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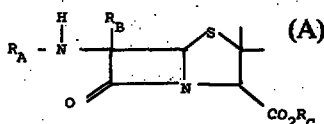
(54) 6-METHOXY-6-(α -CARBOXYACETAMIDO)-PENICILLINS

(71) We, BEECHAM GROUP LIMITED, of Beecham House, Great West Road, Brentford, Middlesex, England, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:-

This invention relates to a class of penicillins which have antibacterial activity and are of value in the treatment of infections in animals, including man and poultry, caused by a wide range of Gram-negative organisms.

In particular the invention relates to a class of 6-methoxy- α -carboxy penicillins. The invention also relates to a process for the preparation of such compounds, and to pharmaceutical compositions comprising them.

British Patent Specification No. 1,339,007 discloses *inter alia* a class of 6-substituted acylamino penicillins of general formula (A).



where R_A represents an acyl group, R_B is a hydroxy or mercapto radical, a substituted or unsubstituted methoxy, ethoxy, methyl, ethyl, methylthio, or ethylthio radical, a carbamoyloxy, carbamoylthio, C_{1-6}

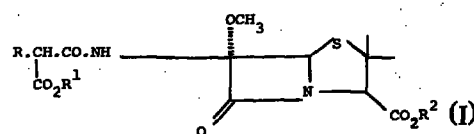
alkanoyloxy, C_{1-6} alkanoylthio, cyano or carboxy radical or a derivative of a carboxy radical such as carbamoyl and R_C is a hydrogen atom or a pharmaceutically acceptable esterifying radical or cation.

In abstract No. 368 of the "Program and Abstracts of the 14th Interscience conference on Antimicrobial Agents and Chemotherapy held on 11th - 13th September, 1974 in San Francisco, California, U.S.A., a report is made of a single 6-methoxy penicillin within formula (A) above, namely 6 α -methoxy-6 β -(2-carboxyphenylacetamido)-penicillanic acid.

This compound is conveniently referred to as 6-methoxycarbenicillin. A single 3-ester of 6-methoxycarbenicillin is disclosed as compound number 5 in British Patent Specification No. 1,425,571.

We have now found that certain novel α -esters of a small class of 6-methoxy- α -carboxy penicillins, including the above-mentioned 6-methoxycarbenicillin, have improved oral absorption compared to the free α -carboxy compounds.

According to the present invention there is provided a compound of formula (I):



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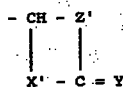
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wherein R is phenyl or 2- or 3-thienyl R² is hydrogen or a pharmaceutically acceptable salting ion or a radical which forms an ester which is hydrolysable *in vivo* in man and R¹ is a pharmaceutically acceptable ester forming radical.

Suitable salting ions for the group R² include metal ions e.g. aluminium, alkali metal ions such as sodium or potassium, alkaline earth metal ions such as calcium or magnesium, and ammonium or substituted ammonium ions for example those from C₁₋₆ alkylamines, such as triethylamine, hydroxy-C₁₋₆ alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or from procaine, dibenzylamine, N,N-dibenzylethylenediamine, 1-phenylamine, N-ethylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bis-dehydroabietyleneethylenediamine, or bases of the pyridine type such as pyridine, collidine or quinoline, or other amines which have been used to form salts with benzylpenicillin.

In vivo hydrolysable pharmaceutically acceptable ester-forming radicals for the groups R¹ and R² are those which hydrolyse in the human body to produce the parent acid. Suitable examples include acyloxyalkyl groups such as acetoxymethyl, pivaloyloxymethyl, α-acetoxyethyl, α-acetoxybenzyl and α-pivaloyloxyethyl groups; alkoxycarbonyloxyalkyl groups, such as ethoxycarbonyloxymethyl and α-ethoxycarbonyloxyethyl; and lactone, thiolactone and dithiolactone groups, i.e. groups of formula:



wherein X' and Y' are oxygen or sulphur and Z' is an ethylene group or a 1,2-phenylene group optionally substituted by C₁₋₆-alkoxy, halogen or nitro.

Preferred ester groups are the phthalide and 5,6-dimethoxyphthalide esters.

Any ester function at the α-position in the side-chain in formula (I) is suitable, so that, the group R¹ may be an alkyl, cycloalkyl, alkenyl, alkynyl, aryl, or heterocyclic group any of which may be substituted. Suitable groups include:

(a) C₁₋₆ alkyl such as methyl, ethyl, *n*- and *iso*-propyl, *n*-, *sec*-, *iso*- and *tert*-butyl, and pentyl;

(b) substituted C₁₋₆ alkyl wherein the substituent is at least one of: chloro, bromo, fluoro, nitro, carbo (C₁₋₆ alkoxy), C₁₋₆ alkanoyl, C₁₋₆ alkoxy, cyano, (C₁₋₆)alkylthio, (C₁₋₆)alkylsulphanyl, (C₁₋₆)alkylsul-

phonyl, 1-indanyl, 2-indanyl, furyl, pyridyl, 4-imidazolyl, phthalimido, azetidino, aziridino, pyrrolidino, piperidino, morpholino, thiomorpholino, N-(C₁₋₆ alkyl)piperazino, pyrrolo, imidazolo, 2-imidazolino, 2,5-dimethylpyrrolidino, 1,4,5,6-tetrahydropyrimidino, 4-methylpiperidino, 2,6-dimethylpiperidino, alkylamino, dialkylamino, alkanoylamino, N-alkylanilino, or substituted N-alkylanilino wherein the substituent is chloro, bromo, C₁₋₆ alkyl or C₁₋₆ alkoxy;

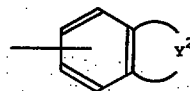
(c) cycloalkyl and (C₁₋₆ alkyl) substituted cycloalkyl having from 3 to 7 carbon atoms in the cycloalkyl moiety,

(d) [2,2-di(C₁₋₆ alkyl)-1,3-dioxolon-4-yl]methyl;

(e) alkenyl having up to 8 carbon atoms;

(f) alkynyl having up to 8 carbon atoms;

(g) phenyl and substituted phenyl wherein the substituent is at least one of chloro, bromo, fluoro, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkanoyl, carbo-(C₁₋₆)alkoxy, nitro, or di(C₁₋₆)alkyl amino; and groups of formula:



wherein Y² is

---CH=CH---O---

---CH=CH---S---

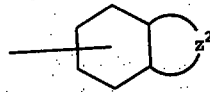
---CH₂---CH₂---S---

---CH=N---CH=CH---

---CH=CH---CH=CH---

---CO---CH=CH---CO---or

---CO---CO---CH=CH---



wherein Z² is C₁₋₆ alkylene such as (CH₂)₃- or -(CH₂)₄-, and substituted derivatives thereof wherein the substituent is methyl, chloro or bromo;

(h) benzyl or substituted benzyl wherein the substituent is chloro, bromo, fluoro, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkanoyl, carbo(C₁₋₆)alkoxy, nitro, or di(C₁₋₆)alkylamino;

(i) heterocyclic groups such as: furyl, quinolyl, methyl-substituted quinolyl, phenazinyl, 1,3-benzodioxolyl, 3-(2-methyl-γ-pyronyl), 3-(γ-pyronyl) or methylpyridyl;

(j) other hydrocarbyl groups such as: ac-indanyl and substituted derivatives thereof wherein the substituent is methyl, chloro or bromo; ac-tetrahydronaphthyl and substituted derivatives thereof wherein the substituent is methyl, chloro or bromo; benzohydryl, trityl, cholesteryl, or bicyclo[4.4.0]decyl.

Preferred groups for R¹ include C₁₋₆ alkyl, benzyl, phthalidyl, indanyl, phenyl, and mono-, di-, and tri- (C₁₋₆)-alkyl substituted phenyl such as *o*-, *m*- or *p*-methylphenyl, ethylphenyl, *n*- or *iso*-propylphenyl, or *n*-, *sec*-, *iso*- or *t*-butylphenyl.

Specific compounds within this invention include the following:

6 α -methoxy, 6 β - (D,L-2-phenoxy-carbonyl-2-thien-2'-ylacetamido) penicillanic acid;

6 α -methoxy, 6 β - (2-phenoxy-carbonyl-2-thien-3'-ylacetamido) penicillanic acid;

6- β - [D,L-2-(*iso*- butyloxycarbonyl)-2-thien-3'-ylacetamido]- 6 α -methoxy-penicillanic acid;

6- β - [D,L-2-(indan- 5-yloxycarbonyl)-2-thien-3'-ylacetamido]- 6 α -methoxy-penicillanic acid;

6 α - methoxy-6- β - [D,L-2- (4-methyl-phenoxy-carbonyl)- 2-thien-3'-ylacetamido] penicillanic acid;

6 α - methoxy-6- β - [D,L-2-(phthalid-3-yloxycarbonyl)- 2-thien-3'-ylacetamido] penicillanic acid;

6- β - [D,L-2- (2-*sec*-butylphenoxy-carbonyl)- 2-thien-3'-ylacetamido]- 6 α -methoxy penicillanic acid;

6- β - [D,L-2-(2- ethylphenoxy-carbonyl)- 2-thien-3'-ylacetamido]- 6 α -methoxy-penicillanic acid;

6- α - methoxy-6- β - [D,L-2- (4-isopropyl - phenoxy-carbonyl) - 2 - thien - 3'-ylacetamido]penicillanic acid;

6- β - [D,L-2-(3,4- dimethylphenoxy-carbonyl) - 2 - phenylacetamido] - 6 α - methoxy-penicillanic acid;

6 α - methoxy-6- β - [D,L-2-(4- methyl-phenoxy-carbonyl)- 2- phenylacetamido]- penicillanic acid;

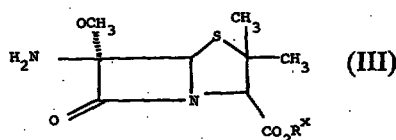
6 α - methoxy-6- β -(D,L-2- phenoxy-carbonyl- 2-phenylacetamido) penicillanic acid;

6 α - methoxy-6- β - [D,L-2-(3- methyl-phenoxy-carbonyl)- 2- phenylacetamido] penicillanic acid;

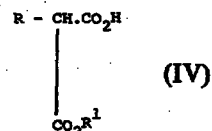
6- β - [D,L-2-(5- indanyloxycarbonyl)- 2-phenylacetamido]- 6 α - methoxy-penicillanic acid;

6- β - (D,L-2- *isobutoxy*-carbonyl - 2-phenyl - acetamido) - 6- α - methoxy-penicillanic acid;

The compounds of formula (I) may be prepared by reacting a compound of formula (III) or an N-silyl or N-phosphorylated derivative thereof:



wherein R^{*} is hydrogen or a carboxyl blocking group; with an N-acylating derivative of an acid of formula (IV):



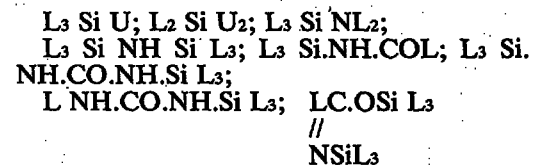
wherein R, and R¹ are as defined with respect to formula (I) above and thereafter if necessary carrying out one or more of the following steps:

(i) removal of any silyl or phosphoryl groups by hydrolysis or alcoholysis;

(ii) removal of any carboxyl blocking groups;

(iii) converting the product to a salt or ester thereof.

