PATENT SPECIFICATION

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(54) DERIVATIVES OF THIENAMYCIN AND ITS ISOMERS

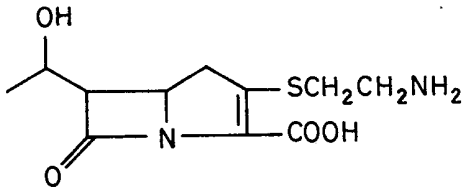
(71) We, MERCK & CO. INC., a corporation duly organized and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

There is a continuing need for new antibiotics, since there is unfortunately no static effectiveness of a given antibiotic because continued wide-scale usage of any such antibiotic selectively gives rise to resistant strains of pathogens. In addition, the known antibiotics suffer from the disadvantage of being effective only against certain types of microorganisms. Accordingly, the search for new antibiotics continues.

This invention is concerned with certain substituted N-methylene derivatives of the antibiotic thienamycin and its position isomers, and their pharmaceutically acceptable salt, ether, ester, and amide derivatives. Compounds in accordance with the present invention have been found to have utility as broad-spectrum antibiotics and this invention also concerns processes for the preparation of such compounds and pharmaceutical compositions containing them.

Thienamycin is disclosed and claimed in U.S. Patent No. 3,950,357 and U.K. Patent No. 1,498,087. Thienamycin may be used as a starting material in the preparation of the compounds of the present invention.

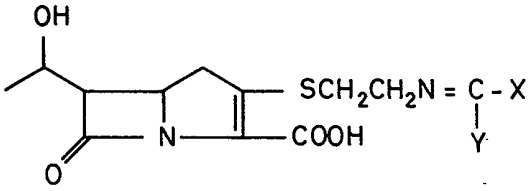
Thienamycin is known to have the formula:



I

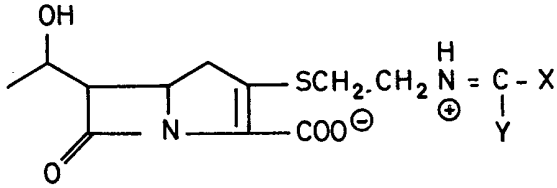
and its position isomers may be similarly represented.

The substituted N-methylene derivatives of the present invention have the following formula:



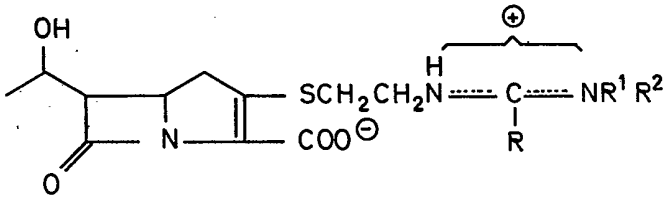
II

or are salts, esters (with the carboxy or the hydroxy group), ethers, amides or anhydrides of compounds of formula II, or the corresponding thioic S-acids or their salts, esters, ethers or anhydrides. Depending upon the basicity of the amino nitrogen (a function of the identity of the methylene substituents X and Y), Formula II may equivalently be represented as an inner salt:



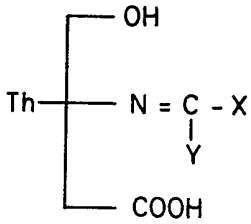
II

and, when the carboxy group is esterified, this tautomer can also form acid-addition salts. Such tautomers are intended to be included when the generic formula II is mentioned. The inner salt is one canonical form of a single resonant structure, which, for example, when Y is $—NR^1R^2$ and X is R, is:



II

For convenience, the compounds of the present invention may also be represented by the symbol:

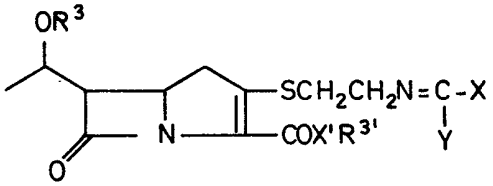


II

where "Th" indicates the bicyclic nucleus of thienamycin or its position isomer and its hydroxyl, amino, and carboxyl functional groups are shown. In the foregoing formulae, X is —OR, —SR or $—NR^1R^2$ and Y, independently of X, is hydrogen, —R, —OR, —SR, or $—NR^1R^2$; where each of R^1 and R^2, independently of the other, is a hydrogen atom, a radical of the type defined below for R, or a nitro, hydroxyl, C_{1-6} alkoxyl, amino, C_{1-6} monoalkylamino, di(C_{1-6} alkyl)amino, or

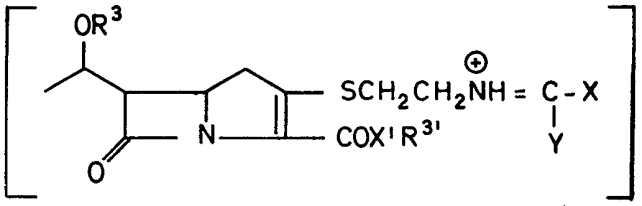
tri(C_{1-6} alkyl)amino radical, or R^1 and R^2 are joined together to form, together with the nitrogen atom to which they are attached, a substituted or unsubstituted monocyclic or bicyclic heteroaryl or non-aromatic heterocyclic radical comprising 4—10 atoms one or more of which may be an additional oxygen, sulphur or nitrogen hetero atom; R is a cyano or carboxy radical or a substituted or unsubstituted carbamoyl; alkoxycarbonyl; C_{1-10} alkyl; C_{2-10} alkenyl; C_{2-10} alkynyl; C_{3-10} cycloalkyl; C_{4-12} cycloalkylalkyl; C_{4-12} cycloalkylalkenyl; C_{3-10} cycloalkenyl; C_{4-12} cycloalkenylalkenyl; C_{4-12} cycloalkenylalkyl; C_{6-10} aryl; C_{7-16} aralkyl; C_{8-16} aralkenyl or C_{8-16} aralkynyl radical or a substituted or unsubstituted monocyclic or bicyclic heteroar(C_{1-6} alkyl), heteroaryl, non-aromatic heterocyclic(C_{1-6} alkyl) or non-aromatic heterocyclic radical having 4 to 10 ring atoms one or more of which is an oxygen, sulphur or nitrogen heteroatom; the substituent(s) on R, R^1, R^2 or the ring formed by joining R^1 and R^2, are halogen, viz. chlorine, bromine, iodine or fluorine; azido; thio; sulpho; phosphono; cyanothio (—SCN); nitro; cyano; amino; hydrazino; C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, tri(C_{1-6} alkyl)amino; C_{1-6} alkylhydrazino, di(C_{1-6} alkyl)hydrazino, tri(C_{1-6} alkyl)hydrazino, hydroxyl; C_{1-4} alkyl; C_{1-6}, alkoxy; C_{1-6} alkylthio; carboxyl; oxo; (C_{1-6} alkoxy)carbonyl; C_{2-10} acyloxy; carbamoyl; (C_{1-4} alkyl)carbamoyl or di(C_{1-4} alkyl)carbamoyl.

Compounds of the present invention can be represented by the following formula:



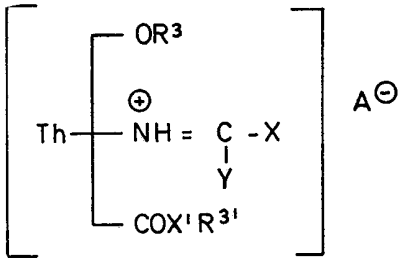
IIa

which may also exist as a salt:



IIa

or, more conveniently by the previously introduced symbol:



IIa

The non-critical counter anion, A, is representatively selected to provide pharmaceutically acceptable salts such as a halide, e.g. chloride or bromide, sulfate, phosphate, citrate, acetate or benzoate.

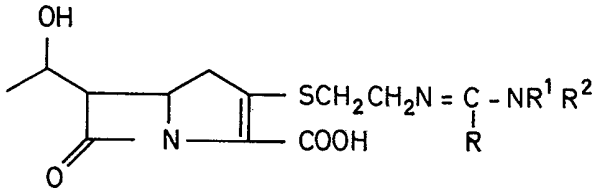
X′ is oxygen, sulphur, NH or $NR^{3'}$. $R^{3'}$ is hydrogen, or, *inter alia*, is representatively selected to provide the pharmaceutically acceptable salt, ester, anhydride ($R^{3'}$ is acyl and X′ is oxygen), and amide residues known in the bicyclic β-lactam antibiotic art and enumerated in greater detail below, R^3 is: (1) acyl (generically the group OR^3 is classifiable as an ester); (2) R^3 is a univalent hydrocarbon or substituted hydrocarbon residue, e.g. alkyl, aryl, alkenyl or aralkyl (such that the group OR^3 is generically classifiable as a ether) or (3) hydrogen. The term "acyl" includes the alkanoyls and their derivatives and analogues such as thio analogues in which the carbonyl oxygen is replaced by sulphur; as well as sulphur and phosphorus acyl analogues such as substituted sulfonyl and sulfinyl radicals, and substituted P (III and V) radicals such as substituted phosphorus, phosphoric,

phosphonous and phosphonic radicals. Such radicals, R^3, of the present invention are enumerated in greater detail below.

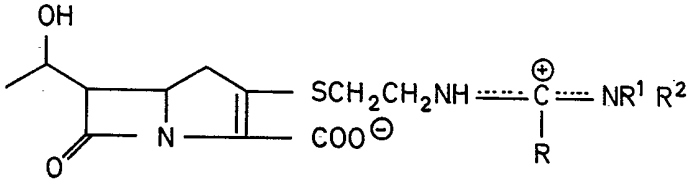
Antibiotics of the present invention have been found to be active against a broad range of pathogens which representatively include both gram-positive bacteria such as *S. aureus, Strep. pyogenes,* and *B. subtilis* and gram-negative bacteria such as *E. coli, Proteus morganii, Klebsiella, Serratia,* and *Pseudomonas.*

The compounds of the present invention (Formulae II and IIa, above) may be divided into four classes:

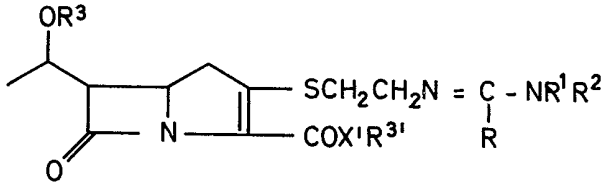
(1) *Amidines,* in which Y = $—NR^1R^2$ and X = hydrogen or R:



which may be represented by the resonant structure:



where R, R^1 and R^2 are as previously defined. Species IIa may similarly be depicted:



where R^3, X′ and $R^{3'}$ are as defined below. Representative examples of such amidine embodiments (the substituent plus the amino group of thienamycin form the amidine structure) are:

The benzamidine: Y = $—NH_2$, X = phenyl;
The formamidine: Y = $—NH_2$; X = H;
The acetamidine: Y = $—NH_2$, X = CH_3;
The 4-pyridylcarboxamidine: Y = $—NH_2$, X = 4-pyridyl;
The N-isopropyl formamidine: Y = $NHCH(CH_3)_2$, X = H;
The N-methyl formamidine: Y = $—NHCH_3$, X = H;
The N,N-dimethylformamidine: Y = $—N(CH_3)_2$, X = H;
The piperidinyl methylenimine: Y = 1-piperidyl X = H.

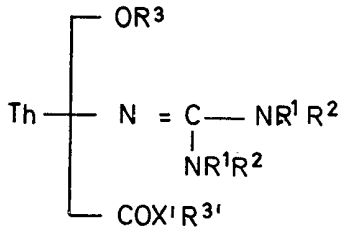
Other preferred amidines are those in which Y = NR^1R^2 and each of R^1 and R^2, independently of the other, is a hydrogen atom; a substituted or unsubstituted C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} cycloalkyl, C_{4-7} cycloalkylalkyl, C_{4-6} cycloalkenyl, C_{4-7} cycloalkenylalkyl, C_{7-10} aralkyl or C_{8-10} aralkenyl radical or a monocyclic heteroar(C_{1-3} alkyl) radical having 5—6 ring atoms, one or more of which is oxygen, sulphur, or nitrogen, the ring or chain substituent(s) of R^1 and R^2 being chlorine, fluorine, hydroxyl, C_{1-3} alkoxy, di(C_{1-3} alkyl)amino or C_{1-3} alkylthio. Examples of the values of R^1 and R^2 are methyl, ethyl, propyl, isopropyl, butyl, *t*-butyl, N,N-dimethylaminoethyl, 2,2,2-trifluoroethyl, 2-methylthioethyl, allyl, methallyl, 2-butenyl, 1-buten-3-yl, cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclohexylmethyl, 2-cyclopropenyl, 1,4-cyclohexadienylmethyl, benzyl, *p*-methoxybenzyl, *p*-dimethylaminobenzyl, cinnamyl, 2-thienylmethyl, 3-thienylmethyl, 2-furylmethyl, and 1-methyl-5-tetrazolylmethyl.

X is a hydrogen atom or a residue of the type defined above for R, preferably C_{1-6} alkyl, C_{1-6} aminoalkyl, C_{2-6} alkenyl, C_{2-6} aminoalkenyl, C_{2-6} alkoxyalkyl, C_{2-12}

(mono, di or tri)-alkylaminoalkyl, C_{1-6} perhaloalkyl, C_{2-6} alkylthioalkyl, or a substituted or unsubstituted aryl, aralkyl, monocyclic heteroaryl, heteroar(C_{1-6} alkyl), non-aromatic heterocyclic or non-aromatic heterocyclic-(C_{1-6} alkyl)ring in which any substituent(s) are as set out in the definition of R^1 and R^2. More specific examples of preferred values of X are methoxymethyl, ethoxyethyl, dimethylaminomethyl, methylaminomethyl, trimethylammoniumethyl, trifluoromethyl, methylthiomethyl, ethylthioethyl, phenyl, benzyl, phenethyl, 2-pyridyl, 3-pyridyl, 4-pyridyl and 2-thiazolyl.

The amidine compounds represent a preferred class, particularly when X′ is oxygen and R^3 and $R^{3\prime}$ are both hydrogen. Especially preferred amidines of the present invention are those in which Y is $—NR^1R^2$ and X is R, where each of R^1, R^2 and R is a hydrogen atom or a substituted or unsubstituted alkyl or alkenyl radical or the type mentioned in the immediately preceding paragraph.

(2) *Guanidines*, in which Y is $—NR^1R^2$ and X is $—NR^1R^2$:



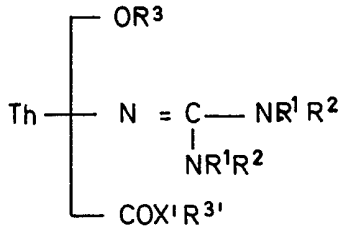
where all symbols are as defined above.

Representative examples of such guanidine compounds (the substituted plus the amino group of thienamycin form the guanidine structure) are:

The guanidine: Y = $—NH_2$, X = $—NH_2$;
The N-methylguanidine: Y = $—NHCH_3$, X = $—NH_2$;
The N,N-dimethylguanidine: Y = $—N(CH_3)_2$, X = $—NH_2$;
The N,N,N-trimethylguanidine: Y = $—N(CH_3)2$, X = $—NHCH_3$;
The N-phenylguanidine: Y = $—NH(C_6H_5)$, X = $—NH_2$;
The nitroguanidine: Y = $—NHNO_2$, X = $—NH_2$;
The aminoguanidine: Y = $—NHNT_2$, X = $—NH_2$.

Other preferred guanidines are those in which X′ is oxygen, R^3 and $R^{3\prime}$ are both hydrogen, and each of R^1 and R^2, independently of the other, is a hydrogen atom or a substituted of unsubstituted C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} cycloalkyl, C_{4-7} cycloalkylalkyl, C_{4-6} cycloalkenyl, C_{4-7} cycloalkenylalkyl, C_{7-10} aralkyl or C_{8-10} aralkenyl radical or a monocyclic heteroar(C_{1-3} alkyl) radical having 5 or 6 ring atoms, one or more of which is oxygen, sulphur, and/or nitrogen, and the substituent(s) is/are chlorine, fluorine, hydroxy, C_{1-3} alkoxy, di(C_{1-3} alkyl)amino or C_{1-3} alkylthio and may be ring or chain substituents. Specific examples of values of R^1 and R^2 are methyl, ethyl, isopropyl, butyl, *t*-butyl, N,N-dimethylaminoethyl, 2,2,2-trifluoroethyl, 2-methylthio ethyl, allyl, methallyl, 2-butenyl, 1-buten-3-yl, cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclohexylmethyl, 2-cyclopropenyl, 1,4-cyclohexadienylmethyl, benzyl, *p*-methoxybenzyl, *p*-dimethylaminobenzyl, cinnamyl, 2-thienylmethyl, 3-thienylmethyl, 2-furylmethyl and 1-methyl-5-tetrazolylmethyl.

