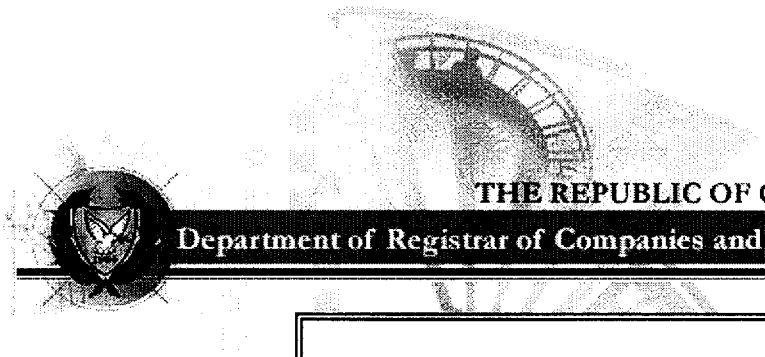

ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ
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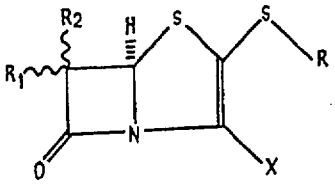
(54) 2-Penem compounds and a method for preparing them

(57) The present invention relates to 2-penem compounds of the formula



I

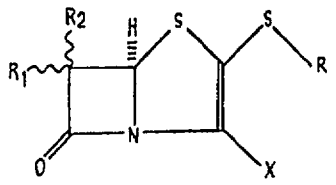
wherein R is lower alkyl, aminoloweralkyl, mono- or diloweralkylaminoloweralkyl, acylaminoloweralkyl, aralkyl, heteroaralkyl, hydroxyloweralkyl, hydroxyaralkyl, carboxyloweralkyl or alkoxycarbonylloweralkyl;
R_1 is hydrogen, lower alkyl, aralkyl or a group of the formula: R_6CHOH- with R_6 being hydrogen, lower alkyl, aralkyl, heteroaryl, heteroaralkyl, hydroxyaralkyl or aryl;
R_2 is hydrogen or methyl; and
X is cyano, tetrazol-5-yl, $-COOR_3$ or $-CONR_4R_5$ wherein
R_3 is hydrogen, an alkali metal cation, phthalidyl or a pivaloyloxymethyl group; and
R_4 and R_5 are independently hydrogen or lower alkyl; with the proviso that when X is $-COOR_3$ both R_1 and R_2 cannot be hydrogen;
to pharmaceutical compositions comprising such compounds and methods for preparing them.

GB 2 042 520 A

SPECIFICATION

2-Penem compounds and a method for preparing them

The present invention relates to 2-penem compound of the formula



I

wherein R is lower alkyl, aminoloweralkyl, mono-or di-loweralkylaminoloweralkyl, acylaminoloweralkyl, aralkyl, heteroaralkyl, hydroxyloweralkyl, hydroxyaralkyl, carboxy-loweralkyl or alkoxycarbonylloweralkyl;
R_1 is hydrogen, lower alkyl, aralkyl or a group of the formula: R_6CHOH- with R_6 being hydrogen, lower alkyl, aralkyl, heteroaryl, heteroaralkyl, hydroxyaralkyl or aryl;
R_2 is hydrogen or methyl; and
x is cyano, tetrazol-5-yl, $-COOR_3$ or $-CONR_4R_5$ wherein
R_3 is hydrogen, an alkali metal cation, phthalidyl or a pivaloyloxymethyl group; and
R_4 and R_5 are independently hydrogen or lower alkyl; with the proviso that when X is $-COOR_3$ both R_1 and R_2 cannot be hydrogen.

The lower alkyl groups referred to above contain 1 to 6 carbon atoms and are exemplified by methyl, ethyl, propyl, butyl, pentyl, hexyl, and the corresponding branched-chain isomers thereof.

The acyl substituents referred to above contain 2-7 carbon atoms and are exemplified by acetyl, propionyl, butyryl, valeryl and the like and which may be optionally substituted by up to three chlorine atoms.

The term "aryl" as used herein refers to phenyl substituted by lower alkyl, lower alkoxy and halogen groups, *e.g.*, *p*-tolyl, *o*-tolyl, *m*-tolyl, *p*-chlorophenyl, *o*-methoxy-phenyl, etc.

The term "heteroaralkyl" as used herein refers to lower alkyl groups substituted by an unsaturated heterocyclic group ("heteroaryl group") such as 2-pyridyl, 3-pyridyl, 4-pyridyl, furyl thienyl or the like. The heteroaryl group may optionally contain 1 to 3 lower alkyl substituents, *e.g.*, 2-methylpyridyl, 3-methylthienyl, etc.

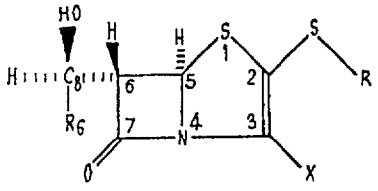
The alkoxy groups referred to above likewise contain 1 to 6 carbon atoms and are exemplified by methoxy, ethoxy, propoxy, and the like.

The term "aralkyl" denotes lower alkyl groups substituted by one or more aryl groups such as benzyl, phenethyl, benzhydryl and the like.

The alkali metal cations referred to above preferably are potassium and sodium but may also be lithium, rubidium or cesium.

The compounds of formula I possess several centers of chirality and all isomeric forms of the compounds of formula I, and mixtures thereof are embraced by this invention.

With respect to those in the penem nucleus itself, the preferred configuration at the 5 and 6 positions are of the abslute stereochemistry R and S, respectively. The two hydrogen atoms attached to the 5 and 6 carbon atomsare thus *trans* to one another. The stereochemistry of the C-8 carbon atom (when R_1 is R_6CHOH-) may be either R or S depending on the exact nature of the R_6 substituent. For instance, the compounds wherein R_6 is methyl preferably have the 8R stereochemistry thus being designated 5R,6S,8R. The most preferred stereochemical configuration for a 6-(R_6CHOH)-compound of this invention is represented by the following formula



III

The R,S-nomenclature may differ depending on the nature of the R_6 substituent. Wherein the R_6 group of formula I has a higher priority in the Cahn-Ingold-Prelog system, *e.g.*, a 2-pyridyl group, a compound having the above shown most preferred stereochemical configuration will be designated 5R, 6S, 8S but be of the same relative spatial configuration at C-5, C-6 and C-8 as a 5R, 6S, 8R compound, wherein the R_6 group has a lower priority, *e.g.* the methyl group.

The compounds may be prepared as their racemic mixtures, *e.g.*, a 5R,6S,8R compound is produced with its enantiomer (mirror image), *i.e.*, a 5S,6R,8S compound, in equal amounts when the starting compound is a racemic mixture. The two enantiomers may be separated by conventional means, *e.g.*, by fractional crystallizations of optically active salt forms, *e.g.*, the salts derived from optically active amino compounds, *e.g.*, (−)-brucine, or (+)- and (−)-ephedrine. Alternatively, the compounds may be produced in their pure

enantiomeric forms by utilizing optically active starting materials in the synthetic procedure.

The designations of absolute spatial configuration are based on X-ray crystal analysis.

One preferred group of compounds of formula I embraces those compounds wherein R_2 is hydrogen, X is $-COOR_3$, R_1 is the group R_6-CHOH- and R, R_3 and R_6 are as defined above. A most particularly preferred group therein embraces compounds having the spatial configuration of formula III, wherein X is -COOH or -COO-alkali metal, R is loweralkyl or aminoloweralkyl and R_6 is hydrogen, lower alkyl or heteroaryl. Of these the compounds wherein R is ethyl or aminoethyl and R_6 is methyl are most highly preferred.

Another preferred group of compounds of formula I embraces those compounds wherein X is cyano, tetrazol-5-yl, or $-CONR_4R_5$ with R_4 and R_5, R_1, R_2 and R being as defined above. A most particularly preferred group therein embraces compounds wherein R_1 is hydrogen or the group R_6CHOH-, $R_2$is hydrogen, X is tetrazol-5-yl and R and R_6 are as defined above.

The compounds of this invention possess antibacterial activity of both the gram-positive and gram-negative type. Thus, when tested in standardized microbiological assays, the compounds of this invention are active against such gram-positive organisms as *Staphylococcus epidermidis*, and *Bacillu subtili*, and such gram-negative organisms as *E. coli* and *Salmonella* at test levels of 0.1 to 100 ug/ml. Additionally, they show activity against such organisms in the presence of beta-lactamase indicating a resistance to these enzymes and are inhibitors of beta-lactamases. For instance, potassium (5R,6S,8R)-6-(1-hydroxy-ethyl)-2-ethylthiopenem-3-carboxylate is active against *Staphylococcus* 76070103 at a test level of less than 0.06 ug/ml and against *E. coli* JR66 at a test level of 0.5 ug/ml. When tested against *B. subtilis* 1119601 (a beta-lactamase-containing organism), this compound exhibits activity at 0.06 ug/ml.

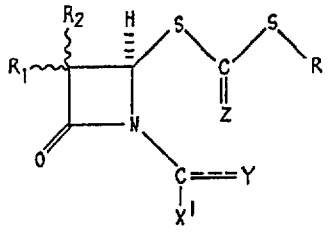
Thus, the present invention includes within its scope pharmaceutical compositions comprising an antibacterially effective amount of a penem of formula I (specifically the compound mentioned in the preceding paragraph or a mixture thereof with its enantiomer) together with a compatible, pharmaceutically acceptable carrier or excipient, and dosage forms, specifically for oral use. One particular pharmaceutical composition comprises the alkali metal (5RS,6RS,8SR)-6-(1-hydroxyethyl)-2-ethylthiopenem-3-carboxylate alone or in combination with the corresponding (5RS,6SR,8RS)- or (5R,6S,8R)-isomer (preferably in a w/w ratio of 20-45/55-80), this composition being substantially free from the other isomers (5RS,6SR,8SR) and (5RS,6RS,8RS). As regards antibacterial spectrum the isomers of the above combination surprisingly complement each other.

The dosage administered of the penems of this invention is dependent upon the age and weight of the animal species being treated, the mode of administration, and the type and severity of bacterial infection being prevented or reduced. Typically, the dosage administered per day will be in the range of 100-5000 mg, with 500-1000 mg being preferred.

For oral administration, the compounds of this invention may be formulated in the form of tablets, capsules, elixirs or the like. Likewise, they may be admixed with animal feed. They may also be applied topically in the form of ointments, both hydrophilic and hydrophobic, in the form of lotions which may be aqueous, non-aqueous or of the emulsion type, or in the form of creams.

The compounds of formula I may be utilized in liquid form such as solutions, suspensins and the like for otic and optic use and may also be administered parenterally via intra-muscular injection.

The compounds of this invention are prepared by cyclising a compound of the formula



II

wherein Z is sulfur or oxygen and wherein R, R_1, R_2 are as defined above any functional group therein being optionally protected, X' is protected tetrazol-5-yl, cyano, protected carboxyl, protected carbamoyl or $-CONR_4R_5$ with substituents R_4 and R_5 being as defined above and at least one of them being lower alkyl; and Y is a phosphonio group being double bonded to the adjacent carbon atom or a phosphonato group with a single bond to the adjacent carbon atom the negative charge of which is compensated by the presence of a cation; if required, separating a mixture of diastereo-isomers before or after removing any protecting group and then subjecting a so-obtained compound to one or more of the facultative steps (i) to (viii):

(i) introducing phthalidyl or pivaloyloxymethyl in substituent X;
(ii) acylation of a compound of formula I wherein R is aminoloweralkyl;
(iii) transamidation or hydrolysis of a compound of formula I wherein R is acylaminoloweralkyl;
(iv) separation of a mixture of enantiomers;
(v) formation of a salt;
(vi) conversion of the carboxyl group representing X into a corresponding amido group $-CONR_4R_5$ with R_4 and R_5 being as defined above;

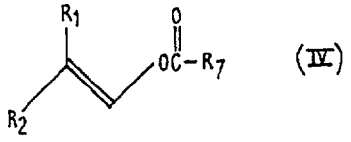
(vii) conversion of the carboxyl group representing X into the cyano group; and
(viii) conversion of the cyano or carbamoyl group representing X into the tetrazol-5-yl group;
with the proviso that when in formula II X' is protected carboxyl and R_1 and R_2 are both hydrogen, one of steps (vi) or (vii) must be carried out.