By the term "N-silyl derivative" of compound (III), we mean the product of reaction of the 6-amino group of compound (III) with a silylating agent such as a halosilane or a silazane of the formula:



wherein U is a halogen and the various groups L which may be the same of different, each represents hydrogen, alkyl, alkoxy, aryl, or aralkyl. Preferred silylating agents are silyl chlorides, particularly trimethylchlorosilane.

The term "N-phosphorylated" derivative of compound (III) is intended to include compounds wherein the 6-amino group of formula (III) is substituted with a group of formula:



wherein R_a is an alkyl, haloalkyl, aryl, aralkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy or dialkylamino group, R_b is the same as R_a or is halogen or R_a and R_b together form a ring.

Suitable carboxyl-blocking derivatives for the group -CO₂R^{*} in formula (III) include salts, ester, and anhydride derivatives of the carboxylic acid. The derivative is preferably one which may readily be cleaved at a later stage of the reaction. Suitable salts include tertiary amine salts, such as those with tri-C₁₋₆ alkylamines. N-ethyl-piperidine, 2,6-lutidine, pyridine, N-methylpyrrolidine, and dimethylpiperazine. A preferred salt is with triethylamine.

Suitable ester groups of formula CO₂R^{*} include the following:

(i) $-\text{COOCR}_c\text{R}_d\text{R}_e$ wherein at least one of R_c , R_d and R_e is an electron-donor e.g. *p*-methoxyphenyl, 2,4,6-trimethylphenyl, 9-anthryl, methoxy, acetoxy, methoxymethyl, benzyl or fur-2-yl. The remaining R_c , R_d and R_e groups may be hydrogen or organic substituting groups. Suitable ester groups of this type include *p*-methoxybenzyloxy carbonyl, 2,4,6-trimethylbenzyloxy carbonyl, bis(*p*-methoxyphenyl) methoxycarbonyl, 3,5-di-*t*-butyl-4-hydroxybenzyloxycarbonyl, methoxymethoxycarbonyl and benzyloxycarbonyl.

(ii) $-\text{COOCR}_c\text{R}_d\text{R}_e$ wherein at least one of R_c , R_d and R_e is an electron-attracting group e.g. benzoyl, *p*-nitrophenyl, 4-pyridyl, trichloromethyl, tri-bromomethyl, iodomethyl, cyanomethyl, ethoxy-carbonylmethyl, arylsulphonylmethyl, 2-dimethylsulphoniummethyl, *o*-nitrophenyl or cyano. The remaining R_c , R_d and R_e groups may be hydrogen or organic substituting groups. Suitable esters of this type include benzoylmethoxy carbonyl, *p*-nitrobenzyloxy carbonyl, 4-pyridyl methoxycarbonyl, 2,2,2-trichloroethoxy carbonyl and 2,2,2-tribromoethoxycarbonyl.

(iii) $-\text{COOCR}_c\text{R}_d\text{R}_e$ wherein at least two of R_c , R_d and R_e are hydrocarbon such as alkyl e.g. methyl or ethyl, aryl e.g. phenyl and the remaining R_c , R_d and R_e group, if there is one, is hydrogen. Suitable esters of this type include *t*-butyl-oxycarbonyl, *t*-amyloxycarbonyl, diphenylmethoxycarbonyl and triphenylmethoxycarbonyl.

(iv) $-\text{COOR}_f$ wherein R_f is adamantyl, 2-benzyloxy-phenyl, 4-methylthiophenyl, tetrahydrofur-2-yl, tetrahydropyran-2-yl, pentachlorophenyl;

(v) Silyloxycarbonyl groups obtained by reaction of a silylating agent as described above with the carboxylic acid group;

(vi) $\text{CO}_2\text{P.R}_a\text{R}_b$, wherein R_a and R_b are as defined above.

The carboxyl group may be regenerated from any of the above esters by usual methods for example, acid - and base - catalysed hydrolysis, or by enzymically - catalysed hydrolysis. Alternative methods of cleavage include:

reaction with Lewis acids, such as trifluoroacetic acid, formic acid, hydrochloric acid in acetic acid, zinc bromide in benzene and aqueous solutions or suspensions of mercuric compounds. (The reaction with the Lewis acid may be facilitated by addition of a nucleophile such as anisole);

reduction with agents such as zinc/acetic acid, zinc/formic acid, zinc/ C_{1-6} alcohol, zinc/pyridine, palladised-charcoal and hydrogen, and sodium and liquid ammonia;

attack by nucleophiles, such as those containing a nucleophilic oxygen or sulphur atom for example alcohols, mercaptans and

water; oxidative methods, for example, those which involve the use of hydrogen peroxide and acetic acid; and irradiation.

A reactive N-acylating derivative of the acid (IV) is employed in the above process. The choice of reactive derivative will of course be influenced by the chemical nature of the substituents of the acid.

Suitable N-acylating derivatives include an acid halide, preferably the acid chloride or bromide. Acylation with an acid halide may be effected in the presence of an acid binding agent for example tertiary amine (such as triethylamine or dimethylaniline), a basic inorganic salt (such as calcium carbonate or sodium bicarbonate) or an oxirane, which binds hydrogen halide liberated in the acylation reaction. The oxirane is preferably a (C_{2-6}) -1,2-alkylene oxide - such as ethylene oxide or propylene oxide. The acylation reaction using an acid halide may be carried out at a temperature of from -50° to $+50^\circ\text{C}$, preferably -20° to $+30^\circ\text{C}$, in aqueous or non-aqueous media such as aqueous acetone, ethyl acetate, dimethylacetamide, dimethylformamide, acetonitrile, dichloromethane, 1,2-dichloroethane, or mixtures thereof. Alternatively, the reaction may be carried out in an unstable emulsion of water and a water-immiscible solvent, especially an aliphatic ester or ketone, such as methyl isobutyl ketone or butyl acetate.

The acid halide may be prepared by reacting the acid (IV) or a salt thereof with a halogenating (e.g. chlorinating or brominating) agent such as phosphorus pentachloride, thionyl chloride or oxalyl chloride.

Alternatively, the N-acylating derivative of the acid (IV) may be a symmetrical or mixed anhydride. Suitable mixed anhydrides are alkoxyformic anhydrides, or anhydrides with other acids such as, trimethyl acetic acid, thioacetic acid, diphenylacetic acid, benzoic acid, phosphorus acids (such as phosphoric or phosphorous acids), sulphuric acid or aliphatic or aromatic sulphonic acids (such as *p*-toluenesulphonic acid). The mixed or symmetrical anhydrides may be generated *in situ*. For example, a mixed anhydride may be generated using N-ethoxy-carbonyl-2-ethoxy-1,2-dihydroquinoline. When a symmetrical anhydride is employed, the reaction may be carried out in the presence of 2,4-lutidine as catalyst.

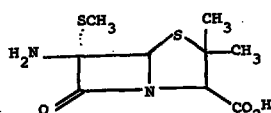
Alternative N-acylating derivatives of acid (IV) are the acid azide, or activated esters such as esters with cyanomethanol, *p*-nitrophenol, 2,4-dinitrophenol, thiophenol, halophenol, including pentachlorophenol, methoxyphenol or 8-hydroxyquinoline; or amides such as N-acylsaccharins or N-acylphthalimides; or an alkylidene iminoester prepared by reaction of the acid (IV) with an oxime.

Some activated esters, for example the

ester formed with 1-hydroxybenztriazole or N-hydroxysuccinimide, may be prepared *in situ* by the reaction of the acid with the appropriate hydroxy compound in the presence of a carbodiimide, preferably dicyclohexylcarbodiimide.

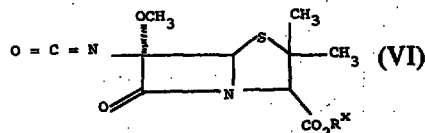
Other reactive N-acylating derivatives of the acid (IV) include the reactive intermediate formed by reaction *in situ* with a condensing agent such as a carbodiimide, for example N,N-diethyl-, dipropyl- or diisopropylcarbodiimide, N,N'-dicyclohexylcarbodiimide, or N-ethyl-N'- γ -dimethylaminopropyl carbodiimide; a suitable carbonyl compound, for example N,N'-carbonyl-diimidazole or N,N'-carbonyl-ditriazole; an isoxazolinium salt, for example N-ethyl-5-phenylisoxazolinium-3-sulphonate or N-*t*-butyl-5-methylisoxazolinium perchlorate. Other condensing agents include Lewis acids (for example BBr₃ in benzene); or a phosphoric acid condensing agent such as diethylphosphoryl cyanide. The condensation reaction is preferably carried out in an organic reaction medium, for example, methylene chloride, dimethylformamide, acetonitrile, an alcohol, benzene, dioxan, or tetrahydrofuran.

The compounds (III) may be prepared for example by the method described by Jen et al (J. Org. Chem. 1973, 38, 2857) from an ester of a compound of formula:



which compound may in turn be prepared from the corresponding 6-isocyano compound as described in our W. German Offenlegungsschrift number 2,407,000.

Compounds of formula (I) may also be prepared by reacting a compound of formula (VI):



wherein R* is as defined above with respect to formula (III) above; with an acid of formula (IV) or a carbanion of formula (IV A): R-CH-CO₂R*; and thereafter if necessary carrying out one or more of the following steps:

- (i) removal of any carboxyl blocking group;
- (ii) converting the product to a salt or ester thereof.

This reaction is preferably carried out at a temperature of -10° to +50°C in an inert organic solvent, such as methylene dich-

loride, in the presence of a basic catalyst such as triethylamine, pyridine or a nitrogen-containing aromatic mono- or bi-cyclic compound such as 1-methyl benzimidazole or imidazo [1,2-a]pyridine.

A third method of preparation of the compounds of formula (I) comprises:

- (a) protecting the 3-carboxylic acid group of a 6- α -methoxy 6- β -acylamino-penicillanic acid with a carboxyl blocking group;

- (b) reacting the protected penicillanic acid to form an imino bond on the 6-amido nitrogen atom;

- (c) reacting the resulting compound to introduce a group QR_i on the imino carbon atom, wherein Q is oxygen, sulphur or nitrogen and R_i is an alkyl group of from 1 to 12 carbon atoms or an aralkyl group of from 7 to 14 carbon atoms, to form an iminoether, iminothioether or amidine (when Q is O, S or N respectively);

- (d) reacting with an acylating derivative of an acid of formula (IV) above;

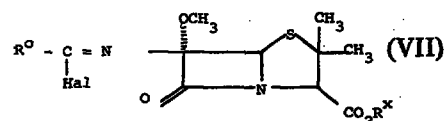
- (e) treating with water or an alcohol; and

- (f) thereafter if necessary carrying out one or more of the following steps:

- (i) removal of any carboxyl blocking groups;

- (ii) converting the product to a salt or ester thereof.