(3) *Substituted Pseudoureas*, in which Y is $—NR^1R^2$ and X is —OR or —SR:



where R^3, $R^{3\prime}$, X′, R^1, and R^2 are as defined, and X is —OR or —SR.

Representative examples of such substituted pseudourea compounds (the substituent plus the amino group of thienamycin form the substituted pseudourea structure) are:

The N,N-dimethyl-O-methyl pseudourea:

$$Y = —N(CH_3)_2,\ X = —OCH_3;$$

The N,N-dimethyl-S-ethyl pseudothiourea:

$$Y = —N(CH_3)_2,\ X = —SCH_2CH_3;$$

The N-phenyl-S-ethyl pseudothiourea:

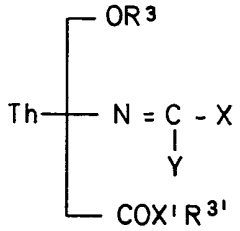
$$Y = —NHC_6H_5,\ X = —SCH_2CH_3;$$

The N-methyl-S-methyl pseudothiourea:

$$Y = —NHCH_3,\ X = —SCH_3$$

Particularly preferred compounds are those in which R^3 and $R^{3'}$ are hydrogen and X′ is oxygen.

(4) *Imido Ethers, and Imido Thioethers*



where R^3, X′, $R^{3'}$ and R are as defined, X is —OR or —SR and Y is hydrogen, R, —OR and —SR.

Representative examples of such imido ester and imido thioester compounds (the substituent plus the amino group of thienamycin form the imido ester or imido thioester structure) are
The methyl formimidate:

$$Y = —OCH_3,\ X = —H;$$

The S-methyl thiobenzimidate:

$$Y = —SCH_3,\ X = \text{phenyl};$$

The methyl benzoyloxycarbimidate:

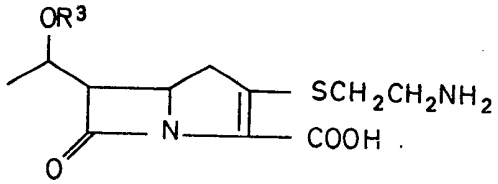
$$Y = —OCH_3,\ X = —OCH_2C_6H_5;$$

The diethyl dithiocarbimidate:

$$Y = —S—C_2H_5,\ X = —S—C_2H_5.$$

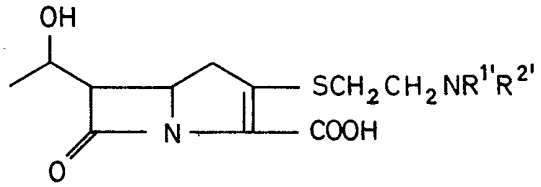
The compounds of the present invention are conveniently prepared from thienamycin and from position isomers of thienamycin, which are discussed later on in the specification. These compounds have Formula IA, above. Compounds of the present invention such as IIa, above, in which the secondary alcoholic group and/or the carboxyl group are derivatized, are conveniently prepared either from the corresponding O—, carboxyl, or O— and carboxyl derivative of thienamycin or its position isomer or from II or thienamycin or its position isomer followed by subsequent reaction to introduce the radicals R^3 and $R^{3'}$ (or —X′ $R^{3'}$) and combinations thereof. Such starting materials are fully disclosed in the specifications of the following copending Patent Applications:

Application No. 7667/77 (Serial No. 1,569,234) is directed to O-derivatives (ester and ether derivatives) of the secondary alcoholic group, which have the following structural formula:



Ia

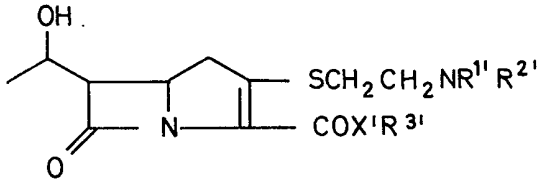
Application No. 48236/76 (Serial No. 1,570,986) is directed to N-acyl derivatives, which have the following structural formula:



Ib

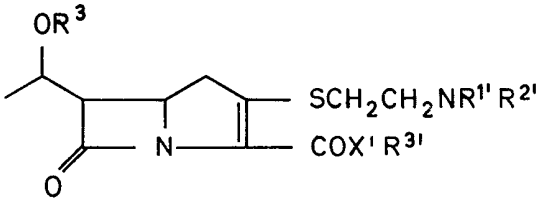
where $R^{1'}$ is acyl and $R^{2'}$ is hydrogen or acyl. Such N-acyl compounds are useful starting materials for the preparation of the substituted pseudourea (3) and the imido ether and imido thioether (4) compounds of the present invention.

Application No. 48239/76 (Serial No. 1,570,989) is directed to N-acyl and carboxyl derivatives having the following structural formula:



Id

Application No. 48237/76 (Serial No. 1,570,987) is directed to N-acyl, O- and carboxyl derivatives of thienamycin having the following structural formula:



Ie

The corresponding O-unsubstituted compounds (herein called Ic) can be prepared analogously.

Thus compounds of the present invention depicted as IIa, above, may be prepared by starting with the corresponding derivative Ia, Ib, Ic, Id, Ie; or compounds IIa may be prepared directly starting with Thienamycin or a position isomer thereof, I, (I→II) followed by the desired derivatization procedure to establish R^3 and/or $X'R^{3'}$ (II→IIa) which is described in the above mentioned copending Patent Applications.

The radicals R^3, $R^{3'}$, X', $R^{1'}$ and $R^{2'}$ are defined as set forth below.

In the generic representation of the compounds of the present invention (IIa, above), the radical represented by —COX'R''' is, *inter alia*, —COOH (X' is oxygen and $R^{3'}$ is hydrogen) and all radicals known to be effective as pharmaceutically acceptable ester, anhydride ($R^{3'}$ is acyl) and amide radicals in the bicyclic β-lactam antibiotic art, such as the cephalosporins and penicillins and the nuclear analogues thereof.

Suitable radicals ($R^{3'}$) include conventional protecting or carboxyl blocking group. The term "blocking group" as utilized herein is used in the same manner and in accordance with the teaching of U.S. Patent 3,697,515. Pharmaceutically acceptable thienamycin derivatives of the present invention falling in this class are given below. Suitable blocking esters thus include those selected from the following list which is representative and not intended to be an exhaustive list of possible ester groups, in which X is oxygen and $R^{3'}$ is given:

(i) $R^{3'}$ is $CR^a—R^b—R^c—$ where at least one of $R^a—$, $R^b—$ and $R^c—$ is an electron-donor, e.g., *p*-methoxyphenyl, 2,4,6-trimethylphenyl, 9-anthryl, methoxy,

CH_2SCH_3, tetrahydrofur-2-yl, tetrahydropyran-2-yl or fur-2-yl. The remaining R^a—, R^b— and R^c— groups may be hydrogen or organic substituting groups. Suitable ester groups of this type include *p*-methoxybenzyloxycarbonyl and 2,4,6-trimethylbenzyloxycarbonyl.

(ii) $R^{3'}$ is CR^a—R^b—R^c— where at least one of R^a—, R^b— and R^c— is an electron-attracting group, e.g., benzoyl, *p*-nitrophenyl, 4-pyridyl, trichloromethyl, tribromomethyl, iodomethyl, cyanoethyl, ethoxycarbonylmethyl, arylsulphonylmethyl, 2-dimethylsulphoniummethyl salt, *o*-nitrophenyl or cyano. Suitable esters of this type include benzoylmethoxycarbonyl, *p*-nitrobenzyloxycarbonyl, 4-pyridylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl and 2,2,2-tribromoethoxycarbonyl.

(iii) $R^{3'}$ is CR^a— R^b— R^c— where at least two of R^a—, R^b— and R^c— are hydrocarbon such as alkyl, e.g., methyl or ethyl, or aryl, e.g. phenyl and the remaining R^a—, R^b— or R^c—, if there is one, is hydrogen. Suitable esters of this type include *t*-butyloxycarbonyl, *t*-amyloxycarbonyl, diphenylmethoxycarbonyl and triphenylmethoxycarbonyl.

(iv) $R^{3'}$ is adamantyl, 2-benzyloxyphenyl, 4-methylthiophenyl or tetrahydropyran-2-yl.

Silyl esters, under this category of blocking groups, may conveniently be prepared from a halosilane or a silazane of the formula:

$$R^4_3SiX'; \quad R^4_2SiX'_2; \quad R^4_3Si.NR^4_2; \quad R^4_3Si.NH.COR^4;$$

$$R^4_3Si.NH.CO.NH.SiR^4_3; \quad R^4NH.CO.NH.SiR^4_3; \text{ or}$$

$$R^4C(OSiR^4_3); \quad HN(SiR^4_3)_2$$

where X3 is a halogen such as chlorine or bromine and the various groups R^4, which can be the same or different, represent hydrogen, alkyl, e.g. methyl, ethyl, *n*-propyl, iso-propyl; aryl, e.g. phenyl; or aralkyl, e.g., benzyl.

More generally stated, pharmaceutically acceptable carboxyl derivatives of the present invention are those derived by reacting thienamycin or an N-protected thienamycin, such as N-acylated thienamycin, or a position isomer thereof with alcohols, phenols, mercaptans, thiophenyls or acylating reagents.

For example, esters and amides of interest are the above-listed starting materials and final products having the following group at the 2-position of the thienamycin nucleus: —$COX'R^{3'}$ where X is oxygen, sulfur, NH or $NR^{3'}$ and $R^{3'}$ is alkyl having 1—10 carbon atoms, straight or branched, such as methyl, ethyl, *t*-butyl, pentyl and decyl; carbonylmethyl including phenacyl, *p*-bromophenacyl, *p*-*t*-butylphenacyl, acetoxyacetylmethyl, pivaloxyacetylmethyl, carboxymethyl and its alkyl and aryl esters; α-carboxy-α-isopropyl; aminoalkyl including 2-methylaminoethyl, 2-diethylaminoethyl, 2-acetamidoethyl, phthalimidomethyl and succinimidomethyl; (C_{1-10} alkoxy)-(C_{1-6} alkyl) in which the alkoxy residue can be branched, straight or cyclic, such as methoxymethyl, ethoxymethyl, isopropoxymethyl, decyloxymethyl, ethoxy-propyl, decyloxypentyl or cyclohexyloxymethyl; (C_{1-6} alkanoyloxy)-(C_{1-6} alkyl) in which the alkanoyloxy portion is straight or branched, such as acetoxymethyl, pivaloyloxymethyl, acetoxyethyl, propionyloxymethyl, or acetoxypropyl; halogenated straight or branched C_{1-6} alkyl in which the halogen is iodine, chlorine, bromine and/or fluorine, e.g. 2,2,2-trichloroethyl, tri-fluoroethyl, 2-bromopropyl, diiodomethyl, 2-chloroethyl, or 2-bromoethyl, and also including C_{1-6} perhaloalkyl; alkenyl having 2—10 carbon atoms, either straight or branched, e.g., allyl, 2-propenyl, 3-butenyl, 4-butenyl, 4-pentenyl, 2-butenyl, 3-pentenyl, 2-methyl-2-propenyl, 3-methyl-3-butenyl, methallyl and 1,4-cyclohexadien-1-yl-methyl; alkynyl having 2—10 carbon atoms, either straight or branched, e.g., 3-pentynyl, propargyl, ethynyl and 3-butyn-1-yl; alkanoyl, either straight or branched, having 1—10 carbon atoms, such as pivaloyl, acetyl and propionyl; C_{3-14} alkoxycarbonylalkyl, C_{4-21} dialkylaminoacetoxyalkyl; C_{2-13} alkanamidoalkyl; aralkyl in which the alkyl residue has 1—3 carbon atoms and the aryl residue 6—10 carbon atoms, such as benzyl, benzhydryl, substituted benzyl or benzhydryl, e.g., benzyl or benzhydryl substituted with 1—3 substituents such as benzyl, phenoxy, halo, C_{1-4} alkyl, alkanoyloxy of 1—5 carbon atoms, C_{1-4} alkoxy, hydroxy, nitro, blocked carboxy, or combinations thereof, e.g., *p*-chlorobenzyl, *o*-nitrobenzyl, 3,5-dinitrobenzyl, *p*-methoxybenzyl, *m*-benzoylbenzyl, *p*-*t*-butylbenzyl, *m*-phenoxybenzyl, *p*-benzoylbenzyl, *p*-nitrobenzyl, 3,5-dichloro-4-hydroxybenzyl, *p*-methoxycarbonylbenzyl, *p*-methoxybenzhydryl, *p*-carboxybenzyl (the latter being either the free acid, ester or the sodium salt), 2,4,6-trimethyl-

benzyl, *p*-pivaloyloxybenzyl, *p*-*t*-butoxycarbonyl benzyl, *p*-methylbenzyl, *p*-benzoyloxybenzyl, *p*-acetoxybenzyl, *p*-2-ethylhexanoylbenzyl, *p*-ethoxycarbonylbenzyl, *p*-benzoylthiobenzyl, *p*-benzamidobenzyl, *o*-pivaloyloxybenzyl, *m*-pivaloyloxybenzyl, *p*-isopropoxybenzyl or *p*-*t*-butoxybenzyl, as well as cyclic analogues thereof; monocyclic and bicyclic heteroaralkyl in which there are 4 to 10 atoms in the ring, the hetero atom or atoms being oxygen, sulfur and/or nitrogen, and 1 to 6 carbon atoms in the alkyl chain, e.g. 2,2-dimethyl-5-coumaranmethyl, 5-indanylmethyl, *p*-trimethylsilylbenzyl, 3,5-bis-*t*-butoxy-4-hydroxybenzyl; 2-thienylmethyl, 2-furylmethyl, 3-*t*-butyl-5-isothiazolmethyl, 6-pivaloyloxy-3-pyridazinylethyl or 5-phenylthio-1-tetrazolylmethyl; phthalidyl; phenylethyl, 2-(*p*-methylphenyl)ethyl, and their arylthioalkyl analogues; aryloxy-(C_{1-6} alkyl) where aryl is preferably a phenyl ring having 0—3 substituents, preferably 0 or 1 substituent in the ortho or para positions, e.g., (4-methoxy)phenoxymethyl, phenoxymethyl, (4-chloro)phenoxymethyl, (4-nitro)phenoxymethyl, (4-benzyloxy)phenoxymethyl, (4-methyl)phenoxymethyl, (2-methoxy)phenoxymethyl, (1-phenoxy)ethyl, (4-amino)-phenoxymethyl, (4-methoxy)phenylthiomethyl, (4-chloro)phenylthiomethyl or phenylthioethyl; phenyl, 5-indanyl, substituted phenyl having 1—3 substituents, preferably one substituent in the ortho or para position, e.g., (4-methyl)phenyl, (4-hydroxy)phenyl, (4-*t*-butyl)phenyl, *p*-nitrophenyl, 3,5-dinitrophenyl or *p*-carboxyphenyl, the latter having either the free acid or the sodium salt form; phenyl-(C_{2-6} alkenyl), such as 3-phenyl-2-propenyl; benzyloxy-(C_{1-3} alkyl) such as benzyloxymethyl, (4-nitro)benzyloxymethyl or (4-chloro)benzyloxymethyl; alkylthioalkyl where the alkylthio residue has 1—10 and preferably 1—6 carbon atoms, and can be branched, straight or cyclic, and the alkyl portion has 1—6 carbon atoms, such as methylthioethyl, ethylthioethyl, cyclohexylthiomethyl, decylthiobutyl, methylthiopropyl, isopropylthioethyl, methylthiobutyl, acetamidomethyl, acetyl thioethyl, pivaloylthiomethyl or methylthiomethyl.