The cyclization is generally conducted at a temperature between 30 to 160°C and preferably at reflux temperatures in an organic solvent such as benzene, toluene or xylene under an inert atmosphere, *e.g.*, nitrogen or argon. Reaction times generally vary from 12-48 hours.

The group Y in the starting material of formula II is a phosphonio group customary for a Wittig reaction, especially a triaryl-, *e.g.* triphenyl- or tri-*p*-methoxy-phenyl-, or tri-lower alkyl, *e.g.* tributylphosphonio, or a phosphonato group, *e.g.* diphenylphosphonato or dimethoxyphosphonato.

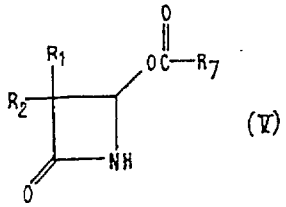
The conventional amino protecting groups, *e.g.* benzyloxy-carbonyl, *p*-nitrobenzyloxycarbonyl and benzhydryloxy-carbonyl, and carboxy protecting groups, *e.g.* benzyl, *p*-nitrobenzyl and benzhydryl, can be removed by hydrogenation. Certain amino and hydroxy protecting groups such as trichloroethoxycarbonyl may be removed prior to the carboxy protecting group by deprotection via zinc/acetic acid in a suitable aprotic solvent such as tetrahydrofuran. Most preferably, however, the allyl protecting group will be utilized as carboxy protecting group. This group is most preferably removed by utilizing a suitable aprotic solvent, such as tetrahydrofuran, diethyl ether or methylene chloride, with potassium or sodium 2-ethylhexanoate or 2-ethylhexanoic acid and a mixture of a palladium compound and triphenyl phosphine as the catalyst. This deprotection method is particularly suitable for the sensitive betalactam carboxylates of this invention. Use of the potassium or sodium 2-ethylhexanoate provides the corresponding salt, while use of 2-ethylhexanoic acid affords the free carboxy, amine or hydroxy group.

The starting materials of formula II are preparable by a reaction sequence starting with a compound of the formula



(IV)

wherein R_1 and R_2 are as defined for formula I and R_7 is phenyl or an alkyl group containing 1-6 carbon atoms. When R_1 is a group of the formula R_6-CHOH- the hydroxy substituent must be blocked prior to reaction with a suitable protecting group, *e.g.* benzyloxycarbonyl, *p*-nitrobenzyl-oxycarbonyl, benzhydryloxycarbonyl, allyloxycarbonyl or trichloroethoxycarbonyl. The compound (IV) is reacted with chlorosulfonylisocyanate, followed by a hydrolytic workup, according to procedures disclosed in *Annalen, 1974*, 539, and German Patents 1906401 and 1945549 to provide the intermediate of formula (V)



(V)

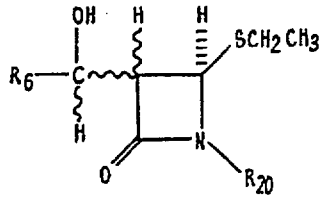
An alternate method of preparation of the intermediate of formula (V) involves ozone oxidation of a 4-phenyl, 4-methoxyphenyl, or 4-vinylazetidinone having the desired R_1 substituent at the 3-position to obtain the 4-carboxylic acid compound. The 4-phenyl and 4-methoxyphenyl compounds are preparable by the process of *Angew, Chem. Int. Ed. 7,* 172 (1968) while the 4-vinyl compound is preparable from the process of *Canadian J. Chem. 50,* 3196 (1972). The 4-carboxylic acid compound is then treated with lead tetra-acetate in an inert solvent to provide the desired intermediate of formula (V).

A further alternative route to intermediates similar to those of formula (V) wherein R_1 is R_6-CHOH- (compounds of formula (VII)) starts with 4-ethylthioazetidin-2-one (preparable according to the procedures of *Liebigs Ann. Chem., 1974* 539-560. This starting material is treated with a suitable amine-protecting group (for the NH function) to afford the 1-protected-4-ethylthioazetidin-2-one. Preferred protecting groups are those such as *t*-butyldimethylsilyl, triethylsilyl, or tetrahydropyranyl, with *t*-butyldimethylsilyl being particularly preferred. Typically, the reaction is conducted in an organic solvent such as dichloromethane or chloroform in the presence of an acid acceptor. The acid acceptor may be an inorganic or organic base, but organic bases such as triethylamine are generally preferred. Typically, temperatures are from 0°C to room temperature, and typical times range from 5-60 minutes, depending upon the nature of the reactants.

The l-protected-4-ethylthioazetidin-2-one is treated with a strong base to form an anion at the 3-position which is reacted without isolation with an aldehyde of the formula

R_6-CHO

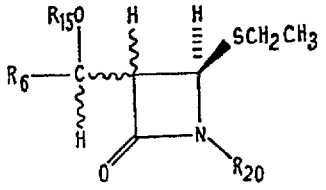
wherein R_6 is as hereinbefore defined, to afford the intermediate of the formula (VI):



(VI)

wherein R_6 is as hereinbefore defined and R_{20} is a nitrogen-protecting group. The base utilized to form the anion is one such as lithium di-isopropylamine, lithium bis-(trimethylsilyl)amide, *n*-butyl lithium or sec-butyl lithium. Generally, an anhydrous aprotic solvent such as tetrahydro-furan or ethyl ether is utilized. Preferred temperatures range from −80°C to −60°C during the production of the anion. After addition of the aldehyde R_6CHO the reaction mixture may be allowed to warm to room temperatures. This reaction produces a mixture of 4 isomers which may be utilized further without separation or which may be optionally separated by chromatography at this stage.

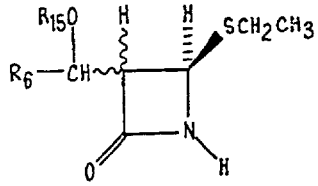
The intermediate of formula (VI) is then treated with a suitable hydroxy-blocking reagent to afford the intermediate of the formula (VI'):



(VI')

wherein R_6 and R_{20} are as hereinbefore defined and R_{15} is a suitable hydroxy protecting group. Suitable hydroxy protecting groups are those such as 2,2,2,-trichloroethoxy-carbonyl, 1,1,1-trichloro-2-methyl-2-propoxycarbonyl, *p*-nitrobenzyloxycarbonyl or allyloxycarbonyl, with 2,2,2-trichloroethoxycarbonyl being preferred. Typicaly, the reaction is conducted in an organic solvent, *e.g.* methylene chloride in the presence of an acid acceptor, *e.g.* triethylamine.

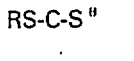
The R_{20}-nitrogen-protecting group may then be removed by conventional methods depending upon the exact nature of the R_{20}-nitrogen-protecting group utilized. This affords the intermediate of the formula (VII)



(VII)

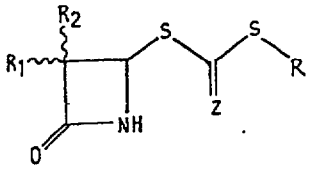
wherein R_6 and R_{15} are as hereinbefore defined.

Treatment of the intermediate of formula (V) with a nucleophile of the formula (VIII) or treatment of the intermediate of formula (VII) with chlorine, followed immediately by a nucleophile of the formula (VIII)



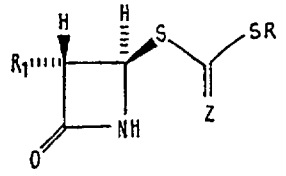
(VIII)

wherein R is as defined for formula (I) and has suitable amino-, hydroxy and/or carboxy protecting groups affords the compound of formula (IX)



(IX)

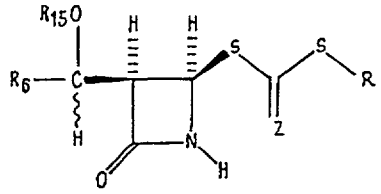
A monosubstituted lactam of formula (V) or (VII), *i.e.* wherein R_2 is hydrogen and R_1 is other than hydrogen, will give predominately the *Trans* product in the nucleophilic reaction together with a small amount of the *cis* product. Thus, the compounds of formula (IX) produced will have predominately the following relative stereochemistry



In the above formula Z is sulfur or oxygen.

The nucleophile of formula (VIII) is generated *in situ* by reaction of carbon disulfide, the appropriate thiol and a base such as potassium or sodium hydroxide. Generally, the addition of chlorine is at low temperatures (−30 to −10°C), but the subsequent reaction with the nucleophile of formula (VIII) is conducted at slightly higher temperatures, *e.g.* −10 to +10°C. This reaction produces predominately the two *trans* isomers, *e.g.* the compounds differing in their relative stereochemistry at the asymetric carbon attached at the 3-position of the azetidin-2-one ring. These two isomers are separated by conventional methods, *e.g.* crystallization and/or chromatography, at this stage of the reaction sequence.

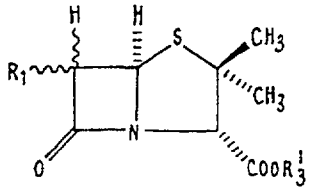
In the foregoing procedure (VI→VI'→VII), if the removal of the R_{20}-nitrogen-protecting group and introduction of the R_{15}-oxygen-protecting group is postponed until after the reaction with chlorine and the nucleophile of formula (VIII), there is produced a product mixture containing predominately the two *cis* isomers of the following formula after appropriate introduction of the R_{15}-hydroxy-protecting group



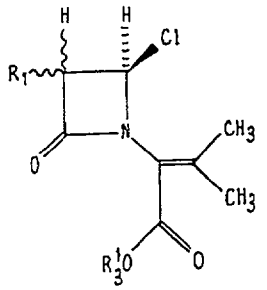
which are then separated by conventional methods, *e.g.* crystallization and/or chromatography, at this stage of the reaction sequence, together with the two *trans* isomers.

The compounds of the above formulae are each produced by the above-described processes in admixture with an equal quantity if their mirror images. Where the pure optically active final products are desired, the intermediates may be resolved by conventional means into their optically active forms. Alternatively, optically active compounds of formula (IX), wherein R_2 is hydrogen are preparable by starting from naturally occurring optically active penicillins. One such particularly preferred process comprises:

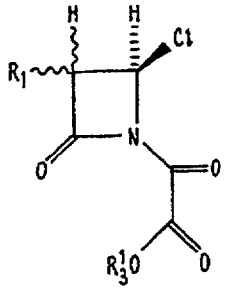
(a) treatment of an optically active compound of the formula



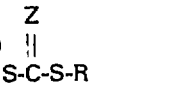
wherein R_3' is a lower alkyl or aralkyl group and R_1 is as hereinabove defined, with elemental chlorine, to afford predominately the *trans* intermediate of the formula



(b) ozonolysis thereof to afford the intermediate of the formula



(c) and reaction thereof with a nucleophile of the formula (VIII)



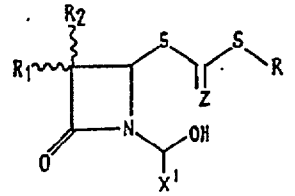
(VIII)

The first step (a) of this process is typically conducted in a suitable organic solvent at temperatures of about −30 to 0°C. Particularly suitable solvents are those such as methylene chloride, chloroform, carbon tetrachloride, toluene and xylene. Preferably, a nitrogen atmosphere is also used. The elemental chlorine is typically added as a solution having concentration of 0.5 to 5 M in a suitable organic solvent, *e.g.* carbon tetrachloride.

The second step (b) of the above described process is typically conducted at low temperatures, *e.g.* about −80 to about −40°C in a non-polar, organic solvent. Most preferably, the same slvent is utilized for this step as for step (a) of the instant process. A particularly suitable solvent is methylene chloride but others, such as chloroform, or xylene, may also be used.

The final step (c) of the above described process may be conducted without isolation and purification of the intermediate. Typically, this reaction is conducted at temperatures of about 0 to 50°C, with room temperatures being most particularly preferred.