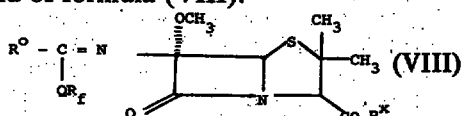
In the above process, after protection of the 3-carboxylic acid group, the protected penicillanic acid is reacted with an agent to form an imino bond on the 6-amino nitrogen atom. Preferably an imino halide is formed of formula (VII):



wherein R^o is the residue of an organic acylamino sidechain of a penicillin, R* is a carboxyl blocking group and Hal represents a halogen atom. A suitable agent for preparing an imino halide is an acid halide in the presence of an acid binding agent such as a tertiary amine, e.g. pyridine, triethylamine, or N,N-dimethylaniline. Examples of suitable acid halides are phosphorus pentachloride, phosgene, phosphorous pentabromide, phosphorus oxychloride, oxalyl chloride and p-toluene sulphonic acid chloride. Phosphorus pentachloride and phosphorus oxychloride are preferred. The reaction may be conducted under cooling, preferably at temperatures from 0°C to -30°C when phosphorus pentachloride is employed. The amount of the tertiary amine is preferably 3-5 mols per mol of phosphorus pentachloride. It is also preferable to use the phosphorus halide in an amount slightly in excess of that of the starting ma-

terial.

The resulting imino compounds are then treated to introduce a $-QR_t$ grouping, onto the imino carbon atom, to produce a compound of formula (VIII):

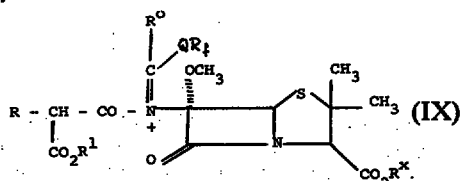


wherein R^o , Q , R_t and R^x are as defined above.

This is preferably effected by reacting an imino halide with a corresponding alcohol when Q is oxygen. Examples of suitable alcohols for reaction with the imino halide are aliphatic alcohols containing from 1 to 12 carbon atoms, preferably 1 to 5 carbon atoms, such as methanol, ethanol, propanol, isopropyl alcohol, amyl alcohol and butyl alcohol, and aralkyl alcohols such as benzyl alcohol and 2-phenyl-ethanol.

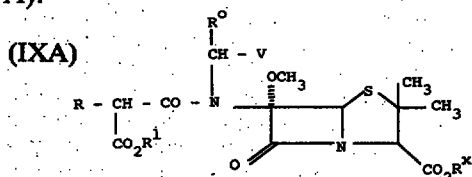
The reaction of the alcohol with the imino halide is preferably effected in the presence of an acid binding agent, such as a tertiary amine, preferably pyridine, and the reaction is usually carried out without isolating the imino halide from the reaction mixture.

Thereafter the compound (VIII) is caused to react with an N-acylating derivative of an acid of formula (IV). The comments made above concerning such N-acylating derivative, and the conditions for carrying out acylations also apply in this case. In particular the presence of a tertiary amine such as pyridine or N,N-dimethylaniline in the reaction system is preferred. The product from such an acylation has a cation of formula (IX):



Finally, the addition compound is treated with water or alcohol. The water treatment may be conducted together with the isolation of the desired material. That is, water or a saturated aqueous solution of sodium chloride is added to the compound and then the aqueous layer formed is separated from the organic solvent layer.

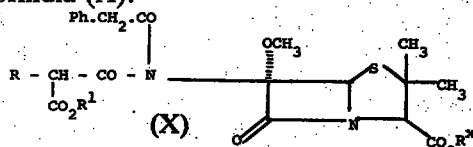
Alternatively a compound of formula (IX A):



wherein R , R^o , R^x , and R^1 are as defined above and V is the residue of an N-acylating

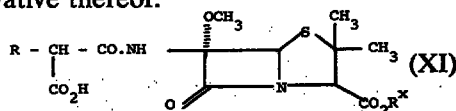
derivative of the acid (IV), that is V is hydroxy, halogen, acyloxy, aryloxy, amino, cyano or azido; may be prepared by reaction of the corresponding N-acylating derivative of (IV) with the Schiff's base formed by reacting 6 α -methoxy-6 β -amino penicillanic acid (or a carboxyl protected derivative thereof) with an aldehyde $R^o \cdot CHO$. The compound (IXA) may be hydrolysed to a compound (I) with water optionally in the presence of acid or base.

A further method for the preparation of compounds of formula (I) is by hydrolysis of an N-acylbenzyl 6 α -methoxy penicillin of formula (X):



wherein R , R^x and R^1 are as defined above. The hydrolysis may be an acid- or base-catalysed chemical hydrolysis or may be an enzymic hydrolysis with the aid of penicillin acylase. The compound (X) may be prepared either from an imino-halide compound of formula (VII) above where R^o is benzyl by reaction with a salt of the acid (IV); or by the action of an acid halide of the acid (IV) with a 6-N-alkali metal derivative of 6 α -methoxy benzylpenicillin or with its 6-N-trimethylsilyl derivative.

The compounds of formula (I) may also be prepared by esterification of a compound of formula (XI) or a reactive esterifying derivative thereof:

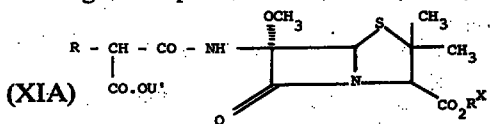


wherein R and R^x are as defined with respect to formula (I) with an alcohol of formula $R^1 OH$ or an esterifying derivative thereof wherein R^1 is as defined in formula (I) and thereafter if as necessary carrying out one or more of the following steps:

(i) removal of any carboxyl blocking groups;

(ii) converting the product to a salt or ester thereof.

Many methods of esterification using several different combinations of reactive esterifying derivatives are known from the literature. For example, the esterification reaction defined above may be achieved by reacting a compound of formula (XI A):



wherein R , R^x are as defined above with a compound of formula (XII):

$$R^1 - V' \quad (XII)$$

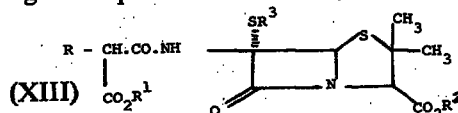
wherein R^1 is as defined in formula (I), under conditions which cause the elimination of the elements of compound $U'V'$ with the consequent formation of an ester of formula (I); the symbols U' and V' in formula (XI A) and (XII) being such that either: U' represents hydrogen or a salt-forming ion and V' represents a hydroxy group, an alkylsulphonyloxy group, an arylsulphonyloxy group or a halogen atom; or U' represents an organic acyl group and V' represents a hydroxy group.

Usually it will be found satisfactory to react compound (XI A) wherein U' is a sodium or potassium ion; with compound (XII) wherein V' is a halogen atom, especially bromine or chlorine.

In the case where the group U' in reagent (XI A) is an organic acyl group, it will be clear that (XI A) is simply a mixed anhydride. The acyl group may be one of a wide variety of aliphatic or aromatic acyl groups but generally the alkoxy carbonyl groups (e.g. C_2H_5OCO- group) are satisfactory.

Another reactive esterifying derivative of compound (XI) above is the acid halide, particularly the acid chloride. This compound may be reacted with the hydroxy compound R^1OH in the presence of an acid binding agent to prepare the desired ester of this invention.

A further method for the preparation of compounds of formula (I) comprises reacting a compound of formula (XIII):



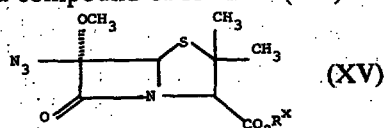
wherein R , R^1 and R^2 are as defined with respect to formula (I) and R^3 is C_{1-6} alkyl or benzyl:

A) with chlorine or bromine at -25° to $-80^\circ C$ and subsequently decomposing the resultant halosulphonium halide with methanol and a base; or

B) with methanol in the presence of a metal ion, such as a tellurium (III), lead (IV) bismuth (V), mercury, lead, cadmium or thallium salt.

Preferably this latter reaction is carried out at -50° to $+25^\circ C$ in a solvent.

Compounds (I) may also be prepared by reducing a compound of formula (XV):



wherein R^* is as defined above; and simultaneously or subsequently acylating with an N-acylating derivative of an acid of formula (IV) above and thereafter if necessary:

(i) removing any carboxyl blocking

group;

(ii) converting the product to a salt or ester thereof.

Suitable N-acylating derivatives of the acid (IV) is as described above.

Various methods of carrying out the reduction of the azido group may be used, but a preferred method is by catalytic hydrogenation using a noble metal catalyst such as platinum, palladium or oxides thereof.

The intermediate of formula (XV) may be prepared as described in British Patent Specification number 1,339,007.

The antibiotic compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibiotics, and the invention therefore includes within its scope a pharmaceutical composition comprising a compound of formula I above together with a pharmaceutical carrier or excipient.

The compositions may be formulated for administration by any route, although an 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 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 glycerides.

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. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection is supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg. of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg. per day, for instance 1500 mg. per day, depending on the route and frequency of administration.

It will be clear that the side-chain of the penicillins of formula (I) contains a potentially asymmetric carbon atom. This invention includes all the possible epimers of compounds (I) as well as mixtures of them.

The following Examples illustrate the preparation of some of the compounds of this invention.

Example 1

(a) Benzyl 6 α -methoxy, 6 β -amino-penicillanate

The corresponding 6 α -methylthio derivative (see West German Offenlegungsschrift number 2,407,000) was converted into the title compound according to Jen et. al. (J. Org. Chem. 1973, 38, 1857).

(b) Benzyl 6 α -methoxy, 6 β -(2-phenoxy-carbonyl-2-thien-3'-yl-acetamido)-penicillanate

A solution of benzyl 6 α -methoxy, 6 β -aminopenicillanate (1.6 mmole) in alcohol-

free methylene chloride (15 ml) and pyridine (0.2 ml) was treated at 0-5° with a solution of the acid chloride prepared from phenyl hydrogen thien-3-ylmalonate (2 mmole) in methylene chloride (4 ml). After 2.5 hours, the solution was washed with water, dilute hydrochloric acid, water, dilute sodium bicarbonate dried and evaporated. Chromatography on silica gel provides the desired di-ester in 52.2% yield. N.m.r. (CDCl₃) δ = 1.35 (6H, s, gem dimethyls), 3.55 (3H, s, OCH₃) 4.52 (1H, s, C₃ proton), 5.09 (1H, s, 2'-proton), 5.27 (2H, s, OCH₂Ph), 5.69 (1H, s, C₅ proton), 7.09 - 7.88 (13H, m, phenyl and thienyl protons).