In addition to the esters and thio esters listed above, amides are also embraced by the present invention, i.e., compounds where X' is the

$$\begin{array}{c} R' \\ | \\ -N- \end{array}$$

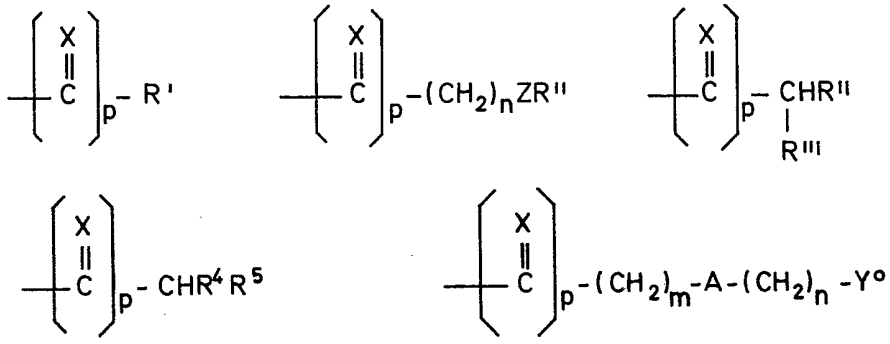
group. Representative of such amides are those in which R' is hydrogen, methyl, ethyl, phenyl, *p*-methoxyphenyl, benzyl, carboxymethyl, methylthioethyl, or heteroaryl; also embraced by —COX'$R^{3'}$ are anhydrides, in which $R^{3'}$ is acyl, for example, benzyloxycarbonyl, ethoxycarbonyl, benzoyl, or pivaloyl.

The preferred —COX'$R^{3'}$ radicals of the present invention are those in which, in Formula IIa above, X' is oxygen, sulphur or NR' (R' is hydrogen or C_{1-6} alkyl); and $R^{3'}$ is C_{1-6} alkyl, C_{2-6} alkenyl, such as methallyl, 3-methylbutenyl or 3-butenyl; methylthioethyl; benzyl or substituted benzyl, such as *p*-*t*-butylbenzyl, *m*-phenoxybenzyl, *p*-pivaloyloxybenzyl or *p*-nitrobenzyl; pivaloyloxymethyl, 3-phthalidyl, acetoxymethyl, propionyloxymethyl, acetylthiomethyl, pivaloylthiomethyl, allyl, 4-butenyl, 2-butenyl, 3-methyl-2-butenyl, phenacyl, acetoxyacetylmethyl, methoxymethyl, *p*-acetoxybenzyl, *p*-pivaloyloxybenzyl, *p*-isopropoxybenzyl, 5-indanylmethyl, 5-indanyl, benzyloxymethyl, ethylthioethyl, methylthiopropyl, methoxycarbonyloxymethyl, ethoxycarbonyloxymethyl, dimethylaminoacetoxymethyl, crotonollacton-3-yl, or acetamidomethyl.

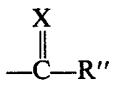
In Formula IIa above, R^3 is, in addition to hydrogen, (1) acyl (generically the group —OR^3 is classifiable as an ester); or (2) R^3 is a radical (e.g. alkyl, aryl or aralkyl) such that the group —OR^3 is classifiable as an ether. For the esters, (1) R^3 is selected from the following definition of acyl radicals ($p = 1$). In the so-called ethers (2) of the present invention, R^3 is selected from the same acyl radicals but in which the carbonyl residue,

$$\begin{array}{c} O \\ \| \\ -C- \end{array} \quad \text{or more generally} \quad \begin{array}{c} X \\ \| \\ -C- \end{array}$$

is omitted ($p = O$). Thus, R^3 is selected from the following radicals where all symbolism is as defined below and p is 1 or 0.



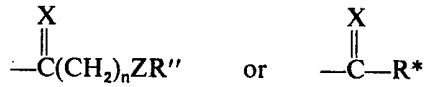
$R^{1'}$ is hydrogen or acyl and $R^{2'}$ is acyl and, when acyl, they are selected from the above radicals in which $p = 1$. Thus, $R^{2'}$, and when acyl, $R^{1'}$ and R^3, can, *inter alia*, be a substituted or unsubstituted aliphatic, aromatic, heterocyclic, araliphatic or heterocyclyaliphatic carboxylic acid radical, a substituted or unsubstituted carbamyl radical or a carbothioic acid radical. One group of acyl radicals can be represented by the general formula:



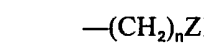
where X is O or S and R'' represents hydrogen; amino; substituted amino such as C_{1-6} alkylamino or (C_{1-6} (alkyl)amino; substituted or unsubstituted straight or branched-chain C_{1-6} alkyl; mercapto; aryloxy, typically comprising 6 to 10 carbon atoms; alkenyl or alkynyl, typically comprising 2 to 6 carbon atoms; aryl, such as phenyl; aralkyl, such as benzyl; cycloalkyl, typically comprising 3 to 6 carbon atoms; or a heteroaryl or heteroaralkyl group (mono- and bicyclic) in which the alkyl residue (if any) typically comprises 1 to 3 carbon atoms and the heterocyclic ring typically comprises 4—10 atoms and the hetero atom or atoms is/are preferably O, N and/or S; such above-listed groups can be unsubstituted or can be substituted by radicals such as OH, SH, SR^8 (R^8 is C_{1-6} alkyl or aryl such as phenyl), alkyl or alkoxy groups having 1 to 6 carbon atoms, halogens, viz. Cl, Br, F or I, cyano, carboxy, sulfamino, carbamoyl, sulfonyl, azido, amino, substituted amino, such as (C_{1-6} alkyl)-substituted amino including quaternary ammonium, C_{1-6} halogenated alkyl such as trifluoromethyl, carboxy(C_{1-6} alkyl), carbamoyl(C_{1-6} alkyl), N-substituted carbamoyl(C_{1-6} alkyl), amidino, guanidino, N-substituted guanidino or guanidino-(C_{1-6} alkyl). Representative examples of such acyl groups that might be mentioned are those in which R'' is benzyl, *p*-hydroxybenzyl, 4-amino-4-carboxybutyl, methyl, cyanomethyl, 2-pentenyl, *n*-amyl, *n*-heptyl, ethyl 3- or 4-nitrobenzyl, phenethyl, β,β-diphenylethyl, methyldiphenylmethyl, triphenylmethyl, 2-methoxyphenyl, 2,6-dimethoxyphenyl, 2,4,6-trimethoxyphenyl, 3,5-dimethyl-4-isoxazolyl, 3-butyl-5-methyl-4-isoxazolyl, 5-methyl-3-phenyl-4-isoxazolyl, 3-(2-chlorophenyl)-5-methyl-4-isoxazolyl, 3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl, D-4-amino-4-carboxybutyl, D-4-N-benzoylamino-4-carboxy-*n*-butyl, *p*-aminobenzyl, *o*-aminobenzyl, *m*-aminobenzyl, *p*-dimethylaminobenzyl, 3-(pyridyl)methyl, 2-ethoxy-1-naphthyl, 3-carboxy-2-quinoxalinyl, 3-(2,6-dichlorophenyl)-5-(2-furyl)-4-isoxazolyl, 3-phenyl-4-isoxazolyl, 5-methyl-3-(4-guanidinophenyl)-4-isoxazolyl, 4-guanidinomethylphenyl, 4-guanidinomethylbenzyl, 4-guanidinobenzyl, 4-guanidinophenyl, 2,6-dimethoxy-4-guanidinophenyl, *o*-sulfobenzyl, *p*-carboxymethylbenzyl, *p*-carbamoylmethylbenzyl, *m*-fluorobenzyl, *m*-bromobenzyl, *p*-chlorobenzyl, *p*-methoxybenzyl, 1-naphthylmethyl, 3-isothiazolylmethyl, 4-isothiazolylmethyl, 5-isothiazolylmethyl, guanylthiomethyl, 4-pyridylmethyl, 5-isoxazolylmethyl, 4-methoxy-5-isoxazolylmethyl, 4-methyl-5-isoxazolylmethyl, 1-imadazolylmethyl, 2-benzofuranylmethyl, 2-indolylmethyl, 2-phenylvinyl, 2-phenylethynyl, 1-aminocyclohexyl, 2- and 3-thienylaminomethyl, 2-(5-nitrofuranyl)vinyl, phenyl, *o*-methoxyphenyl, *o*-chlorophenyl, *o*-phenylphenyl, *p*-aminomethylbenzyl, 1-(5-cyanotriazolyl)methyl, difluoromethyl, dichloromethyl, dibromomethyl, 1-(3-methylimidazolyl)methyl, (2 or 3)-(5-carboxymethylthienyl)methyl, (2 or 3)-(4-carbamoylthienyl)methyl, (2 or 3)-(5-methylthienyl)methyl, (2 or 3)-(methoxythienyl)methyl, (2 or 3)-(4-chlorothienyl)methyl, (2 or 3)-(5-sulfothienyl)methyl, (2 or 3)-(5-carboxythienyl)methyl, 3-(1,2,5-thia-

diazolyl)methyl, 3-(4-methoxy-1,2,5-thiadiazolyl)methyl, 2-furylmethyl, 2-(5-nitrofuryl)methyl, 3-furylmethyl, 2-thienylmethyl, 3-thienylmethyl, tetrazolylmethyl, benzamidinomethyl and cyclohexylamidinomethyl.

The acyl group can also be a radical of the formula:

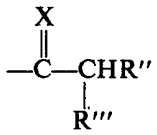


where X is O or S and n is 0, 1, 2, 3 or 4, Z represents oxygen, sulfur, carbonyl or nitrogen, R'' is defined as above and R* is as defined below. Representative members of the substituent

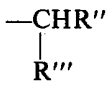


that might be mentioned are allylthiomethyl, phenylthiomethyl, butylthiomethyl, α-chlorocrotylthiomethyl, phenoxymethyl, phenoxyethyl, phenoxybutyl, phenoxybenzyl, phenoxyphenoxymethyl, (dimethylmethoxy)methyl, (dimethylbutoxy)methyl, (dimethylphenoxy)methyl, 4-guanidinophenoxymethyl, 4-pyridylthiomethyl, *p*-(carboxymethyl)phenoxymethyl, *p*-(carboxymethyl)phenylthiomethyl, 2-thiazolylthiomethyl, *p*-(sulfo)phenoxymethyl, 2-pyrimidinylthiomethyl, phenethylthioethyl, 1-(5,6,7,8-tetrahydronaphthyl)oxymethyl, N-methyl-4-pyridylthio, benzyloxy, methoxy, ethoxy, phenoxy, phenylthio, amino, methylamino, dimethylamino, a pyridinium methyl or trimethylammonium-methyl non-toxic salt, cyanomethylthiomethyl or trifluoromethylthiomethyl. R* is 4-pyridylethyl, 4-pyridylpropyl, 4-pyridylbutyl, 3-imidazolylethyl, 3-imidazolylpropyl, 3-imidazolylbutyl, 1-pyrrolylethyl, 1-pyrrolylpropyl and 1-pyrrolylbutyl.

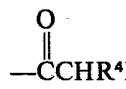
Alternatively, the acyl group can be a radical of the formula:



where R'' is defined as above and R''' is amino, hydroxy, azido, carbamoyl, guanidino, amidino, acyloxy, halo, such as Cl, F, Br, I, sulfamino, tetrazolyl, sulfo, carboxy, carbalkoxy or phosphono. Representative members of the substituent



that might be mentioned are α - aminobenzyl, α - amino - (2 - thienyl)methyl, α-(methylamino)benzyl, α - amino - methylthiopropyl, α - amino - (3 or 4) - chlorobenzyl, α - amino - (3 or 4) - hydroxybenzyl, α - amino - 2,4 - dichlorobenzyl, α - amino - 3,4 - dichlorobenzyl, *D*(−) - α - hydroxybenzyl, α - carboxybenzyl, α - amino - (3 - thienyl)methyl *D*(−) - α - amino - 3 - chloro - 4 - hydroxybenzyl, α - amino(cyclohexyl)methyl, α - (5 - tetrazolyl)benzyl, 2 - thienyl - carboxymethyl, 3 - thienyl - carboxymethyl, 2 - furyl - carboxymethyl, 3 - furyl - carboxymethyl, α - sulfaminobenzyl, 3 - thienyl - sulfaminomethyl, α - (N - methylsulfamino) - benzyl, *D*(−) - 2 - thienyl - guanidinomethyl, *D*(−) - α - guanidinobenzyl, α - guanylureidobenzyl, α - hydroxybenzyl, α - azidobenzyl, α - fluorobenzyl, 4 - (5 - methoxy-1,3 - oxadiazolyl) - aminomethyl, 4 - (5 - methoxy - 1,3 - oxadiazolyl) - hydroxymethyl, 4 - (5 - methoxy - 1,3 - sulfadiazolyl) - hydroxymethyl, 4 - (5 - chlorothienyl) - aminomethyl, 2 - (5 - chlorothienyl) - hydroxymethyl, 2 - (5 - chlorothienyl) - carboxy - methyl, 3 - (1,2 - thiazolyl) - aminomethyl, 3 - (1,2 - thiazolyl)-hydroxymethyl, 3 - (1,2 - thiazolyl) - carboxymethyl, 2 - (1,4 - thiazolyl) - aminomethyl, 2 - (1,4 - thiazolyl) - hydroxymethyl, 2 - (1,4 - thiazolyl)carboxymethyl, 2 - benzothienylaminomethyl, 2 - benzothienylhydroxymethyl, 2 - benzothienylcarboxymethyl, α - sulfobenzyl or α - phosphonobenzyl. The acyl radical can also be α - diethylphosphono or α - monoethylphosphono. Further acyl radicals of interest when X = oxygen are:



where R^4 and R^5 are as defined below. R^4 represents hydrogen, chlorine, fluorine, bromine, iodine, amino, guanidino, phosphono, hydroxy, tetrazolyl, carboxy, sulfo or sulfamino and R^5 represents phenyl, substituted phenyl, a mono- or bicyclic substituted or unsubstituted heterocyclyl containing one or more oxygen, sulfur or nitrogen atoms in the ring, (such as furyl, quinoxalyl, thienyl, quinolyl, quinazolyl, thiazolyl, isothiazolyl, tetrazolyl, oxadiazolyl or thiadiazolyl), phenylthio, phenyloxy alkyl of 1—6 carbon atoms, heterocyclic-thio or substituted heterocyclic-thio groups; or cyano. The substituents on the residues R^4 and R^5 can be halo, carboxymethyl, guanidino, guanidinomethyl, carboxamidomethyl, aminomethyl, nitro, methoxy or methyl. When R^4 is hydrogen hydroxy, amino or carboxy and R^5 is phenyl, or a 5- or 6-membered heterocyclic ring having one or two sulfur, oxygen or nitrogen hetero atom such as tetrazolyl, thienyl, furyl and phenyl, the following acyl radicals are representative: phenylacetyl, 3-bromophenylacetyl, *p*-aminomethylphenylacetyl, 4-carboxymethylphenylacetyl, 4-carboxyamidomethylphenylacetyl, 2-furylacetyl, 5-nitro-2-furylacetyl, 3-furylacetyl, 2-thienylacetyl, 5-chloro-2-thienylacetyl, 5-methoxy-2-thienylacetyl, α-guanidino-2-thienylacetyl, 3-thienylacetyl, 2-(4-methylthienyl)acetyl, 3-isothiazolylacetyl, 4-methoxy-3-isothiazolylacetyl, 4-isothiazolylacetyl, 3-methyl-4-isothiazolylacetyl, 5-isothiazolylacetyl, 3-chloro-5-isothiazolylacetyl, 3-methyl-1,2,5-oxadiazolylacetyl, 1,2,5-thiadiazolyl-4-acetyl, 3-methyl-1,2,5-thiadiazolylacetyl, 3-chloro-1,2,5-thiadiazolylacetyl, 3-methoxy-1,2,5-thiadiazolylacetyl, phenylthioacetyl, 4-pyridylthioacetyl, cyanoacetyl, 1-tetrazolylacetyl, α-fluorophenylacetyl, *D*-phenylglycyl, 4-hydroxy-*D*-phenylglycyl, 2-thienylglycyl, 3-thienylglycyl, phenylmalonyl, 3-chlorophenylmalonyl, 2-thienylmalonyl, 3-thienylmalonyl, α-phosphonophenylacetyl, α-aminocyclohexadienylacetyl, α-sulfaminophenylacetyl, α-hydroxyphenylacetyl, α-tetrazolylphenylacetyl and α-sulfophenylacetyl.