The nitrogen of the lactam of formula (IX) is then reacted with an aldehyde X'-CHO to afford the compound of formula (X)



(X)

wherein X' is protected tetrazol-5-yl, *e.g.* 1-benzyl-tetrazol-5-yl, cyano, protected carboxyl, protected carbamoyl, *e.g.* benzylcarbamoyl, or -$CONR_4R_5$. (R_4R_4 being as above defined and at least one is lower alkyl). The carboxyl protecting group may be any suitable group such as *p*-nitrobenzyl, benzyl, allyl or benzhydryl. In a highly preferred embodment, it will be an allylic group so as to provide the possibility of applying neutral conditions when it is removed at the end of the reaction sequence.

This reaction is usually preferably conducted at reflux temperatures in a non-polar aprotic solvent such as tetra-hydrofuran or benzene. Reaction times of 2-10 hours are generally typical.

The compound of formula (X) is then treated with a chlorinating or brominating agent, *e.g.* thionyl chloride, methanesulfonyl chloride, thionyl bromide, or phosphorous tribromide in the presence of an equivalent of an acid acceptor, *e.g.* pyridine or triethylamine, so as to afford replacement of the hydroxy group in position ∝ relative to the ring nitrogen.

Suitable solvents are those such as methylene chloride, tetrahydrofuran or benzene. Temperatures of about 0-20°C and reaction times of 10-60 minutes are generally preferred.

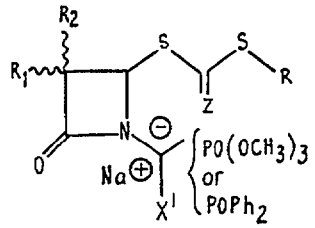
This chloride or bromide is then reacted with a suitable phosphine, *e.g.* tri-*p*-methoxyphenyl phosphine, tributylphosphine or most preferably, triphenylphosphine to afford the compound of the formula (II).

Typically, the reaction is conducted at room temperature in a polar aprotic solvent such as hexamethylphosphoramide or dimethylformamide. Reaction times generally vary from about 12-48 hours.

The transformations of compound (IX) to compound (II) are generally according to the procedures described by Woodward, *et. al., Helv. Chim. Acta.*, 55, 408-423 (1972).

Alternatively, in this synthetic procedure, when trimethoxyphosphine or sodium diphenylphosphinate is used in place of *e.g.* triphenylphosphine the corresponding dimethoxy-phosphonate or diphenylphosphonate is obtained.

Treatment of this phosphonate with a base such as sodium hydride in a polar solvent (dimethylformamide) results in an unisolated intermediate of the structure



which is also embraced by formula (II).

The compounds of formula (I) wherein R_3 is a phthalidyl or pivaloyloxmethyl group are prepared by reaction of the corresponding compound wherein R_3 is an alkali metal cation with chlorophthalide or pivaloyloxymethyl chloride in a solvent such as dimethylformamide. Preferably, a catalytic amount of sodium iodide is added.

While it is possible to prepare compounds of formula (I), wherein X is cyano, tetrazol-5-yl or an amide group, by using the appropriately substituted starting material of formula (II) (as described hereinabove) it is also feasible to convert the carboxyl group representing X in a compound of the formula (I) into an amide group, a cyano group or a tetrazol-5-yl group after the main reaction took place. The preparation of amides is effected according to known methods, for example by reacting the penem-3-carboxylic acid with ethylchloroformate or isobutylchloroformate in the presence of a tertiary amine, such as triethylamine, and the resulting product is further reacted without isolation with the desired amine or aqueous ammonia. In the latter case the resulting carboxamide may be further reacted according to the procedure of U.S. Patent 4,136,096, *e.g.* with *p*-toluenesulfonyl chloride in pyridine, to yield the corresponding cyano compound, *i.e.* the compound of formula (I), wherein X is cyano.

Compounds of formula (I), wherein X is the tetrazol-5-yl group may be obtained from the corresponding amide or cyano compound. If the cyano compound is employed reaction is preferentially carried out with an alkali metal azide in the presence of a Lewis acid, such as aluminum trichloride, in tetrahydrofuran. In general, the process of U.S. Patent 4,136,096 may be followed. Alternatively, by using a penem-3-carboxamide having an *N*-protecting group, *e.g.* penem-3-*N*-benzylcarboxamide, an iminochloride is first prepared by reaction with phosphorous pentachloride in the presence of a weak tertiary organic base, *e.g.* pyridine, and the iminochloride, without isolation, is then further reacted with an azide to obtain the *N*-protected penem-3-tetrazol-5-yl compound which upon removal of the protecting group, *e.g.* by hydrogenation according to known methods (*J. Org. Chem., Vol 18,* p.1283 (1953)) yields the desired compound of formula (I), wherein X is tetrazol-5-yl. In the above reaction other *N*-protecting groups may be used, such as *p*-nitrobenzyl or trichloroethyl.

Compounds preparable by the process of this invention and by following the Preparations and Examples hereinbelow include the following representative compounds of this invention each together with its enantiomer when prepared from racemic starting materials, and alone when prepared from chiral intermediates. The most highly preferred stereochemical isomers are named:
potassium (5R,6S,8R)-6-(1-hydroxyethyl)-2-methylthiopenem-3-carboxylate;
potassium (5R,6S,8R)-6-(1-hydroxyethyl)-2-methylthiopenem-3-carboxylate;
potassium (5R,6S,8R)-6-(1-hydroxyethyl)-2-benzylthiopenem-3-carboxylate;
potassium (5R,6S,8R)-6-(1-hydroxyethyl)-2-*p*-methylbenzyl-thiopenem-3-carboxylate;
potassium (5R,6S,8R)-6-(1-hydroxyethyl)-2-(3-pyridyl) methylthiopenem-3-carboxylate;
sodium (5R,6S,8R)-6-(1-hydroxyethyl)-2-(2-acetylaminoethyl) thiopenem-3-carboxylate;
sodium (5R,6S,8R)-6-(1-hydroxyethyl)-2-(*p*-hydroxybenzyl)thiopenem-3-carboxylate;
(5R,6S,8R)-6-(1-hydroxyethyl)-2-(2-aminoethylthio)penem-3-carboxylic acid;
(5R,6S,8R)-6-(1-hydroxyethyl)-2-(2-hydroxyethylthio)penem-3-carboxylic acid;
(5R,6S,8R)-6-(1-hydroxyethyl)-2-(2-carboxyethylthio)penem-3-carboxylic acid;
(5R,6S,8R)-6-(1-hydroxyethyl)-2-(methoxycarbonylethylthio)penem-3-carboxylic acid;
(5R,6S,8S)-6-(1-hydroxyethyl)-2-(2-aminoethylthio)penem-3-carboxylic acid;
(5R,6S,8S)-6-(∝-hydroxybenzyl)-2-(2-aminoethylthio)penem-3-carboxylic acid;
(5R,6S,8R)-6-(1-hydroxyethyl)-2-(2-dimethylaminoethylthio)penem-3-carboxylic acid;
(5R,6S,8R)-6-(1-hydroxyethyl)-2-(2-methylaminoethylthio)penem-3-carboxylic acid;
potassium (5R,6S,8S)-6-(∝-hydroxybenzyl)-2-methylthiopenem-3-carboxylate;
potassium (5R,6S,8S)-6-[1-hydroxy-1-(3-pyridyl)methyl]-2-methylthiopenem-3-carboxylate;
potassium (5R,6S,8S)-6-(∝-hydroxy-*p*-hydroxybenzyl)-2-methylthiopenem-3-carboxylate;
potassium (5R,6S,8R)-6-(∝-hydroxyphenethyl)-2-methylthio-penem-3-carboxylate;
potassium (5R,6S,8S)-6-(∝-hydroxy-*p*-methylbenzyl)-2-ethylthiopenem-3-carboxylate;
(5R,6S,8R)-6-(1-hydroxyethyl)-2-(1-propylthio)penem-3-carboxylic acid;
(5R,6S,8S)-6-(∝-hydroxybenzyl)-2-(1-propylthio)penem-3-carboxylic acid;
(5R,6S,8S)-6-[1-hydroxy-1-(2-thienyl)methyl]-2-ethylthiopenem-3-carboxylic acid;
potassium (5R,6S)-6-(1-hydroxymethyl)-2-ethylthiopenem-3-carboxylate,
potassium (5R,6R)-6-(1-hydroxymethyl)-2-ethylthiopenem-3-carboxylate,
potassium (5R,6S)-6-methyl-6-(1-hydroxyethyl)-2-ethylthiopenem-3-carboxylate,
(5R,6S,8R)-6-(1-hydroxyethyl)-2-ethylthiopenem-3-carboxamide,

(5R,6S,8R)-6-(1-hydroxyethyl)-2-ethylthio-3-dimethylamino-carbonylpenem,
(5R,6S)-2-methylthiopenem-3-carbonitrile,
(5R,6S)-2-ethylthiopenem-3-carbonitrile,
(5R,6S)-2-(2-aminoethylthio)penem-3-carbonitrile,
(5R,6S)-2-methylthio-3-(5-tetrazolyl)penem,
(5R,6S)-2-ethylthio-3-(5-tetrazolyl)penem,
(5R,6S)-2-(2-aminoethylthio)-3-(5-tetrazolyl)penem,
(5R,6S,8R)-6-(1-hydroxyethyl)-2-methylthiopenem-3-carbonitrile,
(5R,6S,8R)-6-(1-hydroxyethyl)-2-ethylthiopenem-3-carbonitrile,
(5R,6S,8R)-6-(1-hydroxyethyl)-2-(2-aminoethylthio)penem-3-carbonitrile,
(5R,6S,8R)-6-(1-hydroxyethyl)-2-methylthio-3-(5-tetrazolyl)penem,
(5R,6S,8R)-6-(1-hydroxyethyl)-2-ethylthio--(5-tetrazolyl)penem, and
(5R,6S,8R)-6-(1-hydroxyethyl)-2-(2-aminoethylthio)-3-(5-tetrazolyl)penem.

The following preparations and examples illustrate the invention. Throughout these preparations and examples, "NMR" denotes nuclear magnetic resonance spectra; "rotation" denotes optical rotation of the compounds in a suitable solvent; "MS" denotes mass spectra; "UV" denotes ultraviolet spectra; and "IR" denotes infrared spectra. Chromatography is performed on silica gel unless otherwise noted.

PREPARATION A

(I) *4-Ethylthioazetidin-2-one*

Potassium hydroxide (24 g) is dissolved in water (50 ml) and ethanol (300 ml), cooled to 0-5°C and ethanethiol (24 g) added, followed by 4-acetoxyazetidin-2-one (43 g). The solution is stirred under nitrogen at room temperature for 20 hours, then added to 10% aqueous sodium chloride solution (1 liter) and extracted four times with 300 ml portions of dichloromethane. The combined extracts are washed twice with saturated sodium chloride, the combined washings back-extracted with an equal volume of dichloromethane, and the combined organic layers dried over anhydrous magnesium sulfate, and evaporated. The residue is dried to constant weight under high vacuum to give the title product as a brown oil, having infrared spectrum ν max (CH_2Cl_2 solution) at 3300, 1765 cm^{-1}.

(II) *1-(t-Butyldimethylsilyl)-4-ethylthioazetidin-2-one*

A solution of 4-ethylthioazetidin-2-one (43 g) and triethylamine (55 ml) in dichloromethane (300 ml) is stirred at 0-5°C and *t*-butyl(chloro)dimethylsilane (58 g) is added in portions over 5 minutes. The solution is then stirred at room temperature for 0.5 hours. The mixture is washed with 200 ml portions of 0.2N hydrochloric acid, water and sodium bicarbonate solution, dried and evaporated, and the residue distilled at high vacuum to give a small forerun (e.g., 60-70°C/0.1 mm), followed by the title product, boiling point 110-120°C/0.1 mm pressure as a nearly colorless oil, having infrared spectrum ν max (film) at 1755 cm^{-1}.