(c) 6 α -Methoxy, 6 β -(2-phenoxy-carbonyl-2-thien-3'-ylacetamido)-penicillanic acid

A solution of the di-ester from (b) (150 mg) in absolute ethanol (10 ml), water (3 ml) and N-sodium bicarbonate (1 equiv) was treated with 10% Pd/C (200 mg) over 2.5 hours, at 50 p.s.i. Freeze drying provided the title compound as its sodium salt in 62% yield. N.m.r. (D₂O) δ = 1.4 and 1.6 (6H, 2s, gem dimethyls), 3.45 and 3.60 (3H, 2s, OCH₃) 4.35 (1H, s, C₃ proton), 5.1 (1H, s, 2'-proton), 5.6 (1H, s, C₅ proton), 7-7.7 (8H, m, phenyl and thienyl protons).

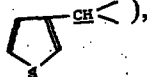
Example 2

(a) Benzyl 6- β - [D,L-2- (iso-butyloxy-carbonyl)- 2-thien-3'-yl- acetamido]-6- α -methoxyphenicillanate

iso-Butyl hydrogen 3-thienylmalonate (1.21 gm) was gently refluxed in dry, alcohol-free methylene dichloride (20 ml) with dimethylformamide (2 drops) to which was added a solution of thionyl chloride (0.5 ml) in dry, alcohol-free methylene dichloride (10 ml) over 15 minutes. Refluxing was continued for a further 45 minutes and the solution cooled and evaporated *in vacuo*. Toluene (5 ml) was added and the solution again evaporated *in vacuo*. Further toluene (5 ml) was added and the evaporation repeated.

Benzyl 6- β - amino-6- α - methylthio-penicillanate, *p*-toluenesulphonate (1.57 gm) was shaken with ice-cold ethyl acetate (110 ml) and N/2 sodium bicarbonate solution (75 ml). The layers were separated and the organic phase washed with ice-cold water (2 $\times$ 75 ml), dried and evaporated *in vacuo*. The residue was dissolved in dry, distilled methanol (27 ml) and dry, distilled dimethylformamide (12 ml) added. The solution was cooled to -10°C and treated with pyridine (0.57 ml). After further cooling to -20°C, mercuric chloride (0.813 gm) was added and the mixture stirred at -10°C for 15 minutes. Dry diethyl ether (110 ml) was added and the solution filtered through Celite (Trade Mark). After further dilution with dry diethyl ether (450 ml) the solution

was washed with water (6 × 75 ml), dried and evaporated in vacuo. The resulting benzyl 6-β-amino-6-α-methoxypenicillanate was dissolved in dry, alcohol-free methylene dichloride (40 ml) and pyridine (0.45 ml) was added, followed by the acid chloride prepared above in dry alcohol-free methylene dichloride (10 ml). The mixture was stirred at 0° to 5°C for 2 hours. Water (20 ml) was added and the methylene dichloride evaporated in vacuo. The residue was shaken with ethyl acetate (75 ml) and water (55 ml) and the layers separated. The organic phase was washed with 10% citric acid (40 ml), water (40 ml), N-sodium bicarbonate solution (40 ml), water (3 × 40 ml), dried and evaporated in vacuo to leave a yellow-brown gum (1.44 gm). The crude product was chromatographed on silica gel using ethyl acetate/60-80° petroleum ether (10% - 15% - 20%) giving the pure ester as a foam in a weight yield of 910 mg. T.l.c.: Rf = 0.16 (SiO₂: Ethyl acetate/60-80° petrol; 1:3). Rf = 0.91 (SiO₂: Chloroform/acetone/acetic acid - 50:50:7). "max (CCl₄): 3310, 1780, 1753, 1710, 1498, 1325, 1264, 1199, 1173, 1108, 1018, and 696 cm⁻¹. N.m.r. (CCl₄), δ = 0.92 [6H, d, (J = 17Hz), -CH<CH₃], 1.28 (6H, s, gem-dimethyls), 1.94 (1H, m, -CH₂CH Me₂), 3.42 (3H, s, 6-α-methoxy), 4.01 (2H, d, [J = 17Hz] -OCH₂CH), 4.40 (1H, s, C-3 proton), 4.78 (1H, s,

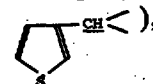


5.25 (2H, s, -OCH₂Ph), 5.56 (1H, s, C-5 proton), 7.29 and 7.42 (7H, m, -OCH₂Ph, thienyl 4-proton, -CONH-), 8.06 (2H, d, thienyl 2- and 5-protons).

(b) 6-β-[D,L-2-(iso-Butyloxycarbonyl)-2-thien-3'-ylacetamido]-6-α-methoxypenicillanic acid

Benzyl 6-β-[D,L-2-(iso-butyloxycarbonyl)-2-thien-3-yl-acetamido]-6-α-methoxypenicillanate (0.9 gm) in distilled ethanol (48 ml) was treated with water (11.5 ml) and freshly prepared N-sodium bicarbonate solution (1.6 ml). 10% palladium on carbon (0.29 gm) was added and the mixture hydrogenated for 1 hour. The mixture was filtered through Celite (Trade Mark) and the residue washed with 50% aqueous ethanol (10 ml). Further catalyst (0.29 gm) was added and hydrogenolysis continued until removal of the benzyl moiety was complete, as shown by T.l.c. on silica in chloroform/acetone/acetic acid - 50:50:7. The mixture was filtered through Celite (Trade Mark), evaporated in vacuo to remove ethanol, washed with diethyl ether (20 ml) and freeze dried, to give the product as its sodium salt 0.5 g. T.l.c.: Rf = 0.68 (SiO₂: Chloroform/acetone/acetic acid 50:50:7) "max (KBr): 1757, 1606, 1505;

1335, 1102, 1012 and 775cm⁻¹. N.m.r. (D₂O) δ = 0.91, [6H, d, (J = 17Hz) -CH f030,] 1.40 (6H, m, gem-dimethyls), 1.92 (1H, m, -CH₂CHMe₂), 3.45 (3H, d, -OCH₃), 4.07 [2H, d, (J = 17Hz), -OCH₂CH], 4.33 (1H, d, C-3 proton), 5.20 (<1H, s, rapidly diminishing,

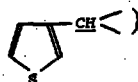


5.63 (1H, d, C-5 proton) 7.32 and 7.58 (3H, m, thienyl protons).

Example 3

(a) Benzyl 6-β-[D,L-2-(indan-5-yloxy-carbonyl)-2-thien-3'-ylacetamido]-6-α-methoxypenicillanate

In a similar fashion to Example 2(a), acylation of benzyl 6-β-amino-6-α-methoxypenicillanate with the acid chloride from indan-5-yl hydrogen 3-thienylmalonate gave the title compound which was purified by chromatography on silica gel in 23% yield. T.l.c.: Rf = 0.15 (SiO₂: Ethyl acetate/60-80° petroleum ether - 1:3). Rf = 0.82 (SiO₂: Chloroform/acetone/acetic acid 50:50:7). "max (CCl₄): 3310, 1779, 1750, 1702, 1483, 1216, 1262, 1230, 1202, 1180, 1157, 1139, 1011 and 699cm⁻¹. N.m.r. (CCl₄), δ = 1.23 (6H, s, gem dimethyls), 2.11 (2H, m, indane 2-methylene), 2.90 [4H, t, (J = 8Hz), indane 1- and 3-methylenes], 3.42 (3H, d, 6-methoxy) 4.40 (1H, s, C-3 proton), 5.06 (1H, d,



5.18 (2H, s, -OCH₂Ph), 5.60 (1H, s, C-5 proton), 7.39 (5H, s, -OCH₂Ph), 6.7-7.6 and 8.14 (7H, m, thienyl and indane aromatic protons, -CONH-).

(b) 6-β-[D,L-2-(Indan-5-yloxy-carbonyl)-2-thien-3'-ylacetamido]-6-α-methoxypenicillanic acid

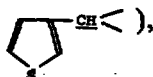
Benzyl 6-β-[D,L-2-(indan-5-yloxy-carbonyl)-2-thien-3-ylacetamido]-6-α-methoxypenicillanate was hydrogenated by the method described in Example 2(b) to give the title compound as its sodium salt. T.l.c.: Rf = 0.62 (SiO₂: Chloroform/acetone/acetic acid - 50:50:7).

Example 4

(a) Benzyl 6-α-methoxy 6-β-[D,L-2-(4-methyl-phenoxycarbonyl)-2-thien-3'-ylacet-amido]penicillanate

In a similar fashion to Example 2(a), acylation of benzyl 6-β-amino-6-α-methoxypenicillanate with the acid chloride from 4-methylphenyl hydrogen thien-3-ylmalonate gave the title compound, purified by chromatography on silica gel, in

67.4% weight yield. T.l.c.: Rf = 0.11 (SiO₂: 60–80° petroleum ether/ethyl acetate – 3:1) Rf = 0.88 (SiO₂: Chloroform/acetone/acetic acid – 50:50:7). ^{max} (CCl₄): 1778, 1752, 1701, 1501, 1315, 1194, 1162, 1019 and 701cm⁻¹. N.m.r. (CCl₄), δ = 1.24 (6H, s, gem-dimethyls), 2.34 (3H, s, tolyl –CH₃), 3.42 (3H, d, –OCH₃), 4.39 (1H, s, C-3 proton), 5.02 (1H, s,

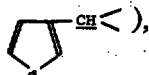


5.21 (2H, s, –OCH₂Ph), 5.58 (1H, s, C-5 proton), 7.0–8.1 (13H, m, phenyl and thienyl aromatics, CONH–).

(b) 6-*α*-Methoxy-6-β-[D,L-2-(4-methylphenoxy-carbonyl)-2-thien-3'-ylacet-amido]penicillanic acid.

Benzyl 6-*α*-methoxy-6-β-[D,L-2-(4-methylphenoxy-carbonyl)-2-thien-3'-ylacet-amido]-penicillanate (1.2 gms) was dissolved in distilled ethanol (60 ml) and treated with water (6 ml).