The radical $R^{3'}$ when acyl, but not $R^{1'}$ or $R^{2'}$, may also be a sulphur (1) or phosphorus (2) radical:

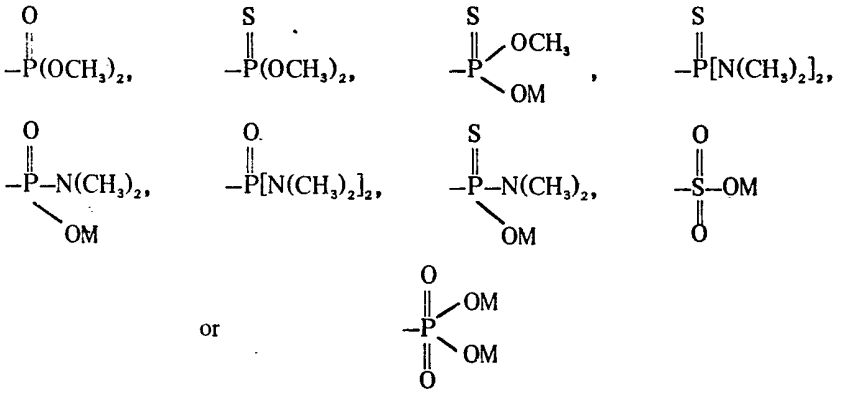
1 2

in which, with respect to 1, each of *m* and *n* is 0 or 1 and $Y^\circ = O^\ominus M^\oplus$, $—N(R'')_2$, or R''; where $M^\oplus$ is hydrogen, an alkali metal or alkaline-earth metal cation or an organic base; and R'' is as defined above, e.g., alkyl, alkenyl, aryl or heteroaryl. With respect to 2, X = O or S; *n* = 0 or 1; and each of Y' and Y'', independently of the other, is $O^\ominus M^\oplus$, $—N(R'')_2$, —R'' or —ZR'' where all symbols are as defined above, e.g., R'' and ZR'' may be alkyl, alkenyl, aryl or heteroaryloxy or Y' and Y'', including R'' residues, are joined together to form cyclic ester, esteramide and amide functions.

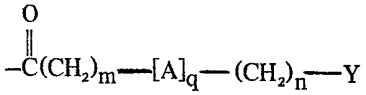
Acyl groups $R^{1'}$, $R^{2'}$ and $R^{3'}$ of particular interest, particularly in the preparation of compounds in accordance with the present invention as described below, are conventionally known N-acyl blocking or protective groups such as carbobenzyloxy, ring-substituted carbobenzyloxy such as *o*- and *p*-nitrocarbobenzyloxy, *p*-methoxycarbobenzyloxy, chloroacetyl, bromoacetyl, phenylacetyl, *t*-butoxycarbonyl, trifluoroacetyl, bromoethoxycarbonyl, 9-fluorenylmethoxycarbonyl, dichloroacetyl, 2,2,2-trichloroethoxycarbonyl, bromo-*t*-butoxycarbonyl, phenoxyacetyl; non-acyl protective groups such as *o*-nitrophenylsulfenyl and (C_{1-6} alkyl) silyl, for example, trimethylsilyl and t-butyldimethylsilyl are also of interest.

The following radicals, according to the foregoing definition of acyl, are especially preferred for $R^{3'}$ of structure IIa: formyl, acetyl, propionyl, butyryl, chloroacetyl, methoxyacetyl, aminoacetyl, methoxycarbonyl, ethoxycarbonyl, methylcarbamoyl, ethylcarbamoyl, phenylthiocarbonyl, 3-aminopropionyl, 4-aminobutyryl, N-methylaminoacetyl, N,N-dimethylaminoacetyl, an N,N,N-trimethylammoniumacetyl salt, 3-(N,N-dimethyl)aminopropionyl, a 3-(N,N,N-trimethyl)ammonium propionyl salt, an N,N,N-triethylammoniumacetyl salt, a

pyridiniumacetyl salt, guanylthioacetyl, guanidinoacetyl, 3-guanidinopropionyl, N^3-methylguanidinopropionyl, hydroxyacetyl, 3-hydroxypropionyl, acryloyl, propynoyl, malonyl, phenoxycarbonyl, amidinoacetyl, acetamidinoacetyl, amidinopropionyl, acetamidopropionyl, guanylureidoacetyl, guanylcarbamoyl, carboxymethylaminoacetyl, sufloacetylaminoacetyl, phosphonoacetylaminoacetyl, N^3-dimethylaminoacetamidinopropionyl, ureidocarbonyl, dimethylaminoguanylthioacetyl, a 3-(1-methyl-4-pyridinium)propionyl salt, 3-(5-aminoimidazol-1-yl)propionyl, 3-methyl-1-imidazoliumacetyl salt, 3-sydnonylacetyl, *o*-aminomethylbenzoyl, *o*-aminobenzoyl,

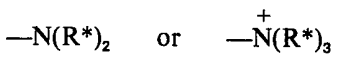


Another class of acyl radicals suitably included in compounds of the present invention are terminally substituted acyls in which the substituent is one of certain basic groups. Such preferred substituted acyls may be represented by the following formula:

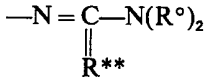


and these radicals and the corresponding radicals in which the

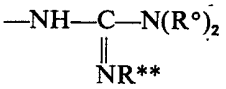
group is omitted are also preferred values of R^3. In the formula q is 0 or 1; each of m and n, independently of the other, is 0, 1, 2, 3, 4 or 5; A is O, —NR°— (where R° is hydrogen or C_{1-6} alkyl) or S, and Y is an amino or substituted amino radical of formula:



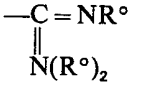
an amidino or substituted amidino radical of formula:



a guanidino or substituted guanidino radical of formula:

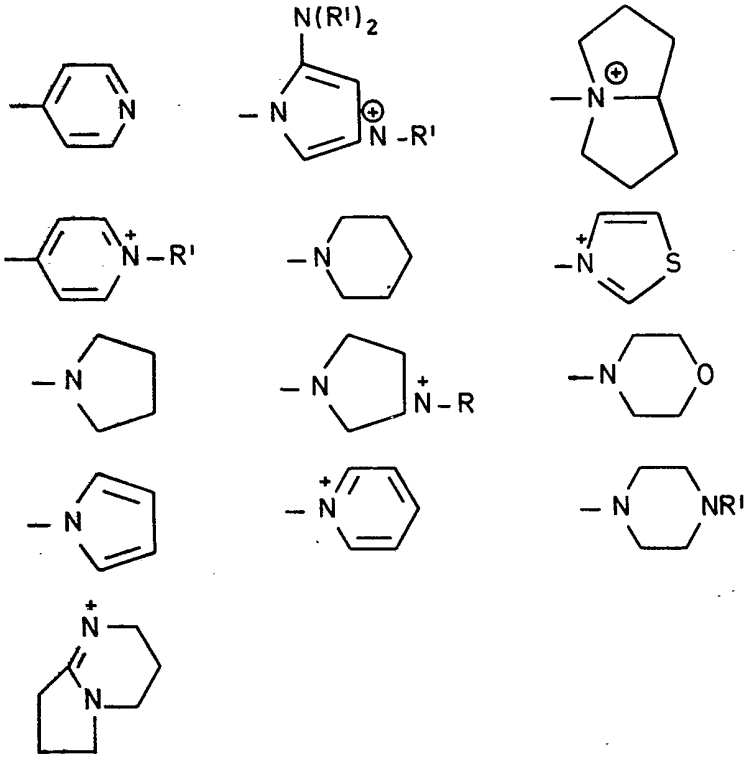


or a guanyl or substituted guanyl radical of formula:

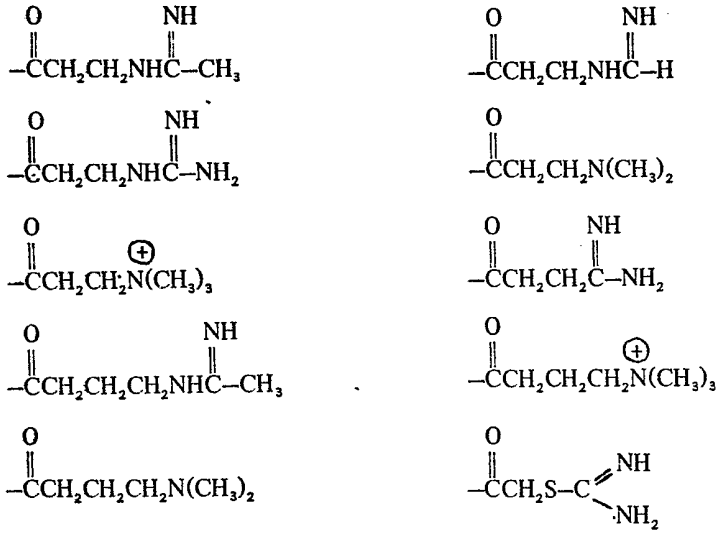


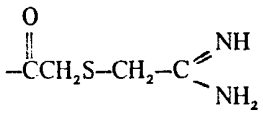
where each R°, independently of the other, is hydrogen; $N(R°)_2$ (where R° is hydrogen or C_{1-6} alkyl); C_{1-6} alkyl, C_{1-6} alkoxyl; (C_{1-6} alkoxy)-(C_{2-6} alkyl), C_{3-6} cycloalkyl or cycloalkyl-(C_{1-3}) or the two R groups are joined to form, together with the N atom to which they are attached, a ring having 3 to 6 atoms; R* is a radical as defined for R except that if cycloalkylalkyl, it must be (C_{3-6} cycloalkyl)-C_{1-3} alkyl; and R** is a radical as defined for R or a (C_{1-6} alkoxy)methyl radical; or Y is a monocyclic or bicyclic heterocyclic aromatic or non-aromatic radical having 4 to 10 nuclear atoms and in which the hetero atom or atoms are nitrogen and optionally oxygen or sulfur.

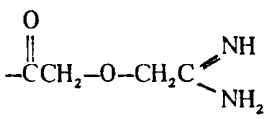
Such heterocycles are representatively illustrated by the following list of radicals (R′ is H or C_{1-6} alkyl):



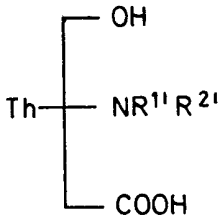
The following specific carboxylic acyl radicals are additionally representative:





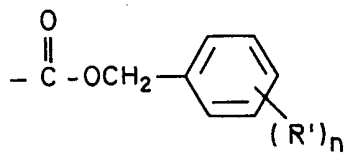


The above-described starting materials are conveniently prepared from an N-protected thienamycin (or position isomer) (1), such as an N-acylated thienamycin (1).

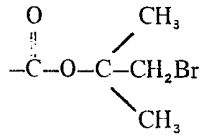


I

where each of $R^{1'}$ and $R^{2'}$ is hydrogen or an acyl radical as above-defined. Preferably $R^{1'}$ is hydrogen and $R^{2'}$ is an easily removable blocking group such as carbobenzyloxy, ring-substituted carbobenzyloxy such as *o*- and *p*-nitrocarbobenzyloxy, *p*-methoxycarbobenzyloxy, chloroacetyl, bromoacetyl, phenylacetyl, *t*-butoxycarbonyl, trifluoroacetyl, bromoethoxycarbonyl, 9-fluoroenylmethoxycarbonyl, dichloroacetyl, *o*-nitrophenylsulfenyl, 2,2,2-trichloroethoxycarbonyl, bromo-*t*-butoxycarbonyl or phenoxyacetyl; non-acyl protective groups such as tri(C_{1-6} alkyl)silyl, for example, trimethylsilyl and *t*-butyldimethylsilyl, are also of interest. The preferred N-blocking groups are (a) substituted and unsubstituted carbobenzyloxy radicals of formula:



where *n* is 0, 1 or 2 and R' is C_{1-6} alkoxy or nitro; and (b) bromo-*t*-butoxycarbonyl, i.e.



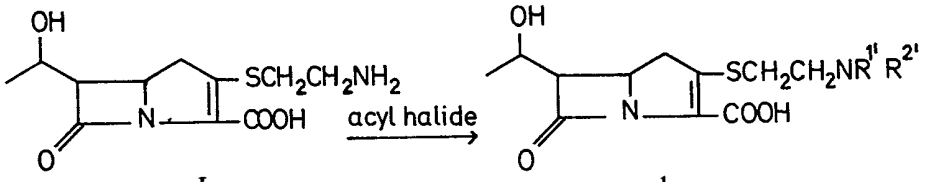
The ultimate N-deblocking procedure for the preparation of Ia, Ic or Ie is accomplished by any of a variety of well known procedures which include hydrolysis and hydrogenation; hydrogenation is suitably carried out in a solvent such as a C_{1-6} alkanol in the presence of a hydrogenation catalyst such as palladium, platinum or oxides thereof.

The N-acylated intermediate compound [1, (or Ia) above] is prepared by treating thienamycin (I) or a position isomer thereof with an acylating agent, for example, an acyl halide or acyl anhydride such as an aliphatic, aromatic, heterocyclic, araliphatic or heterocyclic aliphatic carboxylic acid halide or anhydride. Other acylating agents may also be used, for example, mixed carboxylic acid anhydrides and particularly C_{1-6} alkyl esters of mixed carboxylic-carbonic anhydrides; also, carboxylic acids in the presence of a carbodiimide such as 1,3-dicyclohexylcarbodiimide, and an activated ester of a carboxylic acid such as the *p*-nitrophenyl ester.

Such N-acetylated starting materials are fully described in the specification of our copending Application No. 48236/76 (Serial No. 1,570,986).

The acylation reaction may be conducted at a temperature in the range of from –20° to 100°C., but is preferably conducted at a temperature in the range of from –9°C. to 25°C. Any solvent in which the reactants are soluble and substantially inert may be used, for example polar solvents such as water, alcohols

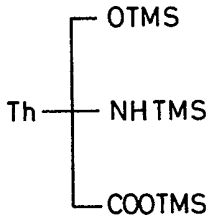
and polar organic solvents in general such as dimethylformamide (DMF), hexamethyl, phosphoramide (HMPA), acetone, dioxane tetrahydrofuran (THF), acetonitrile, heterocyclic amines such as pyridine, ethylacetate, aqueous mixtures of the above, and halogenated solvents such as methylene chloride and chloroform. The reaction is conducted for a period of time of from about five minutes to a maximum of three hours, but in general, a reaction time of 0.5 to one hour is sufficient. The following equation illustrates this process using a carboxylic acid halide; however it is to be understood that by substituting a carboxylic acid anhydride or other functionally equivalent acylating agent similar products may be obtained.



I $\underset{\sim}{1}$

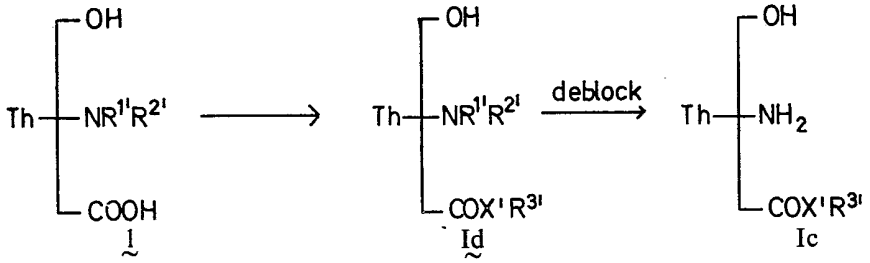
Generally when the above-described acylating reaction uses an acid halide (suitable halides are chlorides, iodides, and bromides) or anhydride the reaction is conducted in water or an aqueous mixture of a polar organic solvent such as acetone, dioxane, THF, DMF or acetonitrile in the presence of a suitable acceptor base such as $NaHCO_3$, MgO, NaOH or K_2HPO_4.