(III) *1-(t-Butyldimethylsilyl)-3-(1-hydroxyethyl)-4-ethylthioazetidin-2-one*

A solution of lithium di-isopropylamide is prepared by adding 1.6 M butyllithium in hexane (6.7 ml) to diisopropylamine (1.01 g) in tetrahydrofuran (5 ml) at 0°C under argon. The resulting solution is added slowly to a solution of 1-(*t*-butyldimethylsilyl)-4-ethylthioazetidin-2-one (2.45 g) in dry tetrahydrofuran (10 ml) at −70 to −80°C. After 5 minutes, freshly distilled acetaldehyde (1 ml) is added, the mixture warmed to 0°C over 0.5 hour and quenched with acetic acid (1 ml). Dichloromethane (50 ml) is then added, and the solution is washed with water and sodium bicarbonate, dried and evaporated. The residue is dried at high vacuum to give a yellow oil (2.30 g) consisting mainly of the four isomers of the title compound, having infrared spectrum ν max (CH_2Cl_2) at 3300 and 1755 cm^{-1}.

Chromatography on silica gel, eluting with 10% ether in dichloromethane gave partial separation, with fractions containing pure samples of the least polar component (a *cis* isomer) and both more polar components (the two *trans* isomers); one of the latter could be crystallized from ether-hexane; melting point 52-53°C.

(IV) *1-(t-Butyldimethylsilyl)-3-(1-trichloroethoxycarbonyloxyethyl)-4-ethylthioazetidin-2-one*

A solution of 1-(*t*-butyldimethylsilyl)-3-(1-hydroxyethyl)-4-ethylthioazetidin-2-one (mainly trans isomers; 7.65 g) and pyridine (4.75 ml) in dichloromethane (100 ml) is stirred at 0-5°C, and trichloroethyl chloroformate (6.15 g) is added dropwise. The solution is stirred to room temperature during 1 hour. After washing with IN sulfuric acid and water, it is dried and evaporated to give the title compound as a pale yellow oil (11.6 g) which can be used without further purification in the next step. A sample partially solidified at −20°C, and two recrystallizations from hexane gave a pure isomer, melting point 92-93°C, having infrared spectrum ν max (CH_2Cl_2) at 1760, 1745 cm^{-1}.

(V) *3-(1-Trichloroethoxycarbonyloxyethyl)-4-ethylthioazetidin-2-one*

1-(*t*-butyldimethylsilyl)-3-(1-trichloroethoxycarbonyloxy-ethyl)-4-ethylthioazetidin-2-one (11.55 g) in tetrahydrofuran (160 ml) is stirred with water (20 ml) and concentrated hydrochloric acid (20 ml) for 2.5 hours at room temperature, then isolated by addition of dichloromethane (250 ml), followed by washing with 10% aqueous sodium chloride (2 × 150 ml). The organic phase is then dried and evaporated to the title compound as a yellow oil (6.5 g), having infrared spectrum ν max (film) at 3400, 1770, 1750 cm^{-1}.

(IV) *Ethyl-[trans-3-(1-Trichloroethoxycarbonyloxyethyl)-2-azetidinon-4-yl]trithiocarbonate*

The product of the previous step (6.5 g) is stirred in dichloromethane (100 ml) at -20°C and a 0.96M solution

of chlorine in carbon tetrachloride (19.4 ml) is added. The resulting solution is added to a rapidly stirred trithiocarbonate solution at 0-5°C prepared from ethanethiol (4.2 ml) in ethanol (50 ml) with addition of 1M aqueous potassium hydroxide (56 ml) followed by carbon disulfide (15 ml). After stirring the mixture at 0-5°C for 15 minutes, excess dichloromethane is added and the solution is washed with water and aqueous sodium bicarbonate, dried and evaporated.

The resulting mixture is chromatographed on silica gel (100 g), initially eluting with 10% dichloromethane in hexane to remove the by-product [CH_3CH_2S-S-CS-SCH_2CH_3, (diethyl tetrathiopercarbonate), a yellow nonpolar oil], then dichloromethane to give the title compound as an approximately 1,3:1 isomeric mixture, the major isomer being the less polar on thin layer chromatography in 5% ether:dichloromethane.

The major isomer is crystallized from the mixture using ether/hexane mixtures, affording in 3 crops a product having a melting point of 92-93°C and having infrared spectrum ν max (CH_2Cl_2) at 3350, 1770 and 1745 cm^{-1} (yellow needless). X-ray crystallography shows this isomer to be the 3S, 4R, 5R isomer.

Chromatography of the final mother liquors on silica gel using 3:1 dichloromethane:hexane gives additional fairly pure major isomer and minor isomer, the latter crystallized with some difficulty from ether-hexane as yellow prisms, melting point 64-67°C.

PREPARATION B

(I) *Ethyl-[1-t-butyldimethylsilyl-3-(1-hydroxyethyl)-2-azetidinone-4-yl]trithiocarbonate (isomeric mixture)*

1-*t*-butyldimethylsilyl-3-(1-hydroxyethyl)-4-ethylthio-2-azetidinone (15.0 g of an isomeric mixture prepared in step III of preparation A) is dissolved in dichloromethane (200 ml) and stirred at −20°C during addition of chlorine in carbon tetrachloride (53 ml of 1.05M solution).

A thiocarbonate solution is prepared from potassium hydroxide (8.9 g) in water (30 ml) and ethanol (300 ml) with addition of ethanethiol (12 ml), then carbon di-sulfide (40 ml). This solution is stirred at 0-5°C and the above chlorination mixture added. After 0.5 hours at 0-5°C, the mixture is extracted with dichloromethane, washing with water and aqueous sodium bicarbonate, dried ($MgSO_4$) and evaporated.

The resulting oil is dissolved in carbon tetrachloride and chromatographed on 300 g silica gel, eluting rapidly with carbon tetrachloride to remove the by-product (CH_3CH_2S-S-CS-S-CH_2CH_3), followed by 20% ether - carbon tetrachloride to give the title compound as an isomeric mixture as a yellow oil (15 g). By PMR spectrum, the ratio of *cis:trans* is determined to be about 2:1.

(II) *Ethyl [1-t-butyldimethylsilyl-3-(1-trichloroethoxy-carbonyloxyethyl)-2-azetidinon-4-yl]trithiocarbonate*

Ethyl [1-*t*-butyldimethylsilyl-3-(1-hydroxyethyl)-2-azetidinon-4-yl]trithiocarbonate (15.0 g) and pyridine (4.3 ml) is stirred in dichloromethane (50 ml) at 0-5°C and trichloroethyl chloroformate (7.4 ml) is added drop-wise. The mixture is stirred at room temperature for 2 hours, then diluted with dichloromethane, washed with 0.2N sulfuric acid, water and sodium bicarbonate. After drying over anhydrous magnesium sulfate, it is evaporated to give a mixture. This mixture is then separated by high pressure liquid chromatography (HPLC) on silica gel, using hexane-dichloromethane mixtures as eluting solvent. The first eluted component is a *trans* isomer (as determined by nuclear magnetic resonance), obtained as an oil. On hydrolysis, it affords the desilylated thiocarbonate, melting point 92-93°C, corresponding to the major isomer of the title compound of Preparation A, step (VI). The second eluted component is a *cis* isomer of the title compound of this example obtained as a yellow oil, ν max (film) 1750 cm^{-1}. The third eluted component is the second *cis* isomer of the title compound, obtained as a waxy yellow solid, melting point 80-85°C. The final component is the remaining *Trans* isomer of the title compound, obtained as a yellow oil which on hydrolysis gives the *trans* desilylated thiocarbonate, melting point 64-67°C, correspondong to the minor isomer of Preparation A, step (VI).

(III) *cis-Ethyl [3-(1-trichloroethoxycarbonyloxyethyl)-2-azetidinone-4-yl]trithiocarbonate (two isomers)*

(i) *Isomer I*

The first eluted *cis*-N-silyl isomer from step (II) is hydrolyzed by stirring in tetrahydrofuran:water:concentrated hydrochloric acid (20:1:1 by volume) at room temperature until thin layer chromatography (tlc) shows the reaction to be complete. The mixture is extracted in ether:water and the organic phase dried and evaporated. The residue is crystallized from ether:hexane to give yellow needles, melting point 108-111°C.

(ii) *Isomer II*

By an identical process starting with the second eluted *cis*-N-silyl isomer of step (II), the corresponding thio-carbonate is obtained from ether:hexane as yellow needles, melting point 118-120°C.

PREPARATION C

(3S,4R,5R)-Ethyl 3-(1-trichloroethoxycarbonyloxyethyl-2-azetidinone-4-yl]trithiocarbonate

A. To a solution of 100 g 6-β-aminopenicillanic acid in 1200 ml 2.5 N sulfuric acid is added 150 g sodium bromide. To the stirred solution at 0°C is added simultaneously 40 g sodium nitrite in 150 ml water and 40 ml bromine. The addition is completed in 10 minutes, maintaining the temperature at 0° to 5°C. The mixture is then stirred rapidly for 1 hour, then filtered. The filter cake is washed with water and taken up in 600 ml ethyl acetate. The ethyl acetate solution is washed with water, cold dilute sodium bisulfite solution and then again with water. After drying over anhydrous sodium sulphate, the solvent is removed under vacuum to afford 67 g

in 85:15 ratio (by NMR data) of 6,6-dibromopenicillanic acid and 6β-bromopenicillanic acid.

IR: 1728 cm^{-1} and 1800 cm^{-1} (chloroform solution)

NMR: δ = 5.7, 1H, s; δ = 4.5, 1H, s; δ = 1.55-1.67, 6H ($CDCL_3$).

B. To a solution of 67 g in 85:15 ratio of 6,6-dibromopenicillanic acid to 6β-bromopenicillanic acid in 500 ml dimethylformamide at 0°C is added 37.3 g finely powdered potassium carbonate. The solution is stirred 5-10 minutes and 38.3 g methyl iodide is added. The reaction mixture is then stirred for 2 hours allowing the temperature to come to ambient. The reaction is followed by thin layer chromatography eluting with methylene chloride. When complete, the reaction is decanted and the solvent removed under high vacuum to leave 100 ml of solution. To this is added 600 ml ethyl acetate. The solution is then washed with water, dried over anhydrous sodium sulphate and concentrated under vacuum to afford 63 g crude methyl ester. Subsequently, 48 g of pure methyl 6,6-dibromo-penicillanate is isolated from this crude product by high pressure liquid chromatography eluting with methylene chloride.

NMR: δ = 5.7, 1H, s; δ = 4.48, 1H, s; δ = 3.73, 3H, s; δ = 1.42, 3H,s; δ = 1.59, 3H, s ($CDCl_3$).

C. To a solution of 13.7 g methyl 6,6-dibromopenicillanate in 250 ml dry tetrahydrofuran at −78°C under nitrogen is added 14.7 ml of 3M methyl magnesium bromide in ethyl ether. After stirring for 30 minutes at −78°C, 8 g of freshly distilled acetaldehyde is added and stirring continued for 45 minutes. The reaction mixture is warmed to −20°C at which time 50 ml 1 M potassium phosphate mono-basic is added and stirring continued for 5 minutes. The reaction mixture is then poured into 1 liter cold ethyl acetate and washed once with 150 ml brine solution and twice with 150 ml water. The ethyl acetate layer is separated, dried over anhydrous sodium sulfate and evaporated under vacuum. The products, methyl 6α-bromo-6β-(1-hydroxyethyl)penicillanate and methyl 6β-bromo-6α-(1-hydroxyethyl)penicillanate, are detected by thin layer chromatography on silica gel eluting with 10% ethyl acetate/chloroform.

D. To a solution of 8.0 g methyl 6-bromo-6-(1-hydroxy-ethyl)penicillanate in 200 ml 95% ethanol is added 800 mg 10% palladium on calcium carbonate. The solution is shaken under 2 atmospheres hydrogen pressure for 5 hours. Disappearance of starting material is followed by thin layer chromatography eluting with 20% ethyl acetate/chloroform. The catalyst is filtered and 100 ml 1 M potassium phosphate buffer at pH 7 is added. The precipitate formed is filtered and washed with ethanol. The ethanol is removed under vacuum and 200 ml ethyl acetate added. After washing twice with 50 ml water, and drying over anhydrous sodium sulfate, the ethyl acetate is removed under vacuum to afford a crude mixture of methyl 6-(1-hydroxyethyl)penicillanate. Column chromatography of 18 g of said mixture eluting with 20% ethyl acetate affords 6.4 g methyl (5R,6S,8R)-6-(1-hydroxyethyl)-penicillanate.