Palladium on carbon 10% (0.40 gm) was added and the mixture hydrogenated for 1 hour. The mixture was filtered through Celite (Trade Mark), the residue being washed with distilled ethanol (5 ml). Further catalyst (0.40 gm) was added and hydrogenation continued until removal of the benzyl moiety ester was complete as shown by T.l.c. on silica gel in Chloroform/acetone/acetic acid in 50:50:7. Water (25 ml) was added and the ethanol removed *in vacuo*. The mixture was made just alkaline with sodium bicarbonate solution, washed with diethyl ether and acidified with 5N hydrochloric acid. Extraction with diethyl ether (2 × 25 ml), washing of the extracts with water (2 × 10 ml), drying and evaporation *in vacuo* gave the title compound as its free acid. T.l.c. Rf = 0.65 (SiO₂: Chloroform/acetone/acetic acid – 50:50:7). N.m.r. (CDCl₃) δ = 1.40 (6H, m, gem-dimethyls), 2.38 (3H, s, tolyl –CH₃), 3.52 (3H, s, –OCH₃), 4.51 (1H, s, C-3 proton), 5.17 (1H, s,



5.71 (1H, s, C-5 proton), 7.0–7.75 (5H, m, tolyl aromatics and thienyl 4-proton), 8.18 (3H, m, thienyl 2- and 5- protons, –CONH–). This material was dissolved in dry diethyl ether and treated with one equivalent of sodium 2-ethylhexoate (as a *ca* 2M solution in 4-methylpentan-2-one) diluted with dry diethyl ether. The solid was filtered, washed with diethyl ether and dried to give the required compound as its sodium salt in 16% yield. ^{max} (KBr): 3410 (broad), 2962, 1758, 1684, 1602, 1504, 1402, 1335, 1196, 1167, 1130, 848 and 779cm⁻¹.

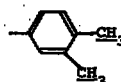
Example 5

(a) Benzyl 6-β-[D,L-2-(3,4-dimethylphenoxy-carbonyl)-2-phenyl-acetamido]-6-*α*-methoxy penicillanate

As described in Example 2(a) using 3,4-dimethylphenyl hydrogen phenylmalonate (1.42 g) the title compound was obtained and chromatographed to give a 64% yield of the pure ester. ^{max} (CHCl₃): 2880, 1770, 1730, 1690, 1490, 1150cm⁻¹.

(b) 6-β-[D,L-2-(3,4-Dimethylphenoxy-carbonyl)-phenylacetamido]-6-*α*-methoxy-penicillanic acid

The benzyl ester was hydrogenated as in example 2(b) to give a 32.8% yield of the title compound as its sodium salt. ^{max} (KBr): 3410, 2970, 1755, 1675, 1600, 1495, 1240, 1150, 700cm⁻¹. N.m.r. (D₂O) δ = 1.47 (6H, m, gem dimethyls), 1.82 (6H, s,



3.54 (3H, d, –OCH₃), 4.31 (1H, s, C-3 proton), 5.75 (1H, s, C-5 proton), 6.6–7.7 (8H, m, aromatic protons), T.l.c.: Rf = 0.66 (SiO₂: Chloroform/acetone/acetic acid – 50:50:7).

Example 6

(a) Benzyl 6-*α*-methoxy-6-β-[D,L-2-(4-methylphenoxy-carbonyl)-2-phenyl-acetamido]penicillanate

In a similar fashion to example 2(a), acylation of benzyl 6-β-amino-6-*α*-methoxy-penicillanate with the acid chloride from 4-methylphenyl hydrogen phenylmalonate gave the title compound which was purified by chromatography on silica gel in 70% yield. T.l.c.: Rf = 0.18 (SiO₂: 60–80° petroleum ether/ethyl acetate – 3:1). ^{max} (CHCl₃): 2910, 1775, 1738, 1690, 1498, 1367, 1330, 1180, and 1010cm⁻¹. N.m.r. (CDCl₃) δ = 1.32 (6H, s, gem-dimethyls), 2.37 (3H, s, tolyl –CH₃), 3.50 (3H, s, –OCH₃), 4.54 (1H, s, C-3 proton), 4.99 (1H, s, PhCH₂), 5.29 (2H, s, –OCH₂Ph), 5.71 (1H, s, C-5 proton), 6.9–8.15 (15H, m, aromatics, –CONH–).

(b) 6-*α*-Methoxy-6-β-[D,L-2-(4-methyl phenoxy-carbonyl)-2-phenyl-acetamido]-penicillanic acid

Benzyl 6-*α*-methoxy-6-β-[D,L-2-(4-methylphenoxy-carbonyl)-2-phenylacetamido]-penicillanate was hydrogenated by the method described in example 4(b) to give the title compound. N.m.r. (CDCl₃), δ = 1.38 (6H, d, gem-dimethyls), 2.35 (3H, s, tolyl –CH₃), 3.49 (3H, s, –OCH₃), 4.37 (1H, s, C-3 proton), 5.00 (1H, s, PhCH₂), 5.68 (1H, s, C-5 proton), 6.86–7.84 (9H, m, aromatics), 8.16 (1H, d, –NHCO–), 9.00 (1H, s, –CO₂H).

The free acid was converted to its sodium salt as described in example 5(b) in 59.4% yield. T.l.c.: Rf = 0.69 (SiO₂: Chloroform/acetone/acetic acid - 50:50:7). "max (KBr): 3400, 2962, 1755, 1685, 1605, 1505, 1345, 1195 and 700 cm⁻¹.

Example 7

(a) *Benzyl 6α-methoxy-6-β-(D,L-2-phenoxy-carbonyl)-2-phenylacetamido)-penicillanate*

Phenyl hydrogen phenylmalonate (1.28 g) was stirred under reflux at 70°C with thionyl chloride (5 ml) for 1½ hours. The solution was cooled and evaporated *in vacuo*. Toluene (5 ml) was added and the solution again evaporated *in vacuo*. Further toluene (5 ml) was added and the evaporation repeated to give the acid chloride which was used to acylate benzyl 6-β-amino-6-α-methoxy-penicillanate as in example 3(a) to give a 22.5% yield of purified product; T.l.c. Rf = 0.16 (SiO₂: ethyl acetate/60-80° petrol: 1:3), Rf = 0.91 (SiO₂: Chloroform/acetone/acetic acid; 50:50:7); "max (CHCl₃): 3250, 2920, 1775, 1740, 1690, 1594, 1497, 1460, 1379, 1319, 1190, 1169, 1030, 699cm⁻¹. N.m.r. (CDCl₃), δ = 1.34 (6H, m, gem-dimethyls); 3.50 (3H, d, OCH₃); 4.51 (1H, d, C3 proton), 4.95 (1H, s, PhCH), 5.28 (2H, s, -CH₂Ph), 5.69 (1H, s, C5 proton), 7.52 (15H, m, 3x Ph-).

(b) *6α-Methoxy-6-β-(D,L-2-phenoxy-carbonyl)-2-phenylacetamido)-penicillanic acid*

Benzyl 6α-Methoxy-6-β-(D,L-2-phenoxy-carbonyl)-2-phenylacetamido)-penicillanate (620 mg) in distilled ethanol (20 ml) was treated with water (4.5 ml) and freshly prepared 1N-sodium hydrogen carbonate solution (0.92 ml), 10% palladium on carbon (620 mg) was added in a nitrogen atmosphere and the mixture hydrogenated for 1 hour. The mixture was filtered through celite (Trade Mark) and the residue washed with 50% aqueous ethanol (10 ml). Further catalyst (0.7 g) was added and the hydrogenolysis continued until removal of the benzyl moiety was complete, as shown T.l.c. on silica-gel in Chloroform/acetone/acetic acid - 50:50:7. The mixture was filtered through Celite (Trade Mark), evaporated *in vacuo* to remove the ethanol, and freeze dried to give the product as its sodium salt, T.l.c.: Rf = 5.69 (SiO₂: Chloroform/acetone/acetic acid - 50:50:7). "max (KBr): 3420(broad), 2967, 1710, 1680, 1597, 1490, 1190, 690cm⁻¹. N.m.r. showed benzyl ester group had been removed.

Example 8

(a) *Benzyl 6-α-methoxy-6-β-[D,L-2-(3-methylphenoxy-carbonyl)-2-phenylacetamido]penicillanate*

As described in example 7(a) using 3-methylphenyl hydrogen phenylmalonate

to give a 76.0% yield of purified material; t.l.c. (SiO₂: ethyl acetate/60-80° petrol: 1:3) Rf = 0.11; "max (CCl₄), 3310, 1779, 1746, 1700, 1490cm⁻¹; n.m.r. (CCl₄), δ = 1.20 (6H, s, gem dimethyls), 2.35 (3H, s, tolyl-CH₃) 3.40, 3.44 (3H, 2 x s, -OCH₃), 4.37 (1H, s, C3 proton), 4.87 (1H, s, PhCH), 5.20 (2H, s, -CO₂CH₂Ph), 5.58 (1H, s, C5 proton), 6.8-7.7 (14H, m, aromatic protons), 8.0-8.2 (1H, m, -NHCO-).

(b) *6-α-Methoxy-6-β-[D,L-2-(3-methyl-phenoxy-carbonyl)-2-phenylacetamido]penicillanic acid*

Benzyl 6-α-methoxy-6-β-[D,L-2-(3-methyl-phenoxy-carbonyl)-2-phenylacetamido] penicillanate was hydrogenated using the method described in example 4(b) to give the free acid; n.m.r. [CCl₄ + (CD₃)₂SO], δ = 1.0 - 1.7 (6H, m, gem-dimethyls), 2.43 (3H, s, tolyl -CH₃), 3.29, 3.57 (3H, 2 x s, -OCH₃), 4.2-4.4 (1H, m, C3 proton), 5.22 (1H, s, PhCH), 5.4 - 5.6 (1H, m, C5 proton), 6.9 - 7.8 (9H, m, aromatic protons), 9.8 - 10.1 (1H, m, -CONH-). The acid was converted to the sodium salt as described in example 5(b), 73.5% yield; t.l.c. (SiO₂: chloroform/acetone/acetic acid; 7:7:1) Rf = 0.66. "max (nujol mull); 3310, 1760, 1685, 1608cm⁻¹.

Example 9

(a) *Benzyl 6-β-[D,L-2-(5-indanyloxy-carbonyl)-2-phenylacetamido]-6-α-methoxy-penicillanate*

Prepared as described in example 7(a) using 5-indanyl hydrogen phenylmalonate to give a 31.4% yield of purified product; t.l.c. (SiO₂: ethyl acetate/60-80° petrol: 1:3) Rf = 0.145; n.m.r. (CDCl₃), δ = 1.2 - 1.7 (6H, m, gemdimethyls), 1.9 - 2.6 (2H, m, indanyl 2-CH₂-), 2.93 (4H, t, (J = 7Hz), indanyl 1 and 3 -CH₂-s), 3.50, 3.53 (3H, 2 x s, -OCH₃), 4.50 (1H, m, C3 proton), 4.95 (1H, s, PhCH), 5.68 (1H, s, C5 proton), 6.8 - 7.8 (13H, m, aromatic protons), 7.9 - 8.1 (1H, m, -CONH-).