In carrying out the reactions described herein, it is generally not necessary to protect the 2-carboxy group or the 1'-hydroxy group; however, in cases where the acylating reagent is exceedingly water-sensitive it is sometimes advantageous to perform the acylation in a non aqueous solvent system. Triorganosilyl (or organo tin) compounds of thienamycin or its position isomers, for example *tris*-trimethylsilyl thienamycin $Th(TMS)_3$:



react rapidly. Such derivatives, which are readily soluble in organic solvents, are conveniently prepared by treating thienamycin with an excess of hexamethyldisilazane and a stoichiometric amount of trimethylchlorosilane at 25°C., with vigorous stirring under a N_2 atmosphere. The resulting NH_4Cl is removed by centrifugation and the solvent is removed by evaporation to provide the desired silyl derivative.

The intermediate starting materials Ic are prepared according to the following scheme; however, it should be noted that direct esterification, without protection of the amino group, is also possible.



$\underset{\sim}{1}$ Id Ic

where all symbols are as previously defined.

In general, the transformation ($\underset{\sim}{1}$→Ic) is accomplished by conventional procedures. Such procedures include:

(1) Reaction of $\underset{\sim}{1}$ (or I) with a diazoalkane such as diazomethane, phenyl-

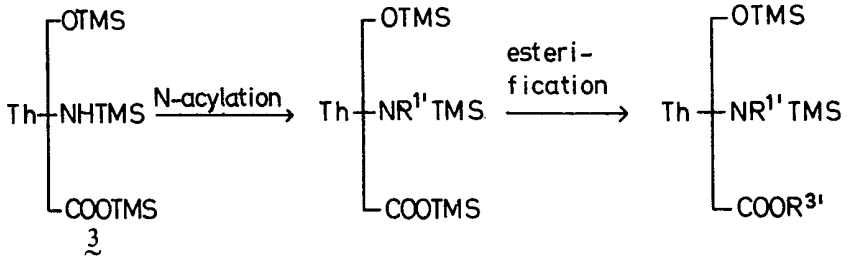
diazomethane or diphenyldiazomethane, in a solvent such as dioxane, ethylacetate or acetonitrile at a temperature of from 0°C to reflux for from a few minutes to 2 hours.

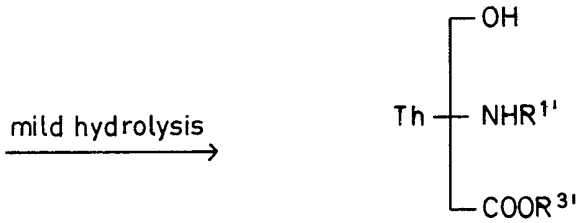
(2) Reaction of an alkali metal salt of 1 with an activated alkyl halide such as methyl iodide, benzyl bromide, or m-phenoxybenzyl bromide, *p-t*-butylbenzyl bromide or pivaloyloxymethyl chloride. Suitable reaction conditions include solvents such as hexamethylphosphoramide at a temperature of from 0°C. to 60°C. for a few minutes to 4 hours.

(3) Reaction of 1 with an alcohol such as methanol, ethanol or benzyl alcohol. This reaction may be conducted in the presence of a carbodiimide condensing agent such as dicyclohexylcarbodiimide. Suitable solvent, at a temperature of from 0°C. to reflux for from 15 minutes to 18 hours, include $CHCl_3$, CH_3Cl and CH_2Cl_2.

(4) Reaction of an N-acylated acid anhydride of 1 prepared by reacting the free acid 1 with an acid chloride such as ethyl chloroformate or benzyl chloroformate, with an alcohol such as those listed in (3) under the same conditions of reaction as given above for (3). The anhydride is prepared by reacting 1 and the acid chloride in a solvent such as tetrahydrofuran (THF) or CH_2Cl_2 at a temperature of from 25°C., to reflux for from 15 minutes to 10 hours.

(5) Reaction of labile esters of 1 such as the trimethylsilyl ester or dimethyl-t-butylsilyl ester with $R^{3'}X°$ wherein X° is halogen such as bromine or chlorine and $R^{3'}$ is as already defined, in a solvent such as THF or CH_2Cl_2 at a temperature of from 0°C. to reflux for from 15 minutes to 16 hours. For example according to the following scheme:



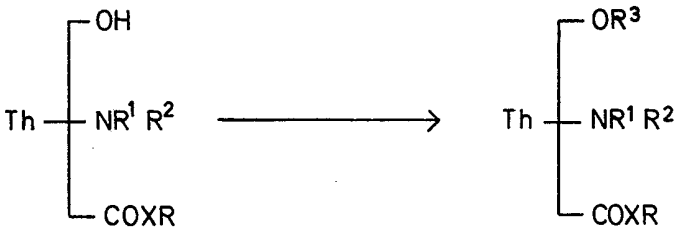


where TMS is triorganosilyl such as trimethylsilyl and all other symbols are as previously defined.

The amides of the present invention are most conveniently prepared by reacting the acid anhydride (Ic, X' = O, $R^{3'}$ = acyl) with ammonia or with the amine of choice, e.g., the alkyl-, dialkyl-, aralkyl- or heterocyclic amines listed above.

The above-recited schemes of esterification are well known in the related bicyclic β-lactam antibiotic art and indeed in organic synthesis generally and there is no undue criticality of reaction parameters in the preparation of the N-acylated and carboxyl derivatives Ic useful as starting materials in the practice of the present invention.

Starting materials Ia and Ie are conveniently prepared by any of a variety of well-known esterification or etherification reactions upon the secondary alcoholic group of Id. Such procedures include:



Id Ie

(1) For the preparation of ethers of the present invention, the acid catalysed reaction of Id with a diazoalkane such as diazomethane, phenyldiazomethane or diphenyldiazomethane in an inert solvent such as dioxane, tetrahydrofuran (THF), a halohydrocarbon such as CH_2Cl_2, or ethyl acetate in the presence of a catalytic amount of a strong acid or Lewis acid such as toluenesulfonic acid, trifluoroacetic acid, fluoboric acid or boron trifluoride at a temperature of from –78°C to 25°C for from a few minutes to 2 hours.

(2) For the preparation of ethers of the present invention, the reaction of Id with an alkylating agent such as active halides, for example methyliodide, benzylbromide or *m*-phenoxybenzylbromide or alkylsulphates such as dimethylsulphate, diethylsulphate and methylfluorosulphonate in the presence of a strong base capable of forming the alcoholate anion of Ib. Suitable bases include alkali and alkaline earth metal oxides and hydroxides, alkali metal alkoxides such as potassium tertiary-butoxide, tertiary amines such as triethylamine, alkali metal alkyls and aryls such as phenyllithium, and alkali metal amides such as sodium amide. Suitable solvents include inert anhydrous solvents such as *t*-butanol, dimethylformamide (DMF), THF, hexamethylphosphoramide (HMPA) and dioxane at a temperature of from –78°C. to 25°C., for from a few minutes to 4 hours.

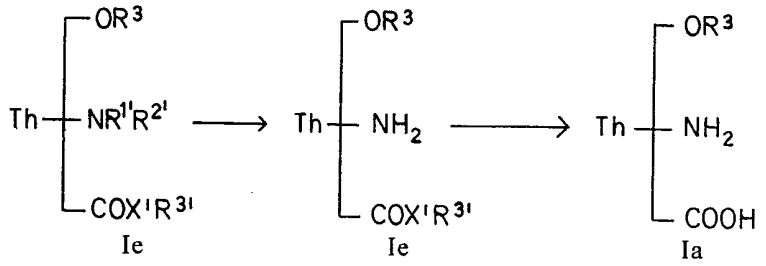
(3) For the preparation of esters, the reaction of Id with any of the above-listed acyl radicals in their acid form. This reaction may be conducted in the presence of a carbodiimide condensing agent such as dicyclohexylcarbodiimide. Suitable solvents include any inert solvent such as $CHCl_3$, CH_2Cl_2, DMF, HMPA, acetone and dioxane at a temperature of from 0°C. to 60°C. for from 15 minutes to 12 hours.

(4) For the preparation of esters of the present invention, the reaction of Id with an acyl halide or an acid anhydride in which the acyl residue is described above. Generally, when the above-described acylating reaction uses an acid halide (suitable halides are chloride, iodide or bromide) or acid anhydride the reaction is conducted in an anhydrous organic solvent such as acetone, dioxane, methylenechloride, chloroform or DMF in the presence of a suitable acceptor base such as $NaHCO_3$, MgO, triethylamine or pyridine at a temperature of from 0°C. to 40°C. for from 1 to 4 hours.

Suitable acyl halides and anhydrides include acetic anhydride, bromacetic anhydride, propionic anhydride, benzoyl chloride, phenylacetyl chloride, azidoacetyl chloride, 2-thienylacetyl chloride, 2-, 3- and 4-nicotinyl chloride, *p*-nitrobenzoyl chloride, 2,6-dimethoxybenzoyl chloride, 4-guanidinophenylacetyl chloride, methanesulfonyl chloride, dibenzylphosphorochloridate, dimethylthiophosphorochloridate, 2-furoyl ethyl carbonic anhydride, methylchloroformate and *bis*(p-nitrobenzyl)phosphorochloridate.

(5) For the preparation of esters of the present invention, the reaction of Id with a suitably substituted ketone or isocyanate such as ketone, dimethyl ketene, methylisocyanate, methylisothiocyanate or chlorosulfonyl isocyanate. The reaction is conveniently carried out in a suitable solvent, e.g. dioxane, tetrahydrofuran or chloroform, at a temperature of from –70°C. to 60°C. for from 15 minutes to 18 hours.

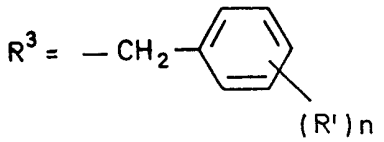
The intermediate compound Ie is then N-deblocked as described above to provide starting materials, Ie ($R^{1'}$ and $R^{2'}$ =H) and Ia. From Ie, Ia is prepared by deblocking the carboxyl group:



Starting material Ia is conveniently and preferably obtained when X′ is oxygen and $R^{3'}$ is a readily removable carboxyl protecting or carbonyl-blocking group (see above). Starting material Ia is prepared by deblocking according to any of a variety of well known procedures which include hydrolysis and hydrogenation. When the preferred carboxyl-blocking groups are used (below), the preferred deblocking procedure is hydrogenation, in which the intermediate compound (Ie), in a solvent such as a C_{1-6} alkanol, is hydrogenated in the presence of a hydrogenation catalyst such as palladium, platinum or oxides thereof.

In this connection, it is noted that suitable "blocking groups" $R^{3'}$ include the sub-generic groups defined above as aralkyl, haloalkyl, alkanoyloxyalkyl, alkoxyalkyl, alkenyl, substituted alkyl, or aralkoxyalkyl, and also including alkylsilyl, where alkyl has 1—10 carbon atoms. For example, suitable "blocking groups" $R^{3'}$ include benzyl, phenacyl, p-nitrobenzyl, methoxymethyl, trichloroethyl, trimethylsilyl, tributyltin, *p*-methoxybenzyl and benzhydryl. These blocking groups are preferred since they are generally recognized easily-removable blocking groups in the cephalosporin and penicillin art.

The preferred carboxyl blocking groups, are benzyl and substituted benzyl of formula:



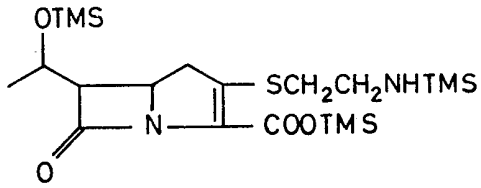
wherein n is 0, 1 or 2 and R′ is C_{1-6} alkoxyl or nitro.

In the alternative it should be noted that the compounds of the present invention, IIa, may be arrived at by operating upon the substituted N-methylene thienamycin derivatives or other position isomers, II, to achieve derivatization by establishment of R^3 and/or —$COX'C^{3'}$. Such procedure is exactly as described above except that compound II replaces the above-described starting materials, such as Ia, Ic and Ie, and, of course, there is no need to N-deblock.

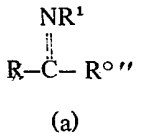
Preparation

The preparation of the compounds of the present invention is conveniently described according to the above-defined four classes, or embodiments, namely: (1) Amidines; (2) Guanidines; (3) Substituted Pseudoureas; and (4) Imido Esters and Imido Thioesters.

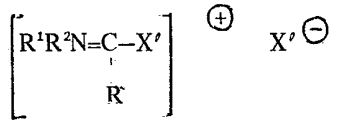
(1) *Amidines.* In general, the compounds of Class (1) may conveniently be prepared by reacting thienamycin (I) or a derivative thereof (Ia, Ic or Ie, when $R^{1'} = R^{2'} = H$) or a suitably protected form of thienamycin or its position isomers such as its silylated derivative (*I*) with an imido ester (a) or a substituted imido halide (b):



1 TMS = trimethylsilyl



(a)



(b)

where R^1, R^2, and R as defined above; X′ is halogen such as chlorine; and $-\overset{O}{\overset{\|}{C}}-R''$ is a leaving group where R″ may be C_{1-6} alkyl such as methyl or ethyl and X° is O or S. Alternatively, the compounds of Class 1 may be prepared by reacting a compound of Class 4 with NH_3 or a primary or secondary amino compound (c) calculated to provide the desired species of Class 1. Reagents (a), (b) and (c) are representatively enumerated below.

Suitable solvents for the preparation of the compounds of Class 1 according to the above reaction schemes, depending upon the identity of the thienamycin substrate and reagent, include water, dioxane, tetrahydrofuran (THF), dimethylformamide (DMF), chloroform, acetone, acetonitrile or mixtures thereof. The reaction may be conducted at a temperature of from 0° to 25°C for from 1 to 6 hours. There is no criticality as to the precise identity of the reaction solvent nor the variables of reaction within the limits described above, provided only that the reaction solvent is inert or substantially inert to the intended course of reaction. Suitable reagents representatively include:

(a) *Imido Esters:*

X° = O or S

Examples are methyl formimidate, ethyl formimidate, methyl acetimidate, ethyl acetimidate, methyl benzimidate, ethyl 4-pyridyl carboximidate, methyl phenylacetimidate, methyl 3-thienylcarboximidate, methyl azidoacetimidate, methyl chloroacetimidate, methyl cyclohexylcarboximidate, methyl 2-furylcarboximidate, methyl *p*-nitrobenzimidate, methyl 2,4-dimethoxybenzimidate, ethyl N = methyl formimidate, methyl N-methyl formimidate and methyl N-isopropyl formimidate.

Such imido ester reagents (a) are conveniently prepared by any of a variety of known procedures, such as

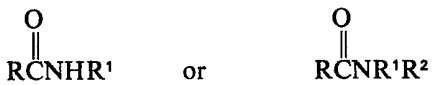
(1) The reaction of a nitrile, RCN, with a C_{1-6} alkanol in the presence of HCl according to the well-known Pinner synthesis.

(2) The reaction of a nitrile, RCN, with a C_{1-6} alkanol in the presence of a base. Typically, the reaction is conducted at 0—40°C in the presence of an excess of the alcohol with a catalytic amount of an alkali metal alkoxide for from 15 minutes to 4 hours.

(3) The reaction of an amide,

with an alkyl chloroformate such as methylchloroformate at 25°C.—45°C. for 1—4 hours.

(4) The reaction of an N-substituted amide,



with an equivalent of an alkylating agent such as triethyloxonium fluoroborate in an inert solvent such as ether or chloroform at 0—23°C for from 10 minutes to 2 hours.

(5) The conversion of a readily available imido ester,

$$\begin{array}{l} RCNR' \\ | \\ OR'' \end{array}$$

(R′ may be hydrogen), to a desired imido ester,

$$\begin{array}{l} RCNR^1 \\ | \\ OR'' \end{array}$$

by reaction of the first-mentioned ester with an alkylamine, $R'NH_2$, in a mixture of water- and an immiscible solvent such as ether or chloroform at 0—23°C. for from 5 minutes to 1 hour.