NMR: δ = 2.4-2.7, 1H, d; δ = 4.41, 1H, s;
δ = 3.74, 3H, s; δ = 3.2-3.33, 1H;
δ = 1.25-1.35, 3H, d; δ = 1.44, 3H, s;
δ = 1.61, 3H, s ($CDCl_3$).

E. To a solution of 6.2 g methyl (5R,6S,8R)-6-(1-hydroxyethyl)penicillanate in 60 ml. dry methylene chloride at 0°C under nitrogen is added 3.8 ml pyridine then 3.3 ml β,β,β-trichloroethylchloroformate. The reaction is stirred 15 minutes until all starting material is reacted (as determined by thin layer chromatography with 20% ethyl acetate/chloroform). The solution is poured into 250 ml cold methylene chloride and washed twice with cold 10% phosphoric acid solution, once with cold dilute sodium bicarbonate, and then with water. After drying over anhydrous sodium sulfate, the solvent is removed under vacuum to afford 10.0 g methyl (5R,6S,8R)-6-(1-trichloroethoxycarbonyloxyethyl)penicillanate.

NMR: δ = 5.13-5.16, 1H, d; δ = 4.78, 2H, s;
δ = 4.43, 1H, s; δ = 3.76, 3H, s;
δ = 3.38-3.58, 1H; δ = 1.45-1.63, 9H; ($CDCl_3$).

F. To a solution of 9.1 g methyl (5R,6S,8R)-6-(1-trichloroethoxycarbonyloxyethyl)penicillanate in 350 ml distilled methylene chloride at −20°C under nitrogen is added 62.3 ml of 1 M chlorine/carbon tetrachloride solution. The reaction is stirred for 15 minutes at about −20°C (until found to be complete by thin layer chromatography eluting with chloroform). The solution is evaporated under vacuum to afford 10.0 g of product comprising (3S,4R,5R)-1-[(2-methyl-1-methoxycarbonyl)prop-1-enyl]-3-(1-trichloroethoxycarbonyloxyethyl)-4-chloroazetidin-2-one.

IR: 1720, 1770-1790 cm^{-1} (chloroform solution)

NMR: δ = 5.79-5.81, 1H, d; δ = 4.75, 2H, s;
δ = 3.74, 3H, s; δ = 2.27, 3H, s; δ = 2.0, 3H, s;
δ = 1.45-1.54, 3H, d ($CDCl_3$).

G. Through a solution of 7.7 g crude (3S,4R,5R)-1-[2-methyl-1-methoxycarbonyl)prop-1-enyl]-3-(1-trichloroethoxycarbonyloxyethyl)-4-chloroazetidin-2-one in 250 ml methylene chloride at about −78°C is passed ozone for 45 minutes. (Disappearance of starting material is followed by thin layer chromatography eluting with chloroform). The reaction is allowed to sit for 1 hour at −78°C with excess ozone. Nitrogen is then bubbled in for 3-5 minutes and then 3 ml dimethylsulfide is added. The solution is allowed to warm to ambient temperature and held for 2 hours. Nitrogen is bubbled through the solution to remove excess dimethylsulfide. Optionally, the solvent may be removed and the residue purified by chromatography to afford (3S,4R,5R)-1-(2-methoxy-1,2-dioxoethyl)-3-(1-trichloroethoxycarbonyloxyethyl)-4-chloroazetidin-2-one.

NMR: δ = 5.97-6.0, 1H, d; δ = 5.76, 2H, s;
δ = 4.93, 2H, s; J = 1 c/s, δ = 1.45-1.55, 3H, d.

H. To a solution of 7.8 g potassium hydroxide in 150 ml water and 150ml ethanol at 0°C is added 15.3 ml ethanethiol. After stirring for 10 minutes 38.5 ml carbon di-sulfide is added. The solution turns deep yellow and is stirred an additional 10 minutes. The solution of step G is cooled to 0°C and poured into this solution. The mixture is then stirred 45 minutes allowing to warm to ambient temperature. The reaction is followed by thin layer chromatography eluting with chloroform. When the reaction is complete, 200 ml methylene chloride is added, followed by 20 g citric acid in 200 ml water. The reaction mixture is stirred 5 minutes and then poured into 500 ml methylene chloride. The organic layer is separated, washed first with water, then with cold dilute sodium bicarbonate solution and then again with water. After drying over anhydrous sodium sulfate, the solvent is removed under vacuum. The crude reaction product is chromatographed on coarse silica gel eluting with 20% chloroform/hexane changing to 100% chloroform to afford 6.4 g (3S,4R,5R)-ethyl [3-(1-trichloroethoxycarbonyloxyethyl)-2-azetidinone-4-yl]-trithiocarbonate, alternatively named as (3S,4R,5R)-[1-trichloroethoxycarbonyloxyethyl]-4-[(ethylthio)-carbonothioylthio]-azetidin-2-one.

Rotation: $[\alpha]_D^{26} = +154.2°$ (0.4% in dioxane)

NMR: δ = 5.6-5.63, 1H, δ = 5.1-5.3, 1H, m; δ = 4.76, 2 H, s; δ = 3.17-3.52, 3H; δ = 1.22-1.54, 6H; ($CDCl_3$).

PREPARATION D

Allyl Glyoxylate Hydrate

Lead tetraacetate (70 g) is added in portions over one half hour to a stirred solution of diallyl tartarate (40g) in ethyl acetate (400 ml). The mixture is then stirred for an additional one half hour, filtered and washed with ethyl acetate. The filtrate is treated with 10 ml water and evaporated at 50°C/100 mm pressure to remove the ethyl acetate. This residue is distilled at about 30 mm pressure. After initial removal of acetic acid, the title product is collected at 70-80°C/30 mm, as a colourless oil.

EXAMPLE 1

a. *Ethyl [1-(Allyloxycarbonylhydroxymethyl)-3-(1-trichloroethoxycarbonyloxyethyl)-2-azetidinone-4-yl]trithiocarbonate*

(i) *Isomer I*

A mixture of the major isomer of the product thiocarbonate from Preparation A (2.13 g), allyl glyoxylate hydrate (1.0 g) (from Preparation D) and benzene (25 ml) is refluxed under argon with a water collector for 20 hours. The solution is cooled, diluted with dichloromethane (70 ml) and washed with water (2 × 100 ml), dried and evaporated to give a thin layer chromatography - pure product as a yellow oil.

(ii) *Isomer II*

Repetition of the procedure of the foregoing paragraph a(i), using the minor isomer of Preparation A (1.02 g) and allyl glyoxylate (0.48 g) in 15 ml benzene with 20 hours reflux is prepared the minor isomer product of this example as a yellow oil.

b. *Ethyl [1-(Allyloxycarbonylchloromethyl)-3-(1-trichloroethoxycarbonyloxyethyl)-2-azetidinone-4-yl]trithiocarbonate*

(i) *Isomer I*

The Isomer I product of the foregoing paragraph a(i) (2.77 g) in dichloromethane (30 ml) and methanesulfonyl-chloride (0.87 g) is stirred at 0°C, and triethylamine (0.78 g), added dropwise. After 5 minutes at room temperature, the solution is diluted with dichloromethane, washed with 5% aqueous tartaric acid and sodium bicarbonate, dried and evaporated to give a brown oil, having infrared spectrum ν max (film) at 1770 and 1750-1735 (broad) cm^{-1}.

(ii) *Isomer II*

The procedure of the foregoing paragraph b(i) is followed using the Isomer II product of paragraph a(ii) (1.30 g) in 20 ml dichloromethane with triethylamine (0.29 g and mesyl chloride (0.33 g). The final solution after workup is filtered through 5 g silica gel, washing with dichloromethane. Evaporation gives the product as a yellow oil (1.0 g), pure by thin layer chromatography with infrared spectrum ν max (film) 1770, 1755 and 1735 cm^{-1}.

C. *Ethyl [1-(Allyloxycarbonyl[triphenylphosphoranyl]methyl)-3-(1-trichloroethoxycarbonyloxyethyl)-2-azetidinone-4-yl]-trithiocarbonate*

(i) *Isomer I*

The crude product of the foregoing paragraph b(i) (2.6 g) is stirred with tripheylphosphine (2.8 g) in dry dimethylformamide (30 ml) at room temperature for 40 hours, then extracted with ether, washing with three portions of water. The solution is then dried over anhydrous magnesium sulfate and evaporated. The residue is chromatographed on silica gel (150 g), eluting with 1:1 dichloromethane: hexane to remove excess triphenylphosphine, then with pure dichloromethane to give recovered starting material. The title product is eluted with 5-10% ether-dichloromethane, and pure fractions pooled, evaporated and dried at high vacuum to afford the title compound having infrared spectrum ν max (CH_2Cl_2) at 1750, 1730 and 1690 cm^{-1}.

(ii) *Isomer II*

Using 1.08 g of the Isomer II prepared in the foregoing paragraph b(ii) and triphenylphosphine (0.75 g) in

dimethylformamide (15 ml) and repeating the procedure of paragraph c(i) with stirring at room temperature for 72 hours affords the desired Isomer II of the title product as a yellow foam.

d. *Allyl trans-6-(1-trichloroethoxycarbonylethyl)-2-ethylthiopenem-3-carboxylate*

(i) *Isomer I*

A solution of the Isomer I phosphorane prepared as in paragraph c(i), (0.975 g) in dry toluene (20 ml) is refluxed under argon in an oil bath at 120-125°C for 65 hours, then cooled, diluted with 20 ml hexane and applied to approximately 20 g silica gel. Elution with 1:1 dichloromethane:hexane followed by dichloromethane gives Isomer I of the title compound, which is crystallized from dichloromethane:ether:hexane to give fibrous needles (0.255 g), melting point 123-127°C and having infrared spectrum ν max (CH_2Cl_2) at 1795, 1745, 1700 cm^{-1}. *Anal.*

Found: C 38.8; H, 3.6; N, 2.9%

$C_{16}H_{18}NO_6S_2Cl_3$ req : C 39.15; H, 3.7; N, 2.8%

(ii) *Isomer II*

By similar heating of the Isomer II of the phosphorane as prepared in paragraph c(ii) (0.90 g) in toluene (10 ml) for 36 hours and plate chromatography, there is obtained Isomer II of the title product as a yellow oil having infrared spectrum νmax (CH_2Cl_2) at 1790, 1750, 1705 cm^{-1}.

e. *Allyl trans-6-(1-hydroxyethyl)-2-ethylthiopenem-3-carboxylate*

(i) Isomer I

Isomer I of paragraph d(i) (0.175 g) is stirred at 25°C for 1 hour with activated zinc dust (0.05 g) in acetic acid (1 ml) and tetrahydrofuran (3 ml). The mixture is diluted with excess dichloromethane and washed with water, aqueous sodium bicarbonate and aqueous sodium chloride, dried and evaporated. The residue is purified on a preparative thin layer chromatography plate eluting with 20% ether-dichloromethane and crystallized from ether-hexane to afford Isomer I of allyl *trans*-6-(1-hydroxyethyl)-2-ethylthiopenem-3-carboxylate, melting point 65-66°C having infrared spectrum νmax (CH_2Cl_2) at 3250, 1790 and 1705cm^{-1}.