(b) *6-β-[D,L-2-(5-indanyloxy-carbonyl)-2-phenylacetamido]-6-α-methoxy-penicillanic acid*

The product from 9(a) was hydrogenated using the method described in example 4(b), n.m.r. (CDCl₃), δ = 1.48 (6H, s, gem-dimethyls), 1.8 - 2.4 (2H, m, indanyl 2-CH₂-), 2.95 [4H, t, (J = 7Hz); indanyl 1 and 3 -CH₂-s], 3.52 (3H, s, -OCH₃), 4.50 (1H, m, C3 proton), 4.98 (1H, s, PhCH), 5.65 (1H, s, C5 proton), 6.8 - 7.8 (8H, m, aromatic protons). The sodium salt was prepared as described in 4(b); 21% yield, t.l.c. (SiO₂: chloroform/acetone/acetic acid; 7:7:1).

Example 10

(a) *Benzyl 6-β-[D,L-2-isobutoxy-carbonyl)-2-phenylacetamido]-6-α-metho-*

xypericillanate

Using the method described in example 2(a) with isobutyl hydrogen phenylmalonate gave the purified ester in 35.9% yield; t.l.c. (SiO₂; ethyl acetate/60-80° petrol; 1:3) R_f = 0.22; ^{max} (CHCl₃; 3300, 1780, 1740, 1720cm⁻¹; n.m.r. (CDCl₃), δ = 0.90 [6H, d, (J = 7Hz), -CH(CH₃)₂], 1.32 (6H, s, gem-dimethyls), 2.0 (1H, m, -CH₂CH(CH₃)₂), 3.45 (3H, 2 x s, -OCH₃), 4.09 [2H, d, (J = 7Hz), -CO₂CH₂CH-], 4.55 (1H, s, C₃ proton), 4.82 (1H, s, PhCH-), 5.30 (2H, s, -CO₂CH₂Ph), 5.73 (1H, s, C₅ proton), 7.5 (10H, m, 2 x Ph-), 8.27 - 8.42 (1H, 2 singlets, -CONH-).

(b) 6-β-(D,L-2- isobutoxycarbonyl- 2-phenylacetamido)- 6-α- methoxypericillanic acid

The benzyl ester was removed by hydrogenation as described in example 4(b) to give the title compound; n.m.r. (CDCl₃), δ = 0.6 - 2.3 (13H, m, -CH(CH₃)₂ and gem-dimethyls), 3.52 (3H, s, -OCH₃), 4.07 [2H, d, (J = 7Hz), -CO₂CH₂CH-], 4.46 (1H, m, C₃ proton), 4.80 (1H, s, PhCH-), 5.62 (1H, s, C₅ proton), 7.51 (5H, s, Ph-), 8.2 - 8.7 (1H, m, -CONH-). This acid was converted to its sodium salt as described in example 4(b); 54.1% yield; t.l.c. (SiO₂; chloroform/acetone/acetic acid; 7:7:1) R_f = 0.60; ^{max} (Nujol (Trade Mark), 3300, 1760, 1690, 1605cm⁻¹.

Example 11

(a) Benzyl 6-α- methylthio- 6-β-(D,L-2- phenoxy-carbonyl- 2- phenylacetamido)- penicillanate

Benzyl 6-β- amino-6-α- methylthio penicillanate toluene-4-sulphonate (1.57g., 3.0 mmole) was shaken with ethyl acetate (100 ml) and 0.5N sodium bicarbonate solution (75 ml) at 0-5° until all had dissolved. The ethyl acetate layer was separated, the aqueous layer extracted with ethyl acetate (2 x 25 ml) and the combined extracts dried (MgSO₄) and evaporated to give benzyl 6-β-amino-6-α- methylthiopencillanate. This was dissolved in dichloromethane (60 ml) containing pyridine (0.67 ml), cooled in an ice bath and treated with 2-phenoxy-carbonyl- 2-phenylacetyl chloride (prepared from phenyl hydrogen phenylmanonate, 1.28 g., 5.0 mmole, as described in example 7(a)) in dichloromethane (20 ml). The solution was stirred for two hours then evaporated to give an oil which was dissolved in ethyl acetate, washed with water, 10% citric acid solution, water, N sodium bicarbonate solution and saturated brine then dried and evaporated to give an oil. Chromatography on silica gel provided the title compound as a pale yellow foam, 1.32 g., 74.5% t.l.c. (SiO₂; ethyl acetate/60-80° petrol; 1:3) R_f = 0.16; ^{max} (nujol mull), 3300, 1780, 1740 and

1690cm⁻¹. n.m.r. (CDCl₃), δ = 7.90 (1H, s, -NHCO-), 7.0 - 7.8 (15H, m, 3 x Ph-), 5.67, 5.63 (1H, 2 x s, C₅ proton), 5.23 (2H, s, -CO₂CH₂Ph), 4.95 (1H, s, PhCH-), 4.50, 4.47 (1H, 2 x s, C₃ proton), 2.25, 2.22 (3H, 2 x s, -SCH₃), 1.35, 1.30 (6H, 2 x s, gem dimethyls).

(b) Benzyl 6-α- methoxy-6-β- (D,L-2- phenoxy-carbonyl- 2- phenylacetamido)- penicillanate

Benzyl 6-α- methylthio-6-β- (D,L-2-phenoxy-carbonyl- 2-phenylacetamido)-penicillanate (0.523g., 0.91 mmole) and mercuric acetate (0.29 g) in methanol (4 ml) were stirred in an atmosphere of nitrogen at room temperature for 1.5 hours. The methanol was removed *in vacuo*, the residue shaken with diethyl ether, filtered through celite (Trade Mark) and the filtrate evaporated to a straw coloured foam. Chromatography on silica gel gave the product, 0.270 g, 52.7%; t.l.c. (SiO₂; ethyl acetate/60-80° petrol; 1:3) R_f = 0.14; n.m.r. (CDCl₃), δ = 8.12, 8.02 (1H, 2 x s, -NHCO-), 7.9 - 7.0 (12H, m, 3 x Ph-), 5.70 (1H, s, C₅ proton), 5.25 (2H, s, -CO₂CH₂Ph), 5.00 (1H, s, PhCH-), 4.49 (1H, s, C₃ proton), 3.50, 3.47 (3H, 2 x s, -OCH₃), 1.33 (6H, s, gem dimethyls).

(c) 6α- Methoxy-6 β- (D,L-2- phenoxy-carbonyl- 2-phenylacetamido)- penicillanic acid

Removal of the benzyl ester as in Example 7(b) produced the title compound.

Example 12

(a) Benzyl 6α-methoxy, 6-β-(D,L-2- phenoxy-carbonyl- 2-thien-2'-ylacetamido)- penicillanate

Phenyl hydrogen thien-2-ylmalonate was dissolved in dichloromethane (75 ml) to which was added three drops of dimethylformamide. To this solution was added oxalylchloride (0.6 ml) and stirred at room temperature for one hour. The solution was evaporated *in vacuo* to give the acid chloride, which was used to acylate benzyl 6-β-amino, 6-α-methoxypericillanate as described in Example 5(a) to give a 44% yield of purified material; t.l.c. (SiO₂; ethylacetate/light petroleum b.p. 60-80°; 1:2) R_f = 0.26; N.M.R. (CDCl₃), δ = 1.29 (6H, s, gem-dimethyls), 3.49 (3H, d, -OCH₃), 4.50 (1H, s, 3-H), 3.25 (2H, s, Ph-CH₂O-), 5.34 (1H, s, CHCONH-), 5.70 (1H, s, 5-H), 7.50 (13H, m, phenyl and thienyl aromatics), 8.11 (1H, d, -CONH-); ^{max} (Nujol (Trade Mark); 3300, 1775, 1650, 1700, 1200, 770cm⁻¹.

(b) 6α-Methoxy, 6-β-(D,L-2- phenoxy-carbonyl- 2-thien-2 β-ylacetamido)- penicillanic acid

Benzyl 6α- methoxy-6 β- (D,L-2-phenoxy - carbonyl - 2 - thien - 2' -ylacetamido)- penicillanate was hydroge-

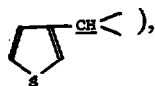
nated using the method described in example 4(b) to give the free acid in a 67% yield; N.M.R. (CDCl_3), $\delta = 1.40$ (6H, d, gem-dimethyls), 3.42 (3H, s, $-\text{OCH}_3$), 4.40 (1H, s, 3-H), 5.15 (1H, s, CHCONH-), 5.57 (1H, s, 5-H), 7.24 (9H, m, thienyl and phenyl aromatics, $-\text{CO}_2\text{H}$), 7.67 (1H, d, $-\text{CONH-}$). The acid was converted to the sodium salt as described in example 4(b) in a 77.9% yield; t.l.c. (SiO_2 ; chloroform/acetone/acetic acid; 50:50:7) $R_f = 0.60$.

Example 13

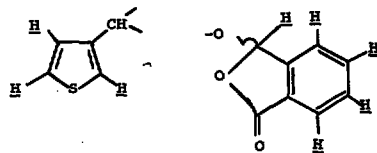
(a) Benzyl 6 α -methoxy-6 β -[D,L-2-(phthalid-3-yloxy-carbonyl)-thien-3'-ylacetamido]-penicillanate

Phthalid-3-yl hydrogen thien-3-ylmalonate (1.59 g), was stirred at room temperature in dry methylene dichloride (35 ml) and oxalyl chloride (2.1 ml) and dimethyl formamide (1 drop) added. After 1½ hours the solution was evaporated *in vacuo* and used to acylate benzyl 6 β -amino-6 α -methoxypenicillanate as in example 2(a).

The product was obtained after chromatography in 22% yield; μ_{max} (CH_2Cl_2); 1782, 1750, 1708, 1218, 1133 cm^{-1} ; N.M.R. (CDCl_3), $\delta = 1.37$ (6H, gem-dimethyls), 3.44 (3H, m, $-\text{OCH}_3$), 4.28 (1H, s, C-3 proton), 5.00 (1H, s,



5.30 (2H, s, $-\text{OCH}_2\text{Ph}$), 5.67 (1H, s, C-5 proton), 7.0-8.2 (14H, m, $-\text{CONH-}$,



$-\text{OCH}_2\text{Ph}$; t.l.c.

$R_f = 0.12$ (SiO_2 ; ethyl acetate/60-80° petrol - 1:2).

(b) Hydrogenation as in example 4(b) gives 6 α -methoxy-6 β -[D,L-2-(phthalid-3'-yloxy-carbonyl)-2-thien-3'-ylacetamido]-penicillanic acid.

Example 14

(a) Benzyl 6 β -[D,L-2-(2-sec-butylphenoxy-carbonyl)-2-thien-3'-ylacetamido]-6 α -methoxy penicillanate

Prepared as described in example 2(a) to give a 29.4% yield after chromatography, N.M.R. (CDCl_3), $\delta = 1.1$ (14H, m, gem dimethyls,

$-\text{CHCH}_2\text{CH}_3$), 2.65 (1H, m, CH_3 , $-\text{CHCH}_2-$), 4.55 (1H, s, C3 proton), CH_3

5.15 (1H, s, CHCONH-), 5.29 (2H, s, $-\text{CH}_2\text{Ph}$), 5.63 (1H, s, C5 proton), 6.9-8.2 (13H, m, aromatic and thienyl protons, $-\text{CONH-}$).