(b) *Substituted Imido Halides:*

N-(Chloromethylene)piperidinium chloride, chlorodimethylforminium chloride, chlorodiethyl forminium chloride.

Such imido halide reagents (b) are conveniently prepared by any of a variety of known procedures, such as:

1. The reaction of an N,N-disubstituted amide,

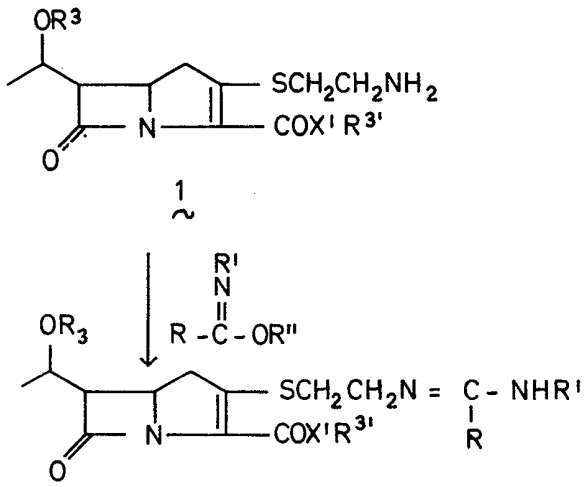
$$\begin{array}{l} O \\ \| \\ RCNR^1R^2 \end{array}$$

with a halogenating agent such as thionyl chloride, phosgene or phosphorus pentachloride in an inert solvent such as chloroform or methylene chloride at 0—40°C for from 1—5 hours.

(c) *Primary and Secondary Amino Compounds:*

Methylamine, ethylamine, 2-aminopyrimidine, dimethylamine, methyl benzylamine, 3-aminomethyl pyridine, 2-aminomethyl thiophene, ethanolamine, dimethylaminoethylamine, N-2-(aminoethyl)pyrrolidine, cyclohexylamine, *n*-heptylamine, isopropylamine, 2-methylallylamine, 3-phenyl-1-propylamine, 2-amino-4-picoline, 2-amino pyridine, 3-amino-4-carbethoxypyrazole, 2-aminothiazole, 5-amino-3-methyl isothiazole, and 3-amino-1,2,4-triazole.

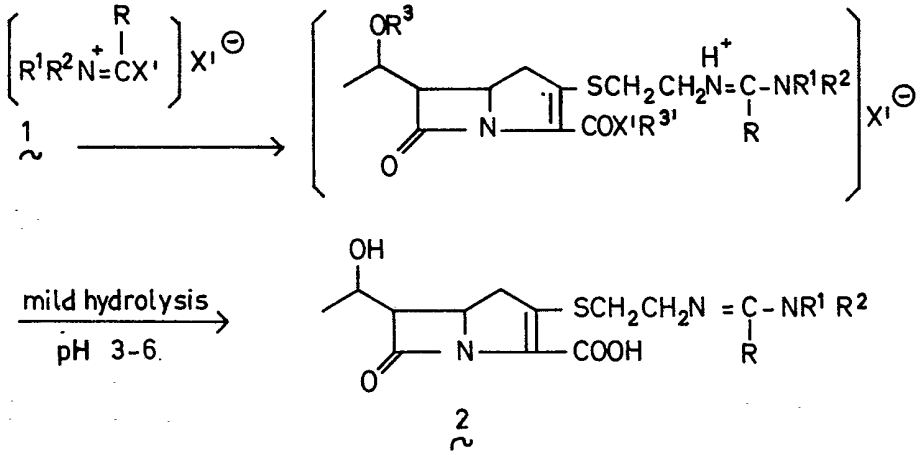
The reaction involving the reagents (a), may be representatively shown by the following diagram:



wherein OR″ is the leaving group of the imido ester reagent and R, R′, $R^{3'}$, R^3 and

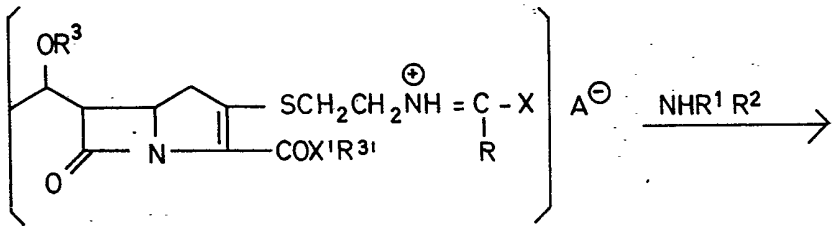
X′ are as defined above. This reaction is particularly suitable for compounds in which R^3 and $R^{3'}$ are hydrogen and X′ is oxygen.

The reaction involving the reagents (b), may representatively be shown by the following diagram;

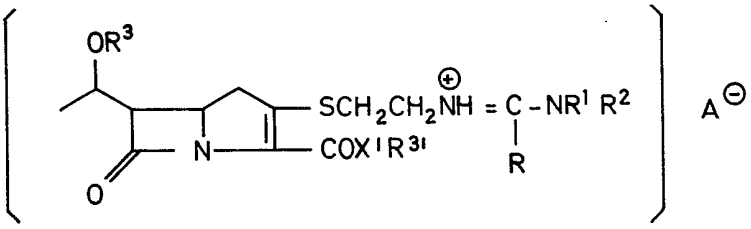


where all symbols are as previously defined. When product 2 is desired, suitable values for R^3 and $R^{3'}$ are trimethylsilyl, and X′ is oxygen.

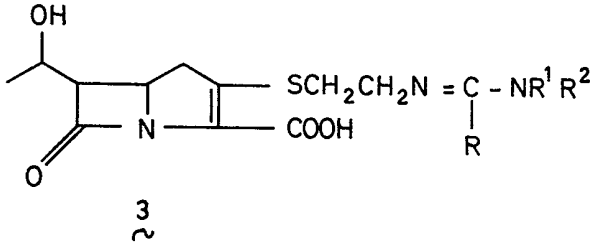
The reaction involving the reagents (c) may representatively be shown by the following diagram:

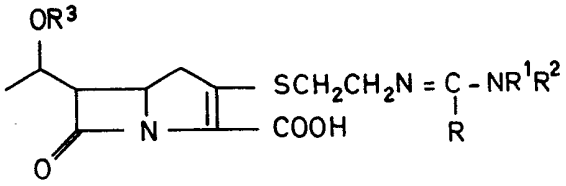


Compound of Class 4.

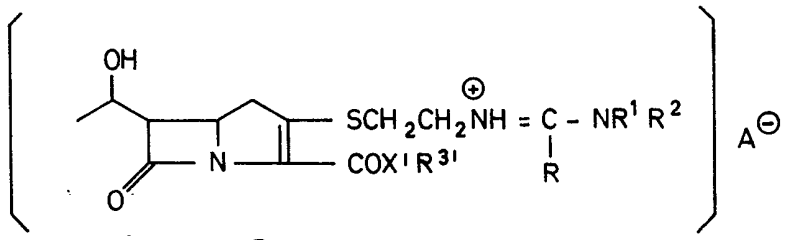


where all symbols are as previously defined and X is —OR or —SR wherein R is preferably C_{1-6} alkyl such as methyl or ethyl. When R^3 and $R^{3'}$ are readily removable blocking or protecting groups they may independently be removed by well known procedures to provide compounds 3, 4 and 5.





4



5

(2) *Guanidines:*

In general, the compounds of Class 2, may conveniently be prepared by reacting thienamycin or its position isomer or an O— or carboxyl derivative thereof (Ia, Ic or Ie, when $R^{1'} = R^{2'} = H$) with (a) an —OR″ (e.g., O-alkyl, O-aryl) pseudourea or an S-alkyl or S-aryl pseudothiourea; or (b) by reacting a compound of Class 3 (above) with ammonia or an amino compound such as an alkyl, aralkyl or heteroaralkyl amine.

Suitable solvents for such reactions include water and buffered aqueous polar organic solvent mixtures at pH 7—9 or anhydrous polar organic solvents such as dimethylformamide or hexamethylphosphoramide at a temperature of from 0°C. to 40°C. for from 1 to 24 hours.

Suitable reagents (a) and (b) include:

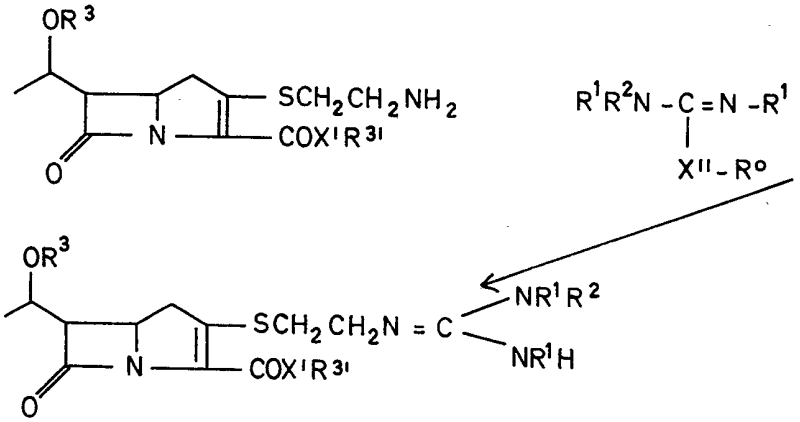
(a) *—OR pseudoureas and —SR pseudothioureas:*

O-Methyl pseudourea, S-Methylpseudothiourea, S-methylpseudothionitrourea, O-2,4-dichlorophenyl pseudourea, S-p-nitrophenyl pseudothiourea and O—N,N-trimethylpseudourea.

(b) *Amino reagents:*

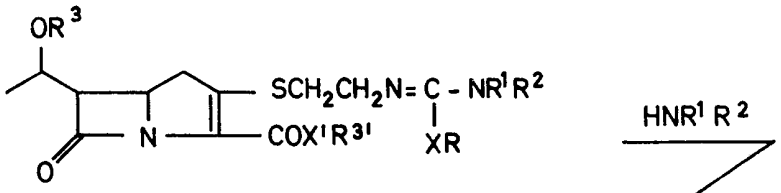
These reagents are the same as those given for the preparation of Class I (c) above.

The reaction involving the reagents (a) may representatively be shown by the following diagram:

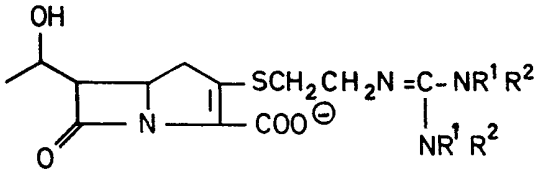


where R^3, X′, $R^{3'}$, R^1 and R^2 are as defined above; X″ is O or S and X″R° is a leaving group: R° is preferably C_{1-6} alkyl or aryl.

The reaction involving the reagents (b), may representatively be shown by the following diagram:



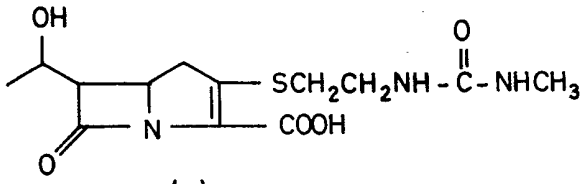
Compound of Class 3.



where all symbols are as previously defined.

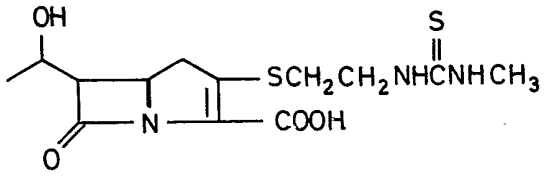
(3) *Substituted Pseudoureas:*

In general, the compounds of Class 3 may conveniently be prepared by reacting a carbamoyl or thiocarbamoyl N-substituted compound (a), for example:



(a)

or

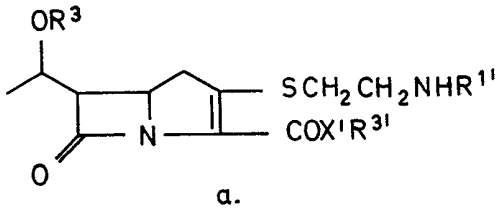


(a)

with an alkylating agent (b) such as an active alkyl or aralkyl halide or sulfate ester.

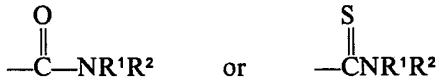
Suitable solvents for the above reaction include C_{1-6} alkanols, dioxane and acetonitrile at a temperature of from 20°C. to 60°C. for from 1 to 4 hours.

Suitable reagents (a) for the above reaction scheme include N-acyl thienamycins:



a.

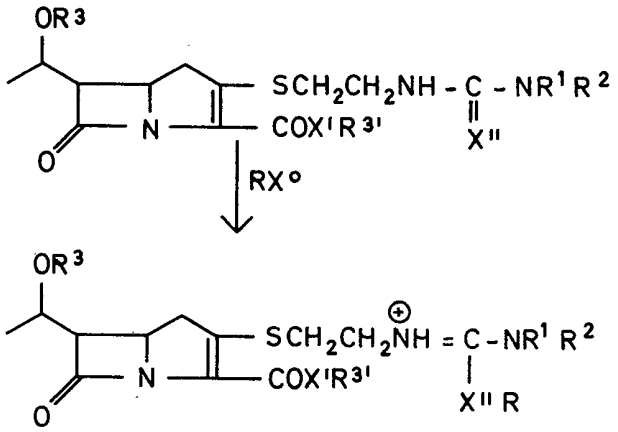
where R^3, X' and $R^{3'}$ are as defined above and $R^{1'}$ is acyl as defined above and is preferably



where R^1 and R^2 are as defined above, such as carbamoyl, methylcarbamoyl, ethylcarbamoyl, phenylcarbamoyl, *p*-bromophenylcarbamoyl, phenylthiocarbamoyl, methylthiocarbamoyl or dimethylcarbamoyl.

Suitable alkylating agents (b) include methyl iodide, benzyl bromide, dimethyl sulfate, diethyl sulfate, alkyl bromide, 2-thienyl bromide, methylallyl bromide, *p*-nitrobenzyl bromide and methyl chloromethyl ether.

The reaction involving the above reagents (a) and (b) may representatively be shown by the following diagram:



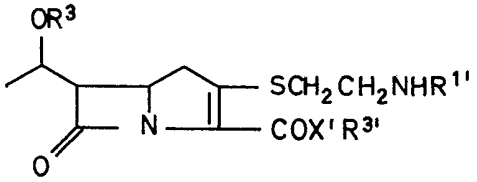
where X'' is O or S; RX° is the alkylating agent; and R^1, R^2, R^3, X', $R^{3'}$ and R are as previously defined.

(4) *Imido Esters and Imido Thio Esters:*

In general, the compounds of Class 4 may conveniently be prepared by reacting a suitable protected N-acyl or N-alkoxy carbonyl derivative, or a thio analogue thereof, of thienamycin (a) with an alkylating agent (b).

Suitable solvents for the above reaction include methylene chloride, tetrahydrofuran, dioxane and chloroform, at a temperature of from –78°C. to 25°C. for from 5 minutes to 3 hours.

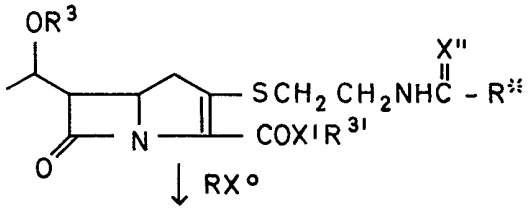
Suitable N-acyl thienamycin starting materials (a) include:

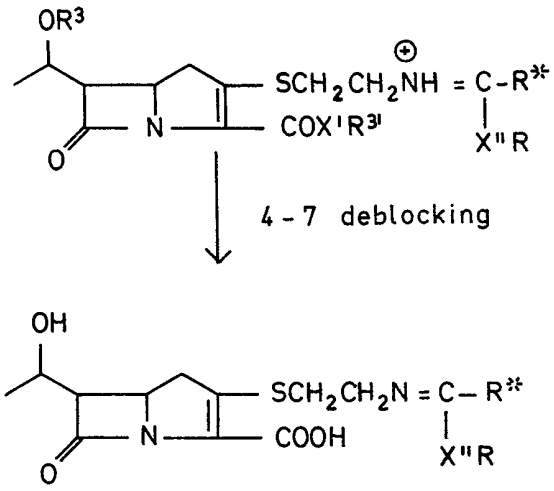


where $R^{1'}$ is acyl such as formyl, benzoyl, thiobenzoyl or thioacetyl; R^3, $R^{3'}$ and X' are as defined.