(ii) *Isomer II*

In a manner similar to that of paragraph e(i), 0.15 g of Isomer II of paragraph d(ii) is deprotected in tetrahydrofuran-acetic acid with zinc dust, and chromatographed on a thin layer chromatography plate to obtain Isomer II of allyl *trans*-6-(1-hydroxyethyl)-2-ethylthio-penem-3-carboxylate, which is crystallized from ether-hexane as cream prisms, melting point 86-88°C, having infrared spectrum νmax (CH_2Cl_2) at 3300, 1795 and 1700 cm^{-1}.

f. Repetition of the procedure detailed in paragraphs a) to e) utilizing the two *cis* isomers of ethyl [3-(1-trichloroethoxycarbonyloxyethyl)-2-azetidinone-4-yl]trithiocarbonate of Preparation B(III), benzyl [3-(1-trichloroethoxycarbonyloxyethyl)-(2-azetidinone-4-yl)]trithiocarbonate, 2-trichloroethoxycarbonyloxyethyl-[3-(1-trichloroethoxycarbonyloxyethyl)-(2-azetidinone-4-yl)]trithiocarbonate, methyl [3-(1-trichloroethoxycarbonyloxyethyl)-(2-azetidinone-4-yl)]trithiocarbonate, 2-allyloxycarbonyl-aminoethyl-[3-(1-trichloroethoxycarbonyloxyethyl)-(2-azetidione-4-yl)-trithiocarbonate (3SR, 4RS, 5SR) isomer p.m.r. (in $CDCl_3$): 1.56 (d,j equal 7,34) 3.54 (m,5H) 4.60 (d,j equal 7,2H) 4.83 (s,2H) 5.1-5.5 (m,4H) 5.55 (d,j equal 2.5,1H) 5.7-6.2 (m,1H) and 6.84 (s,1H). (3SR, 4RS, 5RS) isomer p.m.r. (in $CDCl_3$):
1.50 (d,j equal 7,3H) 3.50 (m,5H) 4.57 (d,j equal 7,2H) 5.1-5.5 (m,4H) 5.68 (d,j equal 2.5, 1H) 5.7-6.2 (m,1H) and 6.96 (s,1H), and *n*-butyl [3-(1-trichloroethoxycarbonyloxyethyl)-(2-azetidinone-4-yl)]-trithiocarbonate, affords the two *cis* isomers of allyl *cis*-6-(1-hydroxy-ethyl)-2-ethylthiopenem-3-carboxylate,
the two isomers of allyl *trans*-6-(1-hydroxyethyl)-2-benzylthiopenem-3-carboxylate,
of allyl *trans*-6-(1-hydroxy-ethyl)-2-(hydroxyethyl)thiopenem-3-carboxylate,
of allyl *trans*-6-(1-hydroxyethyl)-2-methylthiopenem-3-carboxylate,
of allyl *trans*-6-(1-hydroxyethyl)-2-[(2-allyloxycarbonyl-aminoethyl)thio]penem-3-carboxylate (5RS, 6SR, 8RS)-isomer m.p. 86-87°C pmr spectrum ($CDCl_3$):
1.34 (d,j equal 7,3H) 1.79 (d,j equal 6,1H)
3.11 (m,2H) 3.46 (m,2H) 3.70 (dd,j equal 1.5 and 8.5, 1H)
4.22 (m,1H) 4.56 (d,j equal 7,2H) 4.75 (m,2H) 5.0-5.5 (m,6H)
5.63 (s,j, 1.5,1H) and 5.6-6.2 (m,2H).
of allyl *trans*-6-(1-hydroxyethyl)-2-(*n*-butylthio)penem-3-carboxylate, respectively.

g) *Potassium trans-6-(1-hydroxyethyl)-2-ethylthiopenem-3-carboxylate*

(i) *Isomer I*

A solution of Isomer I of allyl *trans*-6-(1-hydroxyethyl)-2-ethylthiopenem-3-carboxylate (52 mg) and 0.5m potassium-2-ethylhexanoate (0.36 ml) in 1.2 ml ethyl acetate and 0.8 ml dichloromethane is stirred with addition of 3 mg triphenylphosphine and 5 mg of tetrakis (triphenylphosphine) palladium-(0), under argon. After a few minutes, precipitation of product occurs and after 30 minutes, excess ethyl acetate is added and the precipitate centrifuged. Washing with ether and drying at high vacuum gives, as a yellowish powder, the title product having infrared spectrum νmax (nujol) at 3300, 1775 and 1600 cm^{-1}. By X-ray crystallography of the starting materials the stereochemistry of this product is designated 5R,6S,8S, together with its enantiomer.

(ii) *Isomer II*

The procedure of the foregoing paragraph is repeated using Isomer II of allyl *trans*-6-(1-hydroxyethyl)-2-ethylthiopenem-3-carboxylate (40 mg), 2 ml of 1:1 ethyl acetate: dichloromethane, 0.26 ml of 0.5m potassium-2-ethylhexanoate, 3 mg triphenylphosphine and 5 mg palladium complex. After 20 minutes, ether

(2 ml) is added gradually and the product centrifuged and dried under high vacuum to give the title product as a cream powder having infrared spectrum vmax (nujol) at 3400, 1780 and 1605cm^{-1}. By X-ray crystallography of the starting materials the stereochemistry of this product is designated 5R,6S,8R, together with its enantiomer.

h. Repetition of the procedure detailed in step g) using the two isomers of allyl *cis*-6-(1-hydroxymethyl)-2-ethylthiopenem-3-carboxylate, of allyl *trans*-6-(1-hydroxy-ethyl)-2-benzylthiopenem-3-carboxylate, of allyl *trans*-6-(1-hydroxyethyl)-2-[(2-hydroxyethyl)thio]penem-3-carboxylate and, of allyl *trans*-6-(1-hydroxymethyl)-2-methylthiopenem-3-carboxylate and of allyl *trans*-6-(1-hydroxyethyl)-2-(*n*-butylthio)penem-3-carboxylate affords the two isomers of potassium *cis*-6-(1-hydroxy-ethyl)-2-ethylthiopenem-3-carboxylate, *i.e.*, the 5R, 6R, 8R and the 5R, 6R, 8S isomers, each together with its enantiomer,
potassium (5R,6S,8S)-6-(1-hydroxyethyl)-2-benzylthiopenem-3-carboxylate and the corresponding 5R, 6S, 8R isomer, each together with its enantiomer,
the two isomers (5R, 6S, 8S and 5R, 6S, 8R) of potassium *trans*-6-(1-hydroxyethyl-2-[(2-hydroxyethyl)thio]penem-3-carboxylate, each together with its enantiomer,
the two isomers (5R, 6S, 8S and 5R, 6S, 8R) of potassium *trans*-6-(1-hydroxyethyl)-2-methylthiopenem-3-carboxylate, each together with its enantiomer, and
the two isomers (5R, 6S, 8S and 5R, 6S, 8R) of potassium *trans*-6-(1-hydroxyethyl-2-(*n*-butylthio)penem-3-carboxylate, each together with its enantiomer, respectively.

Each of the two isomers of allyl *trans*-6-(1-hydroxyethyl)-2[(2-allyloxycarbonylaminoethyl)thio]penem-3-carboxylate (0.04 g) in dichloromethane (0.5 ml) are stirred individually at 25°C under argon with 2-ethylhexanoic acid (0.04 g), triphenylphosphine (0.007 g) and tetrakis(tri-phenylphosphine)palladium (0.007 g). After 3 hours, each solid is collected by centrifuge, washed with ethyl acetate and dried at 25°C *in vacuo*. Resulting are the two isomers (5R, 6S, 8S and 5R, 6S, 8R) of *trans*-6-(1-hydroxyethyl)-2-[(2-aminoethyl)thio]penem-3-carboxylic acid, each together with its enantiomer.

EXAMPLE 2

The two isomers of potassium *trans*--(1-hydroxyethyl)-2-ethylthiopenem--carboxylate (0.27 g) of Example 1 g are individually added to a stirred mixture of dry di-methylformamide (2 ml), pivaloyloxymethyl chloride (0.17 ml) and sodium iodide (0.15 g). The mixture is stirred in the dark under nitrogen for 5 hours, then added to water and extracted with ether. The extract is washed with water, a dilute solution of sodium thiosulfate, and finally with saturated sodium chloride solution, dried and evaporated to obtain the two isomers (5R, 6S, 8S and 5R, 6S, 8R) of pivaloyloxymethyl *trans*--(1-hydroxyethyl)-2-ethylthiopenem-3-carboxylate, each together with its enantiomer.

EXAMPLE 3

A. To a solution of 7.7 g (3S,4R,5R)-3-[1-trichloroethoxycarbonyloxyethyl]-4-[(ethylthio)carbonothioylthio]-azetidin-2-one in 90 ml benzene is added 3.5 g allyl glyoxalate. Under nitrogen this mixture is slowly azeotroped for 24 hours. (The reaction is followed by thin layer chromatography eluting with 10% ethyl ether/methylene chloride). Approximately 2.0 ml additional allylglyoxalate is added and the reaction is azeotroped for 10 additional hours. The reaction is then cooled and 150 ml benzene is added. The resultant solution is washed 5 times with 50 ml portions of water. The solution is dried over anhydrous sodium sulfate and the solvents removed under vacuum. Then, 50 ml toluene is added and removed 3 times under high vacuum to afford as the product 9.2 g crude allyl [(3S,4R,5R)-3-(1-trichloroethoxycarbonyloxyethyl)-4-[(ethylthio)carbonothioylthio]-2-azetidinone-1-yl]-2-hydroxyacetate.

Rotation: $[\alpha]_D^{26} = +46.9°$ (0.2% in ethanol)

NMR: δ = 6.07-6.21, 1H; δ = 4.76, 2H, s;
δ = 3.17-3.52, 3H; δ = 1.22-1.54, 6H.

B. To a solution of 9.0 g crude allyl [(3S,4R,5R)-3-(1-trichloroethoxycarbonyloxyethyl)-4-[(ethylthio)carbonothioylthio]-2-azetidinone-1-yl]-2-hydroxyacetate in 125 ml dry methylene chloride at 0°C is added 2.8 g methylsulfonyl chloride followed by 2.5 g triethylamine. The reaction is followed by a thin layer chromatography eluting with 5% ethyl ether/methylene chloride. After stirring 45 minutes, 125 ml methylene chloride is added. The reaction is then washed once with cold 10% phosphoric acid solution, once with water, and once with cold dilute sodium bicarbonate solution and then twice with water. The solution is dried over anhydrous sodium sulfate and the solvents are removed under vacuum. The crude product is chromatographed on coarse silica gel with 20% hexane/chloroform to afford 6.9 g allyl [(3S,4R,5R)-3-(1-trichloroethoxycarbonyloxyethyl)-4-[(ethylthio)carbonothioylthio]-2-azetidinone-1-yl]-2-chloroacetate.

IR: 1760-1800 cm^{-1} ($CDCl_3$)

NMR: δ = 6.23-6.29, 1H; δ = 4.72, 2H, s;
δ = 1.24-1.56, 6H; ($CDCl_3$).

C. To a solution of 6.9 g allyl [(3S,4R,5R)-3-(1-trichloroethoxycarbonyloxyethyl)-4-[(ethylthio)carbonothioyl-thio]-2-azetidinone-1-yl]-2-chloroacetate in 90 ml dimethylformamide at 0°C is added 4.7 g triphenylphosphine. The reaction is allowed to warm to ambient and is stirred 40 hours. (Completion of reaction is determined by thin layer chromatography eluting with methylene chloride). An additional 780 mg triphenylphosphine is added and the reaction stirred at ambient temperature. After 40

hours, the reaction mixture is poured into 300 ml ethyl ether and washed twice with brine solution and 5 times with water. The solvent is dried over anhydrous sodium sulfate and removed under vacuum. The crude product is chromatographed on coarse silica gel with methylene chloride to afford 6.1 g allyl [(3S,4R,5R)-3-(1-trichloroethoxy-carbonyloxyethyl)-4-[(ethylthio)carbonothioylthio)-2-azetidinone-1-yl]-2-triphenylphosphine acetate.

Rotation: $[\alpha]_D^{26} = +77.0°$

IR: 1760-1780 cm^{-1} (chloroform solution).

NMR: $\delta = 6.3\text{-}6.4$, 1H, $\delta = 4.70$, 2H, s;

δ 1.16-1.49, 6H ($CDCl_3$).

D. A solution of 6.1 g allyl [(3S,4R,5R)-3-(1-tri-chloroethoxycarbonyloxyethyl)-4-[(ethylthio)carbonothioyl-thio[-2-azetidinone-1-yl]-2-triphenylphosphine acetate in 400 ml toluene is refluxed under nitrogen for 22 hours. (Reaction is followed by thin layer chromatography eluting with 5% ethyl acetate/toluene.) The toluene is then removed under high vacuum and the reaction mixture is chromatographed on coarse silica gel with toluene, changing to 10% ethyl acetate/toluene. A mixture of 1.5 g reaction product is isolated which is rechromatographed and then purified by high pressure liquid chromatography with 2% ethyl acetate/toluene to afford 1.18 g allyl (5R,6S,8R)-2-ethylthio-6-[1-trichloroethoxycarbonyloxyethyl]penem-3-carboxylate and 240 mg allyl (5,6,-cis)-2-ethylthio-6-[trichloroethoxycarbonyloxethyl]penem-3-carboxylate.