(b) 6 β -[D,L-2-(2-sec-Butylphenoxy-carbonyl)-2-thien-3'-ylacetamido]-6 α -methoxy-penicillanic acid

Benzyl 6 β -[D,L-2-(2-sec-butylphenoxy-carbonyl)-2-thien-3'-ylacetamido]-6 α -methoxy penicillanate was hydrogenated as described in Example 4(b) to give the title compound; yield 46%. This was converted to its sodium salt using sodium-2-ethyl hexoate; yield 19% t.l.c. $R_f = 0.65$ (SiO_2 ; chloroform/acetone/acetic acid; 50:50:7). μ_{max} (KBr); 3410, 1965, 1755, 1600, 1175, 758 cm^{-1} .

Example 15

Benzyl 6 β -[D,L-2-(2-ethylphenoxy-carbonyl)-2-thien-3'-ylacetamido]-6 α -methoxy penicillanate

Prepared as described in example 2(a) to give a yield of 23.5% after chromatography, t.l.c. $R_f = 0.29$ (SiO_2 ; ethyl acetate/60-80° petrol; 1:2), μ_{max} (CHCl_3); 2950, 1778, 1741, 1490, 1320, 1165 cm^{-1} . N.M.R. (CDCl_3), $\delta = 1.25$ (9H, m, gem-dimethyls, $-\text{CH}_2\text{CH}_3$), 2.5 (2H, q, $-\text{CH}_2\text{CH}_3$); 3.51 (3H, s, $-\text{OCH}_3$), 4.52 (1H, s, C3 proton), 5.18 (1H, s, CHCONH-), 5.28 (2H, s, $-\text{CH}_2\text{Ph}$), 5.75 (1H, s, C-5 proton), 7.4 (12H, m, thienyl and aromatic protons), 8.07 (1H, d, $-\text{CONH-}$).

Hydrogenation as in Example 4(b) gives 6 β -[D,L-2-(2-ethylphenoxy-carbonyl)-2-thien-3'-ylacetamido]-6 α -methoxy penicillanic acid.

Example 16

(a) Benzyl 6 α -methoxy-6 β -[D,L-2-(4-isopropylphenoxy-carbonyl)-2-thien-3'-ylacetamido]-penicillanate

Prepared as described in example 2(a) to give a yield of 47.2% after chromatography; t.l.c. $R_f = 0.41$ (SiO_2 ; ethyl acetate/60-80° petroleum ether: 1:2); μ_{max} (CHCl_3); 2950, 1780, 1740, 1700, 1500, 1140 cm^{-1} . N.M.R. (CHCl_3), $\delta = 1.22$ (12H, m, gem dimethyls, $-\text{CH}(\text{CH}_3)_2$), 2.95 (1H, m, $-\text{CH}(\text{CH}_3)_2$), 3.5 (3H, s, $-\text{OCH}_3$), 4.51 (1H, s, C3 proton), 5.11 (1H, s, CHCONH-), 5.30 (2H, s, CH_2Ph), 5.70 (1H, s, C5 proton), 7.5 (13H, m, thienyl and aromatic protons, $-\text{CONH-}$).

(b) 6 α -Methoxy-6 β -[D,L-2-(4-isopropylphenoxy-carbonyl)-2-thien-3'-ylacetamidox-penicillanic acid

Benzyl 6 α -methoxy-6 β -[D,L-2-(4-isopropylphenoxy-carbonyl)-2-thien-3'-ylacetamidox-penicillanate was hydrogenated by the method described in example 4(b) to give the title compound. This was converted to its sodium salt using sodium-2-ethyl hexoate in 4-methylpentan-2-one. Yield = 37.2%; t.l.c. $R_f = 0.66$ (SiO_2 ; 130

chloroform/acetone/acetic acid; 50:50:7)
max (KBr); 3400, 2960, 1765, 1600, 1200,
847cm⁻¹. N.M.R. (CDCl₃), δ = 1.4 (12H,
m, gem dimethyls, -CH(CH₃)₂), 3.0 (1H, m,
-CH(CH₃)₂), 3.54 (3H, s, -OCH₃), 4.5 (1H,
s, C3 proton), 5.15 (1H, s, -CHCONH-),
5.71 (1H, s, C5 proton), 7.4 (7H, m, thienyl
and aromatic protons), 8.00 (1H, s,
-CONH-).

BIOLOGICAL DATA

1. Antibacterial screen

Antibacterial activity, in terms of MIC

values, of a number of compounds of this
invention are shown in tables 1, 2 and 3.

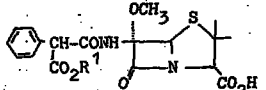
Table 1 relates to α -esters of 6-
methoxycarbenicillin (formula (I), R = Ph,
R² = H);

Table 2 relates to α -esters of 6-
methoxyticarcillin (formula (I), R = 20
3-thienyl, R² = H);

Table 3 relates to the phenyl ester of
6 α -methoxy, 6 β -(2-carboxy-2-thien- 2' α -
ylacetamido)- penicillanic acid (formula (I),
R = 2-thienyl, R² = H, R¹ = Ph).

Table 1

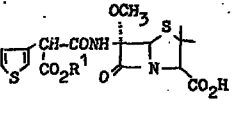
 α -Esters of 6- α -methoxycarbencillin

Example Number	5	6	8	11	9	10
						
	Minimum Inhibitory Conc ⁿ . (μg/ml)					
<i>E. coli</i> JT1	5.0	5.0	2.5	5.0	10	50
<i>E. coli</i> JT4	5.0	12.5	25	25	25	250
<i>E. coli</i> JT 425	5.0	5.0	5.0	10	25	125
<i>Salmonella typhi</i>	5.0	12.5	5.0	10	10	50
<i>Shigella sonnei</i>	5.0	2.5	2.5	2.5	10	50
<i>Ps. aeruginosa</i> 10562	>100	500	500	>100	>100	>500
<i>Ps. aeruginosa</i> 10562(10 ⁻²)	>100	250	250	>100	>100	>500
<i>Serratia marcescens</i> US32	25	25	12.5	25	25	250
<i>Klebsiella aerogenes</i> A	1.0	0.5	0.5	1.0	2.5	25
<i>Enterobacter cloacae</i> N1	5.0	5.0	2.5	5.0	10	50
<i>P. mirabilis</i> C977	5.0	2.5	2.5	2.5	10	50
<i>P. mirabilis</i> 889	5.0	5.0	2.5	5.0	10	50
<i>P. morganii</i>	5.0	2.5	2.5	2.5	10	50
<i>P. rettgeri</i>	2.5	2.5	1.25	2.5	10	50
<i>B. subtilis</i>	>100	>500	>500	>100	>100	250
<i>Staph. aureus</i> Oxford	>100	500	500	>100	>100	50
<i>Staph. aureus</i> Russell	>100	500	>500	>100	>100	50
<i>Staph. aureus</i> 1517	>100	>500	>500	>100	>100	>500
<i>Strep. faecalis</i>	25	>500	>500	>100	>100	>500
β -haemolytic <i>Strep.</i> CN10	-	125	>500	50	>100	0.5

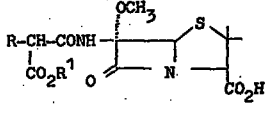
Serial dilution in 5% blood agar

Table 2

α -Esters of 6- α -methoxy ticarcillin

Example Number	1	2	4	3	14	16
	R¹=Ph-	R¹=CH ₂ CH ₂ CH ₃	R¹=CH ₂ CH ₂ CH ₃	R¹=CH ₂ CH ₂ CH ₃	R¹=CH ₂ CH ₂ CH ₃	R¹=CH ₂ CH ₂ CH ₃
Minimum Inhibitory Conc ⁿ (μg/ml)						
<i>E. coli</i> JT1	2.5	25	5.0	5.0	2.5	0.5
<i>E. coli</i> JT4	12.5	50	5.0	5.0	5.0	2.5
<i>E. coli</i> JT425	6.2	25	5.0	5.0	2.5	2.5
<i>Salmonella typhi</i>	6.2	50	2.5	5.0	2.5	2.5
<i>Shigella sonnei</i>	125	5.0	2.5	2.5	0.5	0.5
<i>Ps. aeruginosa</i> 10662	125	>500	>100	250	250	500
<i>Ps. aeruginosa</i> 10662 (10 ⁻²)	125	500	>100	125	250	250
<i>Serratia marcescens</i> US32	25	>500	10	12.5	12.5	5.0
<i>Klebsiella aerogenes</i> A	1.25	50	1.0	2.5	0.5	0.25
<i>Enterobacter cloacae</i> N1	6.2	50	5.0	5.0	2.5	1.25
<i>P. mirabilis</i> C977	1.25	50	2.5	5.0	2.5	1.25
<i>P. mirabilis</i> 889	25	25	2.5	5.0	2.5	1.25
<i>P.morganii</i>	2.5	25	2.5	5.0	2.5	0.5
<i>P. rettgeri</i>	2.5	5.0	2.5	2.5	0.5	0.5
<i>B. subtilis</i>	125	125	>100	>500	250	>500
<i>Staph. aureus</i> Oxford	125	25	>100	500	250	250
<i>Staph. aureus</i> Russell	>250	50	>100	500	500	500
<i>Staph. aureus</i> 1517	>250	250	>100	>500	>500	>500
<i>Strep. Faecalis</i>	>250	>500	>100	>500	>500	>500
β -haemolytic <i>Strep.</i> CN10	25	1.25	50	125	12.5	50

Serial dilution in 5% blood agar

Example Number	12
	R¹=Ph- R=
M.I.C. (μg/ml)	
<i>E. coli</i> JT1	5.0
<i>E. coli</i> JT4	12.5
<i>E. coli</i> JT425	5.0
<i>Salmonella typhi</i>	12.5
<i>Shigella sonnei</i>	2.5
<i>Ps. aeruginosa</i> 10662	250
<i>Ps. aeruginosa</i> 10662 (10 ⁻²)	250
<i>Serratia marcescens</i> US32	12.5
<i>Klebsiella aerogenes</i> A	0.5
<i>Enterobacter cloacae</i> N1	5.0
<i>P. mirabilis</i> C977	2.5
<i>P. mirabilis</i> 889	2.5
<i>P.morganii</i>	2.5
<i>P. rettgeri</i>	2.5
<i>B. subtilis</i>	250
<i>Staph. aureus</i> Oxford	50
<i>Staph. aureus</i> Russell	500
<i>Staph. aureus</i> 1517	>500
<i>Strep. faecalis</i>	>500
β -haemolytic <i>Strep.</i> CN10	25

2. Oral absorption

Mouse blood levels of 6-methoxy-ticarcillin and 6-methoxycarbenicillin were measured after oral dosing of the esters. For some compounds urine was also collected from the mice and biochromatogrammed to determine whether any unhydrolysed ester was excreted. The extent of hydrolysis of the esters during the microbiological assay procedure was measured in mouse blood and saline.