Suitable alkylating agents (b) include: triethyl oxonium, fluoroborate, methyl fluorosulphonate and trimethyloxonium hexafluorophosphate.

The reaction involving the above reagents (a and b) may representatively be shown by the following diagram:





where X'' = O, or S; R* is H, R, OR or SR and R^3, X', $R^{3'}$ and R are as previously defined. When the deblocked species is desired suitable values for X' and R^3, $R^{3'}$ are oxygen and trimethylsilyl; in which case, deblocking is conveniently achieved by mild aqueous hydrolysis of pH 3—6. It is to be noted that the above reaction mixture may be used directly in reaction with the amine (c) as described in the preparation of the amidines of Class 1, above.

The products of this invention (II and IIa) form a wide variety of pharmacologically acceptable salts such as acid addition salts, e.g., with hydrochloric, hydrobromic, sulfuric, nitric, toluene-*p*-sulphonic and methane sulphonic acids. The salts of this invention are pharmacologically acceptable non-toxic derivatives which can be used as the active ingredient in suitable unit-dosage pharmaceutical forms. Also, they may be combined with other drugs to provide compositions having a broad spectrum of activity.

Compounds of the present invention have been found to be valuable antibiotics active against various gram-positive and gram-negative bacteria and, accordingly, find utility in human and veterinary medicine. Such compounds can therefore be used as antibacterial drugs for treating infections caused by gram-positive or gram-negative bacteria, for example, *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Serratia, Salmonella typhosa, Pseudomonas* and *Bacterium proteus.* The antibacterials of the invention may further be utilized as additives to animal feeding stuffs, for preserving foodstuffs and as disinfectants. For example, they may be used in aqueous compositions in concentrations ranging from 0.1 to 100 parts of antibiotic per million parts of solution in order to destroy and inhibit the growth of harmful bacteria on medical and dental equipment and as bactericides in industrial applications, for example, in water-based paints and in the white water of paper mills to inhibit the growth of harmful bacteria.

The products of this invention may be used alone or in combination as an active ingredient in any one of a variety of pharmaceutical preparations. These antibiotics and their corresponding salts may be used in capsule form or as tablets, powders or liquid solutions or as suspensions or elixirs. They may be administered orally, intravenously or intramuscularly.

The compositions are preferably presented in a form suitable for absorption by the gastro-intestinal tract. 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 polyvinylpyrrolidone; fillers for example, lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; lubricants, for example, magnesium stearate, talc, polyethylene glycol, silica; disintegrants, for example, potato starch or acceptable wetting agents such as sodium lauryl sulphate. The tables may be coated according to well known methods. Oral liquid preparations may be in the form of aqueous or oily suspension, solution, emulsions, syrups or elixirs, or may be presented as a dry product, for reconstitution with water or other suitable vehicles before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxy-ethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated

edible oils, for example almond oil, fractionated coconut oil, oily esters, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoates or sorbic acid. Suppositories will contain conventional suppository bases, e.g. cocoa butter or other glycerides.

Compositions for injection may be presented in unit dose form in ampoules, or in multidose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compositions may also be prepared in suitable forms for absorption through the mucous membranes of the nose and throat or bronchial tissues and may conveniently take the form of powder or liquid sprays or inhalants, lozenges, throat paints, etc. For medication of the eyes or ears, the preparations may be presented as individual capsules, in liquid or semi-solid form, or as drops etc. Topical applications may be formulated in hydrophobic or hydrophilic bases as ointments, creams, lotions, paints or powders.

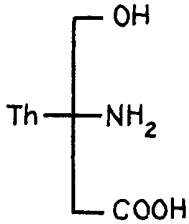
Also, in addition to a carrier, the compositions may include other ingredients such as stabilizers, binders, antioxidants, preservatives, lubricators, suspending agents, viscosity agents or flavoring agents. In addition, there may also be included in the composition other active ingredients to provide a broader spectrum of antibiotic activity.

For veterinary medicine the composition may, for example, be formulated as an intramammary preparation in either long or quick-release bases.

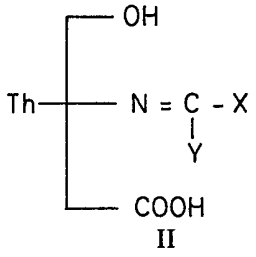
The dosage to be administered depends to a large extent upon the condition of the subject being treated and the weight of the host, the route and frequency of administration, the parenteral route being preferred for generalized infections and the oral route for intestinal infections. In general, a daily oral dosage consists of from 2 to 600 mg. of active ingredient per kg. of body weight of the subject in one or more applications per day. A preferred daily dosage for adult humans lies in the range of from about 15 to 150 mg. of active ingredient per kg. of body weight.

The compositions may be administered in several unit dosage forms, for example, in solid or liquid orally ingestible dosage form. The compositions per unit dosage, whether liquid or solid, may contain from 0.1% to 99% of active material, the preferred range being from 10—60%. The composition will generally contain from 15 mg. to 1500 mg. of the active ingredient; however, in general, a dosage in the range of from 100 mg. to 1000 mg. is preferred. In parenteral administration the unit dosage is usually the pure compound in a slightly acidified sterile aqueous solution or a soluble powder intended for solution.

The following Examples illustrate the present invention. Examples 1, 2, 8, 17, 18, 22 to 27 and 44 to 50 illustrate the preparation of starting materials and not of compounds in accordance with the present invention. In the Examples, the thienamycin nucleus (I, above) is represented by the following symbol:

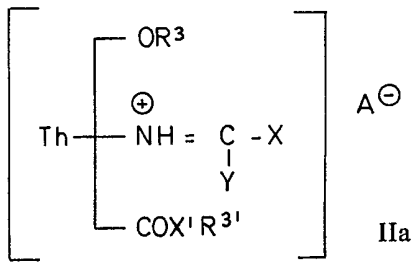


where the secondary alcoholic group, the amino group and the carboxyl group are illustrated. Thus, compounds of the present invention can conveniently be represented as follows:



II

and

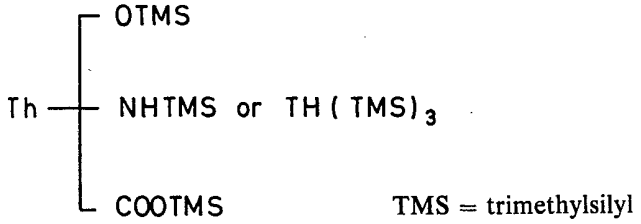


IIa

where X, Y, R^3, X', $R^{3'}$ and A are as previously defined.

In the Examples, the words "Dowex", "Nujol", "Porosil", "Teflon", "Supercel", "Linde", "Celite", "Branson", "Sonifier" and "Difco" are trade marks, proportions of liquid mixtures are on a volume basis, "mmole" means "millimole".

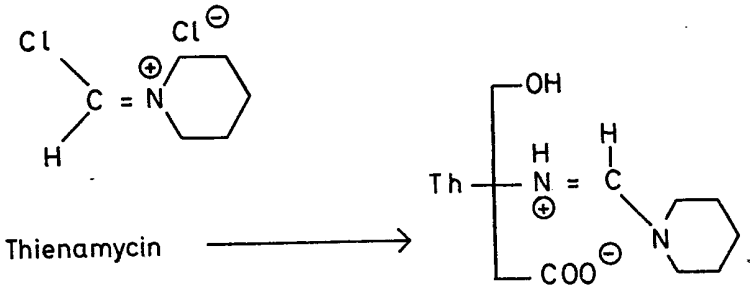
Example 1.



Preparation of Silylated-Thienamycin

Thienamycin (80.0 mg.) is suspended in 40 ml. tetrahydrofuran (THF) under a N_2 atmosphere and is concentrated to 10 ml.; hexamethyldisilazane (1.0 ml.) and trimethylchlorosilane (300 μl) are added. The mixture is reacted for 20 mins. at 25°C. with vigorous stirring. The suspension is then centrifuged to remove ammonium chloride. The supernatant is evaporated to an oil under a nitrogen stream for future reaction.

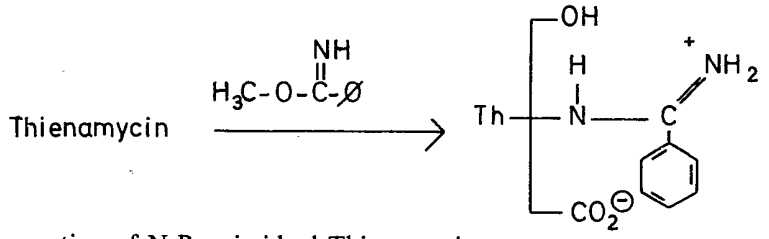
Example 1a.



Preparation of Thienamycin N-Piperidin-1-yl Methylene Derivative

Thienamycin (57 mg., 162 μmol) is silylated according to the procedure previously described. The silylated antibiotic $Th(TMS)_3$ is dissolved in methylene chloride (6 cc) in a septum stoppered flask under positive nitrogen pressure and cooled in a dry ice-acetone bath. To the magnetically stirred solution is added a solution (180 μl) of triethylamine (644 μmol) in methylene chloride. This is followed by the addition of a solution of N-(chloromethylene)piperidinium chloride (67 mg., 405 μmol) in methylene chloride (465 μl). After 1 hour in a dry-ice bath, the reaction solution is rapidly added to a tetrahydrofuran: pH 7, 0.1*N* phosphate buffer (1:1) solution (50 ml.). The mixture is then concentrated under vacuum to 10 ml. to give a homogeneous solution. The solution is washed twice with ethyl acetate (2 x 5 ml.) and ether (2 x 5 ml.) and briefly pumped under vacuum. This aqueous solution is then chromatographed on an XAD—2 resin solution (60 ml. bed). The product is eluted in 10% aqueous tetrahydrofuran (following water elution) to give 12.9 mg. (22%) product (as measured in solution assuming ϵ 8,030 same as Thienamycin. Paper chromatography R_f 0.42 (4:1:5, n-BuOH:EtOH:water).

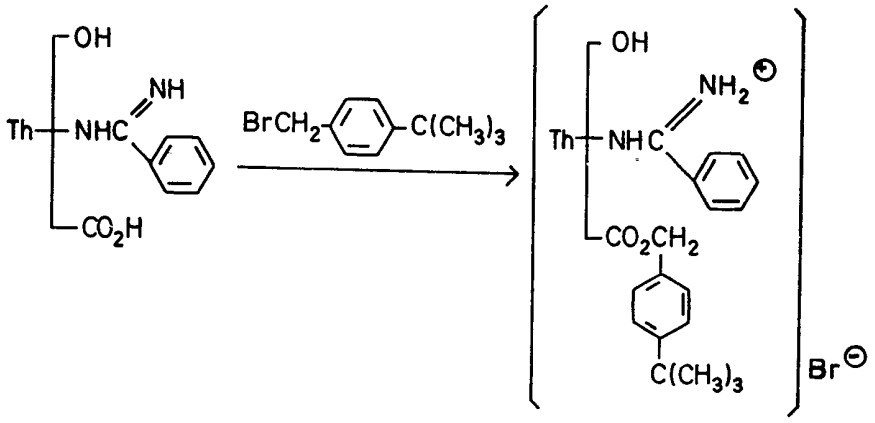
Example 2.



Preparation of N-Benzimidoyl Thienamycin

Thienamycin (59 mg., 212 μmol) is dissolved in a 33% N,N-dimethylformamide pH 7 phosphate buffer (0.05*N*) solution (4.5 ml.) and adjusted to pH 9.5 using 2.5*N* NaOH with an automatic dispensing burette. The solution is magnetically stirred at 25°C. and methylbenzimidate.HCl (340 mg., 1981 μmol) is added at once. After 30 min. the solution is extracted twice with an equal volume of chloroform and adjusted with dilute aqueous phosphoric acid to pH 7.0. The buffered solution is chromatographed on XAD—2 resin (65 ml.). The column is first eluted with water followed by 10% aqueous tetrahydrofuran wich elutes the product. This fraction is concentrated to one-half volume and freeze-dried to give 50 mg. of the product. Electrophoretic mobility (50 V/cm., 20 min., pH 7 0.1N phosphate buffer) is 1.5 cm. towards the anode. UV $\lambda_{max} = 300$ nm (ε 6,960) pH 7 0.1*N* phosphate buffer.

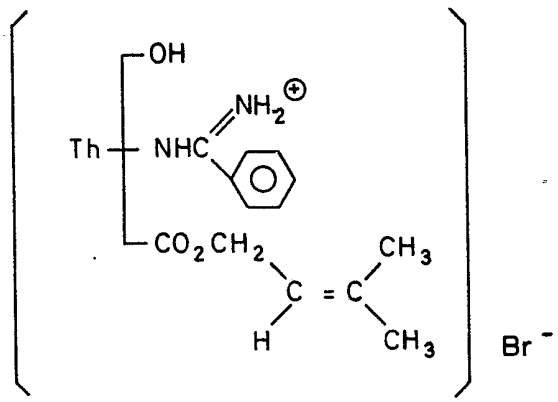
Example 3.



Preparation of N-Benzimidoyl Thienamycin, *p-tert*-Butylbenzyl Ester

Benzimidoyl Thienamycin (3.2 mg.) is suspended in hexamethylphosphoramide (75 μl.) containing *p-tert*-butylbenzyl bromide (3.8 μl) and magnetically stirred at 22°C. After 45 minutes a solution results which is stirred for an additional hour. The product is then precipitated out of solution with ether and the crude product chromatographed on a 250-μ-thick silica gel plate developed in 7:3 chloroform:ethanol. The band at R_f 0.6 is removed and eluted with ethanol to give N-benzimidoyl thienamycin *p-tert*-butylbenzyl ester hydrobromide. Mass Spec. m/e 521 (M^+), 487, 444, 418, 341, 323, 297, 226, 147.

Example 4.

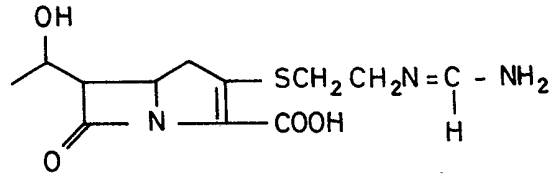


Preparation of N-Benzimidoyl Thienamycin 3-Methyl-2-Buten-1-yl Ester

Benzimidoyl thienamycin (5.9 mg.) is dissolved in hexamethylphosphoramide (100 μl.) containing 1-bromo-3-methyl-2-butene (4.8 μl.) and triethylamine (0.5 μl.) and magnetically stirred at 22°C. After 1 hour the crude reaction is chromatographed on a 250-μ-thick silica gel plate developed in 8:2, chloroform:ethanol. The band of R_f 0.1—R_f 0.3 is removed and eluted with ethanol. Benzimidoyl thienamycin 3-methyl-2-buten-1-yl ester hydrobromide is isolated as a solid after precipitation from an ethanol-chloroform solution with hexane.

Example 5.

Preparation of N-Formimidoyl-thienamycin

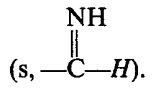


Thienamycin (517 mg) is dissolved in pH 7 0.1*N* phosphate buffer (25 ml.) and cooled in an ice bath with magnetic stirring. The solution is adjusted to pH 8.5 using 2.5*N* sodium hydroxide solution dispensed from an automatic burette. While maintaining a pH of 8.5, methyl formimidate hydrochloride (711 mg.) is added portionwise over 2—3 minutes. After an additional 10 minutes, the pH of the solution is brought to 7.0 using 2.5*N* hydrochloric acid. The solution is chromatographed on a column of XAD—2 resin (150 cc) which is eluted with water. The N-formimidoyl thienamycin derivative elutes in 1.5—2.0 column volumes (200—300 cc) and is lyophilized to a white solid (217 mg.).