5R,6S,8R Rotation: $[\alpha]_D^{26} = +172.8°$ (0.25%) in ethanol).

5,6-cis Rotation: $[\alpha]_D^{26} = +156.4°$ (0.45% in ethanol).

E. To a solution of 1.18 g allyl (5R,6S,8R)-2-ethylthio-6-[1-trichloroethoxycarbonyloxyethyl]penem-3-carboxylate in 9.0 ml tetrahydrofuran under nitrogen is added 3 ml acetic acid and 500 mg activated zinc powder. The reaction is stirred for 2 1/2 hours during which time additional 400 mg zinc metal is added in two portions. The reaction is followed by thin layer chromatography eluting with 5% ethyl acetate/toluene. The reaction mixture is then filtered and 150 ml methylene chloride added. After washing twice with water, 3 times with cold 3% sodium bicarbonate solution and twice with brine solution, the solution is dried over anhydrous sodium sulfate. Removal of the solvents under vacuum affords 720 mg allyl (5R,6S,8R)-2-ethylthio-6-(1-hydroxyethyl)-penem-3-carboxylate.

Similarly 220 mg allyl (5,6-cis)-2-ethylthio-6-[trichloro-ethoxycarbonyloxyethyl]penem-3-carboxylate is converted by above procedure to yield 130 mg allyl (5,6-cis)-2-ethylthio-6-(1-hydroxyethyl)penem-3-carboxylate.

F. To a solution of 700 mg allyl (5R,6S,8R)-2-ethylthio-6-(1-hydroxyethyl)penem-3-carboxylate in 4 ml methylene chloride and 8 ml ethyl acetate under nitrogen is added 46.6 mg triphenylphosphine. To this is added 4.86 ml 0.5 molar potassium-2-ethylhexanoate in ethyl acetate. Then, 51.1 mg tetrakis(triphenylphosphine)palladium-(0) is added and the solution is stirred for 15 minutes. An additional 100 mg triphenyl phosphine and 25 mg tetrakis(triphenylphosphine)palladium-(0) is added, followed by 10 ml ethyl ether. The product slowly precipitates and after 1 hour the solution is filtered and washed with ethyl acetate and ethyl ether, to afford 45 mg potassium (5R,6S,8R)-2-ethylthio-6-(1-hydroxyethyl)penem-3-carboxylate. To the mother liquor is added 10 ml ethyl ether. After refrigeration overnight, a second crop of crystals is filtered to yield an additional 90 mg of the potassium salt.

NMR: $\delta = 1.25\text{-}1.49$, 6H; $\delta = 2.76\text{-}3.14$, 2H;

$\delta = 3.85\text{-}3.94$, 1H; $\delta = 4.12\text{-}4.37$, 1H;

$\delta = 5.65\text{-}5.67$, 1H, d; ($D_2O$)

Rotation: $[\alpha]_D^{26} = -145.2°$

IR: 1600 cm^{-1} and 1770 cm^{-1} (nujol).

To a solution of 130 mg allyl (5,6-cis)-2-ethylthio-6-(1-hydroxyethyl)penem-3-carboxylate in 0.7 ml methylene chloride and 1.4 ml ethyl acetate is added 7.0 mg $Pd(Ph_3P)_4$,7 mg triphenyl phosphine and 0.63 ml of 0.5 molar potassium-2-ethyl hexanoate in ethyl acetate. The product precipitates immediately, and after stirring for 1/2 hour is filtered, washed with ethyl acetate and ethyl ether to afford 105 mg potassium (5,6-cis)-2-ethylthio-6-(1-hydroxyethyl)-penem-3-carboxylate.

Rotation: $[\alpha]_D^{26} = -145.9°$ (0.1% in water)

NMR: $\delta = 1.23\text{-}1.43$, 6H; $\delta = 2.78\text{-}3.12$, 2H;

$\delta = 3.84\text{-}4.02$, 1H; $\delta = 4.15\text{-}4.23$, 1H;

$\delta = 5.72\text{-}5.77$, 1H, d; ($D_2O$).

G. Repetition of the procedures detailed in steps A - F utilizing (3S,4R,5R)-benzyl[3-(1-trichloroethoxy-carbonyloxyethyl)-(2-azetidinone-4-yl)]trithiocarbonate, (3S,4R,5R)-2-trichloroethoxycarbonyloxyethyl[3-(1-trichloroethoxycarbonyloxyethyl)-2-azetidinone-4-yl)]-trithiocarbonate, and (3S,4R,5R)-*n*-butyl[3-(1-trichloroethocycarbonyloxyethyl)-(2-azetidinone-4-yl)]trithiocarbonate affords the (5,6-cis)- and (5R,6S,8R)-potassium-6-(1-hydroxyethyl-2-benzylthiopenem-3-carboxylate, the (5,6-cis)- and (5R,6S,8R)-potassium-6-(1-hydroxyethyl)-2-(hydroxyethyl)-thiopenem-3-carboxylate and the (5,6-cis)- and (5R,6S,8R)-potassium-6-(1-hydroxyethyl)-2-(*n*-butylthiopenem-3-carboxylate, respectively.

Using (3S,4R,5S)-ethyl (3-[1-trichloroethoxycarbonyloxy-1-(3-pyridyl)-methyl]-(2-azetidinone-4-yl)trithiocarbonate, the procedure detailed in steps A - F is repeated to afford the (5,6-cis)- and (5R,6S,8S)-potassium-6-[1-hydroxy-1-(3-pyridyl)methyl]-2-ethylthiopenem-3-carboxylate.

Following the procedure detailed in paragraphs A - E using (3S,4R,5R)-2-allyloxycarbonylaminoethyl[3-(1-

trichloroethoxycarbonyloxyethyl)-(2-azetidinone-4-yl)]trithiocarbonate there is obtained (5,6-cis)- and (5R,6S,8R)-allyl 6-(1-trichloroethoxycarbonyloxyethyl)-2-[(2-allyloxycarbonylaminoethyl)thio]penem-3-carboxylate. Treatment of these products separately with zinc affords (5R,6R,8R)- and (5R,6S,8R)-allyl 6-(1-hydroxyethyl)-2-[(2-allyloxycarbonylaminoethyl)thio]penem-3-carboxylate which are then each separately treated with 2-ethyl-hexanoic acid to afford, separately, (5,6-cis)- and (5R,6S,8R)-6-(1-hydroxyethyl)-2-[(2-aminoethyl)thio]penem-3-carboxylic acid.

EXAMPLE 4

2-Ethylthiopenem-3-carboxamide

2-Ethylthiopenem-3-carboxylic acid (0.24 g) is stirred in acetone (10 ml) at 0-5°, and triethylamine is added (0.21 ml) followed by ethylchloroformate (0.15 ml). After 0.5 h at 0-5°, concentrated aqueous ammonia (0.2 ml) is added. After a further 0.5 h at 0-5°, the mixture is worked up in dichloromethane, washing with aqueous tartaric acid and sodium bicarbonate solution, dried and evaporated. The residue is recrystallized from ethyl acetate to give the amide as needles, m.p. 172-175°.

EXAMPLE 5

2-Ethylthiopenem-3-carbonitrile

A mixture of 2-ethylthiopenem-3-carboxamide (0.08 g), dry pyridine (2 ml) and p-toluenesulfonyl chloride (0.11 g) is stirred at room temperature for 24 hours, and worked up in dichloromethane, washing with aqueous tartaric acid and sodium bicarbonate solution, dried and evaporated. The residue is dissolved in 2 ml dichloromethane and filtered to recover unreacted amide, and the filtrate is chromatographed on silica gel with ether-dichloromethane (1:20 v/v) to give the nitrile. IR spectrum (in dichloromethane): 1785 cm^{-1}.

EXAMPLE 6

2-Ethylthio-3-(5-tetrazolyl)penem

A mixture of 2-ethylthiopenem-3-carbonitrile (0.1 g), sodium azide (0.22 g), aluminum chloride (0.12 g) and dry tetrahydrofuran (2.5 ml) is heated at 50-60° for 18 hours, then worked up in water and dichloromethane. The organic phase is dried, evaporated and chromatographed on silica gel with ether-dichloromethane to afford the product.

IR spectrum vmax 1785 cm^{-1}.

EXAMPLE 7

A. *2-Ethylthio-N-benzyl-penem-3-carboxamide*

2-Ethylthiopenem-3-carboxylic acid (0.12 g) and trietylamine (0.11 ml) are stirred in acetone (5 ml) at 0-5° and ethyl chloroformate (0.08 ml) is added. After 0.5 h, a solution of benzylamine (0.12 g) in dichloromethane (2 ml) is added and the mixture stirred at room temperature for 0.5 h. Dichloromethane is added, and the solution washed with aqueous tartaric acid and sodium bicarbonate solution, dried and evaporated. The residue is chromatographed on silica gel with 5% ether-dichloromethane to give the product as an oil. IR spectrum: ν max (dichloromethane) 3300, 1785 and 1650 cm^{-1}.

B. *2-Ethylthio-3-(1-benzyl-5-tetrazolyl)-penem*

To a solution of the benzylamide (1 mmol) in dry toluene (3 ml) and pyridine (0.1 ml) phosphorous pentachloride (0.21 g) is added. The mixture is stirred at room temperature for 2 hours, the precipitate filtered and washed with dry toluene, and the filtrate evaporated at room temperature and high vacuum. A solution of the residue in acetone (3 ml) is added to a stirred solution of sodium azide (0.5 g) in water (2 ml) and acetone (3 ml). After stirring for 1 hour at room temperature, the product is extracted with dichloromethane and purified by silica gel chromatography with ether-dichloromethane.

C. *2-Ethylthio-3-(5-tetrazolyl)-penem*

A solution of 2-ethylthio-3-(1-benzyl-5-tetrazolyl)-penem (0.15 g) in ethyl acetate (5 ml) containing triethylamine (10 mg) is shaken in 4 atmospheres of hydrogen at room temperature over 10% palladium-on-carbon (0.1 g) for 1 hour, and the mixture filtered, evaporated and chromatographed on silica gel in dichloromethane-ether to obtain the product. IR spectrum vmax 1785 cm^{-1}.

EXAMPLE 8

2-Ethylthio-3-(5-tetrazolyl)-penem

A solution of 1-(1-triphenylphosphoranyl-1-(1-benzyl-5-tetrazolyl)-methyl)-4-ethylthio(thiocarbonyl)thio-2-azetidinone (1.5 g) in toluene (20 ml) is heated under reflux in nitrogen for 40 hours, and the product isolated by chromatography on silica gel, eluting with dichloromethane followed by ether-dichloromethane to give 2-ethylthio-3-(1-benzyl-5-tetrazolyl)-penem. A solution of the latter in ethyl acetate containing triethylamine is shaken in 4 atmospheres of hydrogen at room temperature over 10% palladium-on-carbon (0.1 g) for 1 hour, and the mixture is filtered, evaporated and chromatographed on silica gel in dichloromethane-ether to obtain the title product, IR spectrum ν max 1785 cm^{-1}.

FORMULATIONS

The following formulations are to exemplify some of the dosage forms in which the antibacterial agents of

this invention may be employed. In each, the active ingredient is designated by the term "Drug" which is meant to indicate one of the following compounds:
potassium (5R,6S,8R)-6-(1-hydroxyethyl)-2-ethylthiopenem-3-carboxylate, (5R,6S,8R)-6-(1-hydroxyethyl)-2-(2-amino-ethylthio)penem-3-carboxylic acid, and (5R,6S,8R)-6-(1-hydroxyethyl)-2-ethylthiopenem-3-carboxylic acid. It will be appreciated, however, that each of these compounds may be replaced by equally effective quantities of other compounds defined by formula I, specifically those of the list preceding Preparation I.