The following methods were used:

Species: Albino male mice CS1 strain 18-22 g.

Route: Oral

Dose: Each ester was dosed to contain

100 mg/kg of the parent penicillin free acid.

Assay: Samples were assayed in terms of the parent penicillins using *Neisseria catarrhalis* as the assay organism.

Chromatography: Urine was collected from mice receiving compounds of Examples Nos. 2, 3, 4, 6 and 10. Samples were biochromatogrammed. A butanol: ethanol: water system (4:1:5) was used and strips were visualised on agar plates seeded with *Neisseria catarrhalis*.

The results for the mouse blood levels are shown in tables 4 and 5.

No blood levels were detected after dosing with 6-methoxy-carbenicillin at 100 mg/kg under the same conditions.

Table 4

Mouse blood levels of 6-methoxy ticarcillin after oral dosing of the series of α carboxy esters at 100 mg/kg

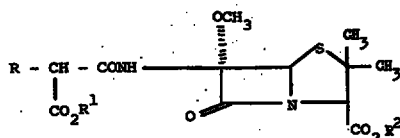
Example No.	Ester Type	Mouse No.	Conc μ g/ml of 6-methoxy ticarcillin at mins after dosing					
			10	20	30	60	120	240
2	isobutyl	1	4.6	8.0	10.5	4.9	3.6	0.54
		2	4.6	8.6	11.5	9.0	4.3	0.94
		3	3.1	6.1	11.0	8.6	2.8	0.58
		4	3.0	4.1	11.3	7.8	3.1	0.59
		5	6.4	5.6	9.4	7.9	2.5	1.6
		Mean	4.3	6.6	10.7	7.6	3.3	0.85
4	4-methyl phenyl	1	1.3	1.7	3.2	1.72	0.48	0.31
		2	1.2	1.6	3.7	2.2	0.21	<0.10
		3	0.99	1.95	3.0	2.1	0.50	0.27
		4	1.25	1.95	1.7	1.85	0.52	0.51
		5	1.1	3.5	2.0	1.4	—	—
		Mean	1.2	2.14	2.7	1.85	0.43	0.29
3	5-indanyl	1	4.5	8.1	8.5	2.8	0.62	0.44
		2	3.8	9.0	5.2	3.8	1.45	1.0
		3	3.1	8.0	8.0	2.55	1.5	0.78
		4	2.7	6.8	4.4	7.0	0.5	0.36
		5	4.8	3.5	8.5	3.7	—	—
		Mean	3.8	7.1	6.9	4.0	1.0	0.64

Table 5
 Mouse blood levels of 6-methoxy carbenicillin
 after oral dosing of a series of
 α carboxy esters at 100 mg/kg

Example No.	Ester Type	Mouse No.	Conc μ g/ml of 6-methoxy ticarcillin at mins after dosing					
			10	20	30	60	120	240
11	phenyl	1	3.4	5.4	10.5	3.9	3.0	0.85
		2	5.0	7.0	6.4	4.3	2.9	0.53
		3	3.9	6.1	7.4	5.6	2.0	1.4
		4	3.8	15.9	8.4	2.1	1.4	0.80
		5	2.9	—	5.8	3.5	1.7	0.78
		Mean	3.8	6.1	7.7	3.9	2.2	0.87
5	3,4-dimethyl phenyl	1	9.2	7.4	19.0	15.0	7.8	1.8
		2	13.0	9.2	17.5	11.0	7.7	4.9
		3	12.0	11.5	14.5	8.5	7.5	3.7
		4	7.8	13.0	20.0	4.4	5.3	3.1
		5	8.0	—	—	—	—	—
		Mean	10.0	10.3	17.8	9.7	7.1	3.4
6	4-methyl phenyl	1	6.5	10.0	9.4	11.5	3.8	1.8
		2	6.5	10.5	11.5	15.0	3.1	1.1
		3	3.8	10.2	9.6	7.4	4.9	2.0
		4	2.1	6.5	12.0	9.5	3.2	2.6
		5	2.4	10.5	9.6	8.9	3.1	0.62
		Mean	4.3	9.5	10.4	10.5	3.6	1.6
8	3-methyl phenyl	1	1.4	5.4	12.0	9.4	4.3	3.5
		2	4.6	8.8	11.9	6.5	4.9	2.4
		3	2.7	9.3	12.0	5.3	4.0	1.8
		4	3.1	8.4	13.5	9.0	—	0.7
		5	2.6	5.1	13.5	6.8	5.4	1.2
		Mean	2.9	7.4	12.6	7.4	4.7	1.9
9	5-indanyl	1	2.9	15.0	22.0	5.8	3.7	2.3
		2	1.4	22.0	15.2	15.2	5.8	1.6
		3	5.6	14.0	14.5	12.0	5.0	3.0
		4	2.5	20.0	9.2	7.0	3.7	1.9
		5	5.4	—	—	8.8	—	—
		Mean	3.6	17.8	15.2	9.8	4.6	2.2
10	isobutyl	1	6.2	9.2	9.0	5.5	8.0	1.4
		2	4.7	9.8	15.0	10.7	8.8	2.0
		3	4.8	14.0	16.5	12.0	5.2	3.0
		4	3.9	11.7	13.5	14.0	4.7	4.1
		5	4.7	13.0	15.5	12.0	4.9	1.5
		Mean	4.9	11.5	13.9	10.8	6.3	2.4

WHAT WE CLAIM IS:-

1. A compound of formula (I):



where R is phenyl or 2- or 3-thienyl and R² is hydrogen, a pharmaceutically acceptable salting ion or a radical which forms an ester which is hydrolysable *in vivo* in man and R¹ is a pharmaceutically acceptable ester-forming radical.

2. A compound as claimed in claim 1 wherein R is 3-thienyl.

3. 6-α-Methoxy, 6-β-(2-phenoxycarbonyl-2-thien-2'-ylacetamido)-penicillanic acid.

4. 6-α-Methoxy, 6-β-(2-phenoxycarbonyl-2-thien-3'-ylacetamido)-penicillanic acid.

5. 6-β-[2-(Isobutyloxycarbonyl)-2-thien-3'-ylacetamido]-6-α-methoxy-penicillanic acid.

6. 6-β-[2-(Indan-5-yloxycarbonyl)-2-thien-3'-ylacetamido]-6-α-methoxy-penicillanic acid.

7. 6-α-Methoxy-6-β-[2-(4-methylphenoxy carbonyl)-2-thien-3'-ylacetamido]-penicillanic acid.

8. 6-α-Methoxy-6-β-[2-(phthalid-3-yloxycarbonyl)-2-thien-3'-ylacetamido]-penicillanic acid.

9. 6-β-[2-(2-Sec-butylphenoxy carbonyl)-2-thien-3'-ylacetamido]-6-α-methoxy penicillanic acid.

10. 6-β-[2-(2-Ethylphenoxy carbonyl)-2-thien-3'-ylacetamido]-6-α-methoxy penicillanic acid.

11. 6-α-Methoxy-6-β-[2-(4-isopropylphenoxy carbonyl)-2-thien-3'-ylacetamido] penicillanic acid.

12. 6-β-[2-(3,4-Dimethylphenoxy carbonyl)-2-phenylacetamido]-6-α-methoxy penicillanic acid.

13. 6-α-Methoxy-6-β-[2-(4-methylphenoxy carbonyl)-2-phenylacetamido]-penicillanic acid.

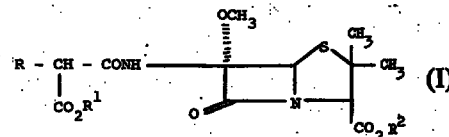
14. 6-α-Methoxy-6-β-(2-phenoxycarbonyl-2-phenylacetamido)-penicillanic acid.

15. 6-α-Methoxy-6-β-[2-(3-methylphenoxy carbonyl)-2-phenylacetamido]-penicillanic acid.

16. 6-β-[2-(5-Indanyloxycarbonyl)-2-phenylacetamido]-6-α-methoxy penicillanic acid.

17. 6-β-(2-Isobutoxy carbonyl-2-phenylacetamido)-6-α-methoxy penicillanic acid.

18. A process for the preparation of a compound of formula (I):



wherein R, R¹ and R² are as defined in claim 1, which process comprises:

a) reacting a compound of formula (III) as hereinbefore defined or an N-silyl or N-phosphorylated derivative thereof; with an N-acylating derivative of an acid of formula (IV) as hereinbefore defined, and removing any silyl or phosphoryl groups by hydrolysis or alcoholysis; or

b) reacting an isocyanate of formula (VI) as hereinbefore defined; with an acid of formula (IV) or a carbanion of formula (IVA) as herein before defined; or

c) protecting the 3-carboxylic acid group of a 6-α-methoxy 6-β-acylamino-penicillanic acid with a carboxyl block group; reacting the protected penicillanic acid to form an imino bond on the 6-amido nitrogen atom; reacting the resulting compound to introduce a group QR_i on the imino carbon atom, wherein Q is oxygen, sulphur or nitrogen and R_i is an alkyl group of from 1 to 12 carbon atoms or an aralkyl group of from 7 to 14 carbon atoms, to form an iminoether, iminothioether or amidide (when Q is O, S, or N respectively); reacting with an N-acylating derivative of an acid of formula (IV) herein; and treating with water or an alcohol; or

d) hydrolysing an N-acylbenzyl 6-α-methoxy penicillin of formula (X) as hereinbefore defined; or

e) esterifying a compound of formula (XI) as herein before defined or a reactive esterifying derivative thereof; with an alcohol of formula R¹ OH or an esterifying derivative thereof; or

f) reacting a compound of formula (XIII) as hereinbefore defined:

(A) with chlorine or bromine at -25° to -80°C and subsequently decomposing the resultant halo-sulphonium halide with methanol and a base; or

(B) with methanol in the presence of a metal ion; or

g) reducing a compound of formula (XV) as hereinbefore defined and simultaneously or subsequently acylating with an N-acylating derivative of an acid of formula (IV);

and after a, b, c, d, e, f, or g if necessary carrying out one or both of the following steps:

(i) removal of any carboxyl blocking groups;

(ii) converting the product to a salt or ester thereof.

19. A process as claimed in claim 18, substantially as described in any one of

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examples 1 to 16.

20. A compound as claimed in claim 1, whenever prepared by a process as claimed in claim 18 or claim 19.

21. A pharmaceutical composition comprising a compound as claimed in any

one of claims 1 to 16, together with a pharmaceutical carrier or excipient.

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