonsäure.

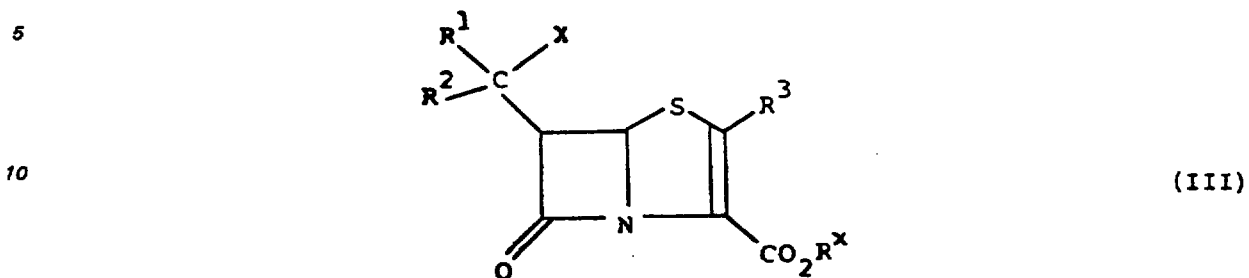
10. Die Verbindung 6-Äthyliden-2-äthylsulfonfylpentem-3-carbonsäure oder ein pharmazeutisch

65 verträgliches Salz davon.



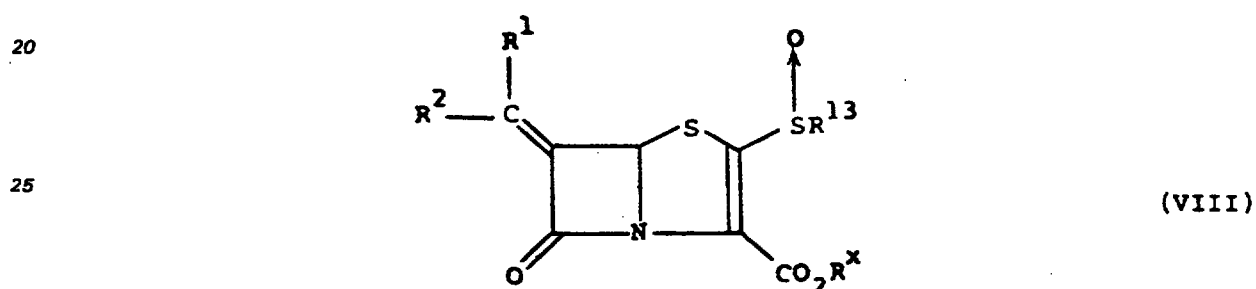
11. Ein Verfahren zur Herstellung einer Verbindung wie in Anspruch 1 beansprucht, welches Verfahren die folgenden Schritte umfaßt, entweder

(a) Eliminieren der Elemente einer Verbindung der Formel $H-X$ aus einer Verbindung der Formel (III):



15 in welcher R^1 , R^2 und R^3 wie in Anspruch 1 definiert sind, X eine abspaltbare Gruppe bedeutet, und R^x ein Wasserstoffatom oder eine Carboxyl-Hemmgruppe darstellt; oder

(b) wenn R^3 eine Gruppe der Formel $-SR^a$ ist, die Umsetzung eines Sulfoxids der Formel (VIII):



30 in welcher R^1 , R^2 und R^x wie oben definiert sind, und R^{13} eine organische Gruppe ist, welche verschieden ist von der Gruppe R^a (wobei R^a wie in Anspruch 1 definiert ist), mit einem Thiol der Formel (IX) oder eines reaktionsfähigen Derivats derselben:



und, im Anschluß an Stufe (a) oder (b), falls notwendig, die Durchführung einer oder mehrerer der folgenden Schritte:

(i) Entfernen jeglicher Carboxyl-Hemmgruppe R ;

40 (ii) Umwandlung des Produkts in ein pharmazeutisch verträgliches Salz oder einen *in-vivo* hydrolysierbaren Ester.

12. Eine pharmazeutische Zusammensetzung welche eine Verbindung, wie in einem der Ansprüche 1 bis 10 beansprucht, und einen pharmazeutisch verträglichen Träger enthält.

45 13. Eine pharmazeutische Zusammensetzung wie in Anspruch 12 beansprucht, welche zusätzlich ein Penicillin oder Cephalosporin enthält.

14. Die Verwendung einer Verbindung wie in einem der Ansprüche 1 bis 10 beansprucht zur Herstellung eines Medikaments für die Behandlung einer bakteriellen Infektion.

15. Die Verwendung einer Verbindung wie in einem der Ansprüche 1 bis 10 beansprucht zur Herstellung eines Medikaments mit β -Lactamase-Hemmwirkung.