Injectable Suspension Formulation	mg/ml
Sterile drug	250.0
Benzyl Alcohol	9.0
Methylparaben	1.8
Propylparaben	0.2
Sodium Carboxymethylcellulose	5.0
Polyethylene Glycol 4000	10.0
Providone	5.0
Sodium Citrate	15.0
Disodium Edetate	0.1
Water for Injection	q.s.
To make	1.0ml

Dissolve parabens in a portion of the water for injection by heating it to 65-70°C. Cool to 25-35°C. Charge and dissolve benzyl alcohol, sodium citrate, disodium edetate, PEG 4000, providone and sodium carboxymethylcellulose. Filter the solution and sterilize by autoclaving. Make a slurry of the sterile active and pass it through a colloid mill. Mix it well with solution from Step 3 and pass it through the mill. Bring the suspension to the final volume/weight and fill into sterile containers.

Capsule Formulation

Item No.	Ingredient	mg/capsule	mg/capsule
1	Drug	250	500
2	Lactose, USP	106	123
3	Corn Starch, Food Grade	40	70
4	Magnesium Stearate,USP	4	7
		400 mg	700 mg

Mix Item Nos. 1, 2 and 3 in a suitable mixer for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the above mixture into suitable 2-piece hard gelatin capsules.

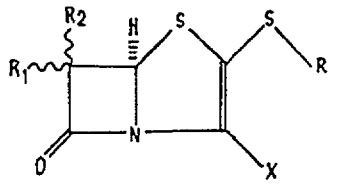
Tablet Formulation

Item No.	Ingredient	mg/tablet	mg/tablet
1	Drug	250	500
2	Lactose, USP	106	112
3	Corn Starch, Food Guide as 10% paste in water	20	40
4	Corn Starch, Food Guide	20	40
5	Magnesium Stearate	4	8
		400 mg	800 mg

Mix Item Nos. 1 and 2 in a suitable mixer for 10-15 minutes. Granulate the mixture with Item No. 3. Pass the wet granulation through a coarse screen (1/4"). Dry the wet granules for 8-12 hours at 40-50°C. Using a suitable mill, pass the dried granules through a medium screen (No. 12 to No. 16). Add Item No. 4 and mix for 10-15 minutes. Add Item No. 5 and mix further for 1-3 minutes. Compress the mixture to appropriate size and weight on a suitable tablet machine.

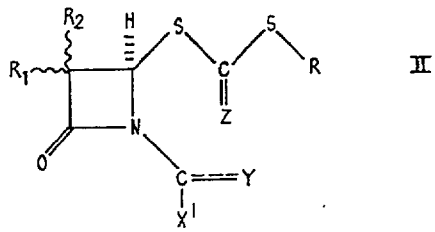
CLAIMS

1. A process for preparing compounds of the formula



I

wherein R is lower alkyl, aminoloweralkyl, mono-or di-loweralkylaminoloweralkyl, acylaminoloweralkyl, aralkyl, heteroaralkyl, hydroxyloweralkyl, hydroxyaralkyl, carboxyloweralkyl or alkoxycarbonylloweralkyl; R_1 is hydrogen, lower alkyl, aralkyl or a group of the formula: R_6CHOH- with R_6 being hydrogen, lower alkyl, aralkyl, heteroaryl, heteroaralkyl, hydroxyaralkyl or aryl;
R_2 is hydrogen or methyl; and
X is cyano, tetrazol-5-yl, $-COOR_3$ or $-CONR_4R_5$ wherein
R_3 is hydrogen, an alkali metal cation, phthalidyl or a pivaloyloxymethyl group; and
R_4 and R_5 are independently hydrogen or lower alkyl; with the proviso that when X is $-COOR_3$ both R_1 and R_2 cannot be hydrogen, which comprises cyclising a compound of the formula



II

wherein R, R_1, R_2 are as defined above any functional group therein being optionally protected, X' is protected tetrazol-5-yl, cyano, protected carboxyl, protected carbamoyl or $-CONR_4R_5$ with substituents R_4 and R_5 being as defined above and at least one of them being lower alkyl; Z is sulfur or oxygen; and Y is a phosphonio group being double bonded to the adjacent carbon atom or a phosphonato group with a single bond to the adjacent carbon atom the negative charge of which is compensated by the presence of a cation; if required, separating a mixture of diastereoisomers before or after removing any protecting group and then subjecting a so-obtained compound to one or more of the facultative steps(i) to (viii):

(i) introducing phthalidyl or pivaloyloxymethyl in substituent X;
(ii) acylation of a compound of formula I wherein R is aminoloweralkyl;
(iii) transamidation or hydrolysis of a compound of formula I wherein R is acylaminoloweralkyl;
(iv) separation of a mixture of enantiomers;
(v) formation of a salt;
(vi) conversion of the carboxyl group representing X into a corresponding amido group $-CONR_4R_5$ with R_4 and R_5 being as defined above;
(vii) conversion of the carboxyl group representing X into the cyano group; and
(viii) conversion of the cyano or carbamoyl group representing X into the tetrazol-5-yl group;

with the proviso that when in formula II X' is protected carboxyl and R_1 and R_2 are both hydrogen, one of steps (vi) or (vii) must be carried out.

2. The process according to claim 1, wherein Y is a triarylphosphonio or trialkylphosphonio group the aryl or alkyl moieties being optionally substituted.

3. The process according to claim 1 or 2, wherein Y is triphenylphosphonio.

4. The process according to any one of claims 1 to 3, wherein the cyclisation reaction is carried out in an inert solvent at a temperature between 30 to 160°C.

5. The process according to any one of claims 1 to 4, wherein a compound of formula II is used, wherein R_2 is hydrogen, R_1 is the group R_6CHOPg- with R_6 being as defined in claim 1 and Pg being a hydroxy protective group, R is lower alkyl or protected aminoloweralkyl and X' is protected carboxyl.

6. The process according to any one of claims 1 to 5, wherein a (3S,4R)-compound of formula II is used.

7. The process according to any one of claims 1 to 6, wherein potassium (5R,6S,8R)-6-(1-hydroxyethyl)-2-ethyl-thiopenem-3-carboxylate, potassium (5R,6S,8S)-6-(1-hydroxy-1-(3-pyridyl)methyl)-2-ethylthiopenem-3-carboxylate or (5R,6S,8R)-6-(1-hydroxyethyl)-2-(2-aminoethylthio)penem-3-carboxylic acid is prepared.

8. The process according to any one of claims 1 to 4, wherein the cyclisation reaction of a compound of formula II is followed by conversion of the 3-carboxy group into cyano or tetrazol-5-yl or wherein, in formula II, X' is protected tetrazol-5-yl.

9. The process according to claim 8, wherein 2-methyl-thiopenem-3-carbonitrile, 2-ethylthiopenem-3-

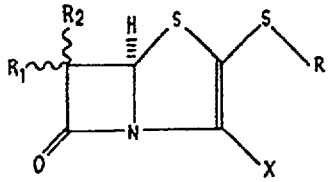
carbonitrile, 2-aminoethylthiopenem-3-carbonitrile, the 6-(1-hydroxy-ethyl) derivatives thereof or the 3-(5-tetrazolyl)analogs of all of the foregoing are prepared.

10. A process for preparing a pharmaceutical composition which comprises admixing a compound of formula I as defined in claim 1 with a pharmaceutical carrier or excipient.

11. A process as claimed in claim 1 or 10, substantially as herein described with particular reference to the Examples and Formulations.

12. A compound when prepared according to the process of any one of claims 1 to 9 and 11.

13. A compound of the formula

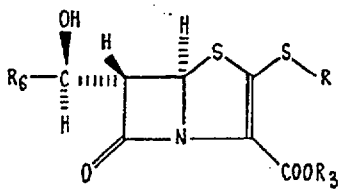


I

wherein R is lower alkyl, aminoloweralkyl, mono- or di-loweralkylaminoloweralkyl, acylaminoloweralkyl, aralkyl, heteroaralkyl, hydroxyloweralkyl, hydroxyaralkyl, carboxyloweralkyl or alkoxycarbonyloweralkyl: R_1 is hydrogen, lower alkyl, aralkyl or a group of the formula: R_6CHOH- with R_6 being hydrogen, lower alkyl, aralkyl, heteroaryl, heteroaralkyl, hydroxyaralkyl or aryl;
R_2 is hydrogen or methyl; and
X is cyano, tetrazol-5-yl, $-COOR_3$ or $-CONR_4R_5$ wherein R_3 is hydrogen, an alkali metal cation, phthalidyl or a pivaloyloxymethyl group; and
R_4 and R_5 are independently hydrogen or lower alkyl; with the proviso that when X is $-COOR_3$ both R_1 and R_2 cannot be hydrogen.

14. A compound of claim 13, wherein in formula I R is as defined in claim 13, R_2 is hydrogen, X is $-COOR_3$ and R_1 is the group R_6-CHOH-, with R_3 and R_6 being as defined in claim 13.

15. A compound of claim 14 having the following stereo-specific structure



wherein R, R_3 and R_6 are as defined in claim 13, and a mixture thereof with its enantiomer.

16. A compound of claim 15, wherein R_3 is hydrogen or an alkali metal cation, R is lower alkyl or aminolower alkyl and R_6 is hydrogen, lower alkyl or heteroaryl; and a mixture thereof with its enantiomer.

17. A compound of claim 16, said compound being potassium (5R,6S,8R)-6-(1-hydroxyethyl)-2-ethylthiopenem-3-carboxylate.

18. A compound of claim 16, said compound being (5R,6S,8R)-6-(1-hydroxyethyl)-2-(2-aminoethylthio)penem-3-carboxylic acid.

19. A compound of claim 16, said compound being potassium (5R,6S,8S)-6-(1-hydroxy-1-(3-pyridyl)methyl)-2-ethylthiopenem-3-carboxylate.

20. A compound of claim 13, wherein in formula I R_1, R_2 and R are as defined in claim 13 and X is cyano, tetrazol-5-yl or $-CONR_4R_5$ with R_4 and R_5 being as defined in claim 13.

21. A compound of claim 20, wherein in formula I R_1 is hydrogen or the group R_6CHOH- with R_6 being as defined in claim 13, R_2 is hydrogen, R is as defined in claim 13 and X is cyano or tetrazol-5-yl.

22. A compound of claim 21, said compound being selected from 2-methylthiopenem-3-carbonitrile, 2-ethyl-thiopenem-3-carbonitrile, 2-aminoethylthiopenem-3-carbonitrile, from the 6-(1-hydroxyethyl) derivatives thereof, and from the 3-(tetrazol-5-yl) analogs of all of the foregoing.

23. A pharmaceutical composition comprising a compound of formula I as defined in claim 13 as an active ingredient.

24. The pharmaceutical composition of claim 23 comprising alkali metal (5RS,6RS,8SR)-6-(1-hydroxyethyl)-2-ethylthiopenem-3-carboxylate together with either alkali metal (5RS,6SR,8RS)-6-(1-hydroxyethyl)-2-ethylthiopenem-3-carboxylate or alkali metal (5R,6S,8R)-6-(1-hydroxyethyl)-2-ethylthiopenem-3-carboxylate, said composition being substantially free from alkali metal (5RS,6RS,8RS)-6-(1-hydroxyethyl)-2-ethylthiopenem-3-carboxylate and alkali metal (5RS,6RS,8RS)-6-(1-hydroxyethyl)-2-ethylthiopenem-3-carboxylate.

25. The pharmaceutical composition of claim 24 containing 20-45 percent by weight of the (5RS,6RS,8SR)-isomer and 55-80 percent by weight of either the (5RS,6SR,8RS)- or the (5R,6S,8R)-isomer.

26. The pharmaceutical composition of claim 23 comprising alkali metal (5RS,6RS,8SR)-6-(1-hydroxyethyl)-2-ethylthiopenem-3-carboxylate, said composition being substantially free from the corresponding (5RS,6SR,8RS)-(5RS,6SR,8SR)- and (5RS,6RS,8RS)-isomers.

27. A pharmaceutical dosage form comprising the composition of any one of claims 24 to 26.
28. The dosage form of claim 27 for oral use.
29. A pharmaceutical composition when prepared by the process of claims 10 and 11.
30. The pharmaceutical composition of Claim 23 comprising alkali metal (5R,6S,8R)-6-(1-hydroxyethyl)-2-ethylthiopenem-3-carboxylate in the chiral form or together with its enantiomer.

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