UV (pH 7 0.1N phosphate buffer) λ_{max} 297 nm (8,590).

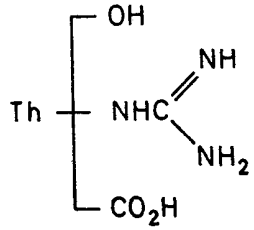
ir (Nujol mull) 1767 cm^{-1} (β-lactam)

nmr (D_2O) δ 1.37 (d, J = 6Hz, CH_3—CH), 3.0—3.75 (m, —CH_2—),4.2—4.8 (m, C_{5H}, C_{6H}, C_{7H}), 7.86



(s, —C—*H*).

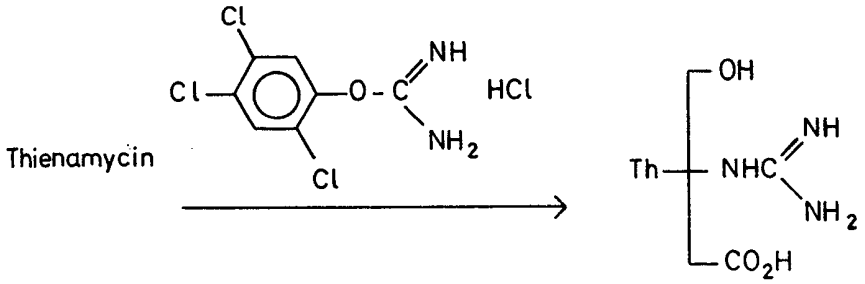
Example 6.



Preparation of N-Guanyl thienamycin

Thienamycin (8.9 mg.) is dissolved in pH 7 0.1*N* phosphate buffer (0.7 ml.) and N,N-dimethylformamide (0.3 ml.) and the solution brought to pH 9.5 by the addition of 2.5N sodium hydroxide solution. To the magnetically solution is added O-methylisourea· hydrogen sulfate (43 mg.) causing a slight drop in pH. Additional sodium hydroxide solution is added to bring the pH back to 9.5 and the solution is stirred 30 minutes at 23°C. The solution is then acidified to pH 7.0. A sample of the solution containing a mixture of thienamycin and N-guanyl thienamycin shows two bioactive zones after electrophoresis (50 V/cm., 20 minutes, 0.05N pH 7 phosphate buffer) and bioautography on *S. aureus* plates.

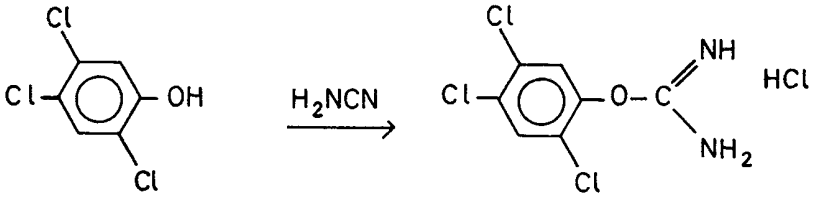
Example 7.



Preparation of N-Guanyl thienamycin

Thienamycin (11 mg.) is dissolved in pH 7 0.1*N* phosphate buffer (1 ml.) and adjusted to pH 8.3 with 0.1*N* sodium hydroxide by means of an automatic dispensing burette. To the magnetically stirred solution is added O-2,4,5-trichlorophenylisoureahydrochloride (76 mg.) portionwise to allow the automatic burette to maintain a nearly constant pH. The reaction is run for 4 hours to 22°C. and is then readjusted to pH 7.0 by the addition of dilute acid. A sample of this solution containing thienamycin and N-guanyl thienamycin is electrophoresed (50 V/cm., 25 minutes, pH 7 0.1N phosphate buffer) and shows a positive Sakaguchi spray zone at 2.0 cm. towards the anode and a positive ninhydrin spray zone at 1.5 cm. in the same direction.

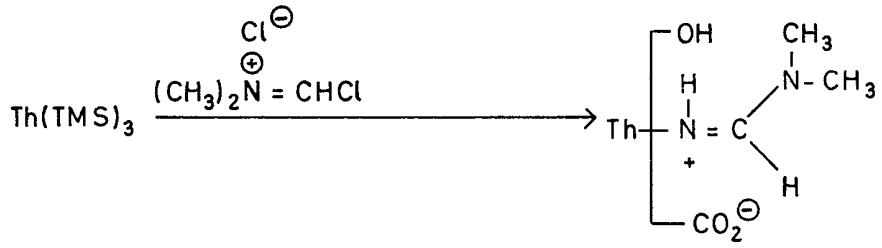
Example 8.



Preparation off O-2,4,5-Trichlorophenylisourea·Hydrochloride

A solution of cyanamide (0.28 mg.) in ether (0.50 ml.) is mixed with 2,4,5-trichlorophenol (12.5 g.); the mixture is heated to 70°C. and the melt magnetically stirred while the reaction flask is flushed with nitrogen. Dry hydrogen chloride gas is then slowly bubbled into the melt and the reaction is allowed to cool to 22°C. The resulting solid is washed thoroughly with ether and filtered to give O-2,4,5-trichlorophenylisourea·hydrochloride as a white solid, m.p. 205—206°C.

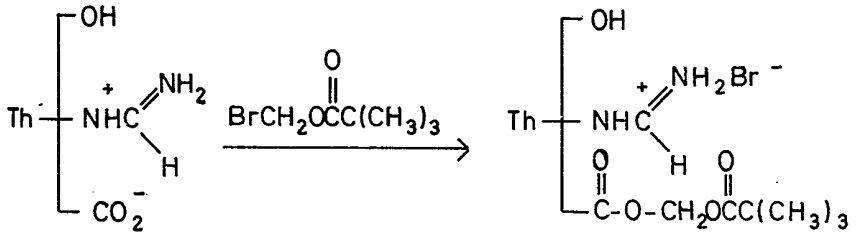
Example 9.



Preparation of N-Dimethylaminomethylene thienamycin

Thienamycin (16.5 mg.) is silylated with hexamethyldisilazane (200 μl.) and trimethylchlorosilane (60 μl.) in the usual manner. The silylated thienamycin is suspended in ethanol-free chloroform (1 ml.) with magnetic stirring under a nitrogen atmosphere. The mixture is cooled to −45°C. and a solution of triethylamine (21 μl.) in chloroform (21 μl.) is added followed by a solution of (chloromethylene)-dimethylammonium chloride (11.5 mg.) in chloroform (50 μl.). The mixture is warmed to −25°C. over 1 hour and 0.1*N* pH 7 phosphate buffer (5 ml.) is added. The mixture is vigorously stirred for 15 minutess. The aqueous phase is separated and contains N-dimethylaminomethylene thienamycin, which has an electrophoretic mobility (50 V/cm., 1 hour, pH 7 buffer) of 3.6 cm. towards the cathode.

Example 10.

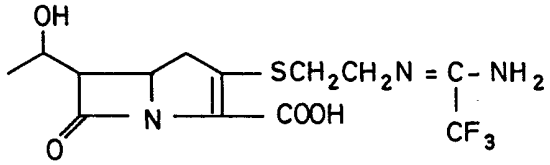


Preparation of N-Formimidoyl Thienamycin Pivaloxymethyl Ester Hydrobromide

N-aminomethylene thienamycin (10 mg.) is dissolved in hexamethylphosphoramide (200 μl.) containing bromomethyl pivalate (10 μl.) and triethylamine (1 μl.) and magnetically stirred at 22°C. After 2 hours the hexamethylphosphoramide solution is dissolved in 2 ml. methylene chloride and the product precipitated with a 50:50 hexane-ether solution. The precipitate is dissolved in an aqueous 10% tetrahydrofuran solution and chromatographed on an XAD—2a resin packed column. N-Formimidoyl thienamycin pivaloxymethyl ester is isolated as a solid after tetrahydrofuran elution of the column and lyophilization.

Example 11.

Preparation of N-Trifluoroacetimidoyl thienamycin



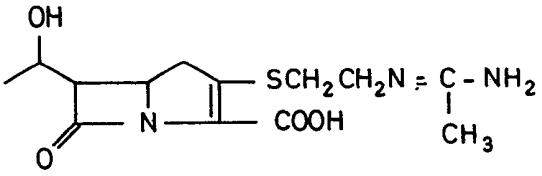
Thienamycin (199 mg.) is dissolved in pH 7 0.1*N* phosphate buffer (7 ml.) and adjusted to pH 8.5 with 1N sodium hydroxide solution. While this pH is maintained with an automatic burette, a solution of methyl trifluoroacetamidate (355 μl) in dioxane (2.5 ml.) is added in one portion. After 30 minutes the pH is readjusted to 7.0 by the addition of 1*N* hydrochloric acid. The solution is then chromatographed on Dowex 50—X4 resin (200 cc, Na^+ cycle, 200—400 mesh) and is eluted with water. The N-trifluoroacetimidoyl thienamycin derivative elutes in the first half column volume. This eluate is rechromatographed in a similar manner on Dowex 50—X4 (100 cc, Na^+ cycle, 200—400 mesh) and the first column volume concentrated and chromatographed on XAD—2 resin (30 cc). The N-trifluoroacetimidoyl thienamycin derivative elutes in 2.5—5.0 column volumes which is lyophilized to a white solid (15 mg.). UV (pH 7 0.1N phosphate buffer) λ_{max} 302 nm (ε 4,450).

ir (Nujol mull) 1750 cm^{-1} (β-lactam).

Electrophoresis: (50 v/cm, 20 min, pH 7, 0.1N phosphate buffer) viscosity 2.0 cm (toward cathode)

Example 12.

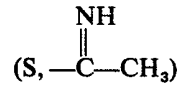
Preparation of N-Acetimidoyl thienamycin



Thienamycin (190 mg) is dissolved in pH 7 0.1*N* phosphate buffer (13 ml.) and cooled in an ice bath with magnetic stirring. The solution is adjusted to pH 8.5 using 2.5*N* sodium hydroxide solution dispensed from an automatic burette. While maintaining a pH of 8.5, ethyl acetimidate hydrochloride (400 mg.) is added portionwise over a few minutes. After an additional 40 minutes the solution is adjusted to pH 7.0 with 2.5*N* hydrochloric acid. The solution is then chromatographed on Dowex 50—X8 resin (250 cc, Na^+ cycle, 100—200 mesh) and is eluted with water. The N-acetimidoyl derivative elutes in 1—2 column volumes (240—520 cc) and is lyophilized to a white solid (88 mg.). UV (pH 7 0.1N phosphate buffer) λ_{max} 297 nm (ε 7,620).

ir (Nujol mull) 1774 cm^{-1}, β-lactam.

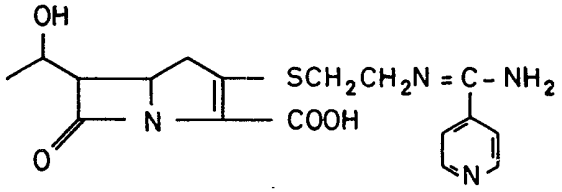
nmr (D_2O) δ 1.27 (d, J = 6 Hz, CH_3—CH) 2.24



3.2—3.5 (m, —CH_2), 3.5—3.9 (m, —CH_2—)
4.2—4.6 (m; C_{5H}, C_{6H}, C_{7H}).

Example 13.

Preparation of N-[(4-pyridyl)(imino)methyl]thienamycin



Thienamycin (80 mg., 0.294 mmole) is dissolved in aqueous sodium bicarbonate (24.7 mg., 0.294 mmole in 2.0 ml.) at 25°C. Methyl isonicotinimidate (80 mg., 0.588 mmole) is dissolved in the solution and progress of the reaction is followed by timed aliquots using high performance liquid chromatography (*HPLC*): Waters instrument; 0.2 x 61 cm. C_{18} Bondapak reverse phase column; 1.5 ml/min aqueous 10% THF; UV (254 nm.) and R.I. monitors. The reaction is essentially complete in 40 minutes, and the reaction solution is chromatographed directly over an 18.4 x 270 mm. XAD resin column, first eluting with deionised, distilled water, then changing to aqueous 10% THF. The eluate is monitored by UV and HPLC is used to locate the pure product. Correct fractions are combined and lyophilized to yield a colorless, fluffy powder (80 mg. 73%). UV$\lambda_{max}^{H_2O}$ 298 nm (ε 7,800); IR (Nujol mull) 1762 cm^{-1} (β-lactam); NMR (60 MHz, D_2O), δ 1.27, 3H (d, J = 7Hz, CH_3·CH(OH)); δ 7.75 and 8.80, 4H, (m, m, 4-pyridyl); HPLC, 1.58 x retention of thienamycin, conditions as above.

Example 14.

Following the procedure of Example 13, but replacing the reagent with methyl picolinimidate, there is obtained: *N-[(2-pyridyl)(imino)methyl]thienamycin* (85 mg 77%) UV$\lambda_{max}^{H_2O}$ 267, 300 nm (ε, 8,150, 7,600); IR (Nujol mull) 1764 cm^{-1} (β-lactam); NMR (60 MHz, D_2O), δ 1.24, 3H (d, J = 7Hz, CH_3·CH(OH)); δ 7.80, 8.07, 8.80, 4H, (m, m, m, 2-pyridyl); HPLC, 1.8 x retention of thienamycin. The formulae of the products of this Example and the products of Examples 15 and 16 can be deduced by comparison with Example 13.

Example 15.

Following the procedure of Example 13, but replacing the reagent with methyl nicotinimidate, there is obtained: *N-[(3-pyridyl)(imino)methyl]thienamycin* (77 mg., 70%): UV $\lambda_{max}^{H_2O}$ 264, 299 nm, (ε 5570, 6120); IR (Nujol mull), 1766 cm^{-1} (β-lactam); NMR, (60 MHz, D_2O), δ 1.24, 3H, (d, J = 7Hz, CH_3·CH(OH)); δ 7.6, 8.2, 8.9, 4H, (m, m, m, 3-pyridyl); HPLC, 1.57 x retention of thienamycin.

Example 16.

Following the procedure of Example 13, but replacing the reagent with methyl 4-thiazolecarboximidate, there is obtained: *N-[(4-thiazoly)(imino)methyl]thienamycin* (99 mg, 89%): UV $\lambda_{max}^{H_2O}$ 300 nm, (ε 7530); IR (Nujol Mull) 1764 cm^{-1} (B-lactam); NMR (60 MH_z, D_2O), δ 1.23, 3H, (d, J = 7Hz, CH_3·CH(OH)); δ 8.60, 9.17, 2H (d, d, J = 2Hz, 4-thiazolyl); HPLC, 1.8 x retention time of thienamycin.

Example 17.

Preparation of N-Allylformamide

A mixture of allylamine (5.00 g., 87.6 mmole) and methylformate (5.26 g., 87.6 mmole) is stirred at 25°C., for 2 hours. At the end of this time, the reaction flask is fitted with a short path distillation head and the desired N-allylformamide is collected at 89—90°C./0.7 mm as a colorless oil. Yield 7.0 g. (94%). IR($CHCl_3$) 3380, 1680 cm^{-1}; nmr ($CHCl_3$) δ 8.1 (1H, br s), δ 6.4—7.9 (1H, very br), δ 5.5—6.3 (1H, m), δ 4.9—5.5 (2H, m), δ 3.85 (2H, m).

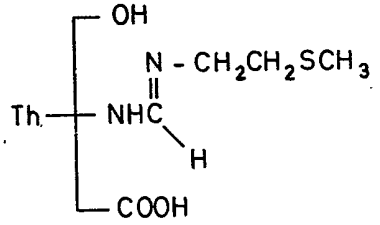
Example 18.

Preparation of Ethyl Allylimidate Hydrochloride

Ethyl chloroformate (2.66 g., 24.47 mmole) is added by syringe to N-allylformamide (2.08 g., 24.47 mmole) in a dry flask under N_2. The resulting mixture is then stirred at 25°C., for 2 hours during which time CO_2 is rapidly evolved. The reaction mixture is then heated to 45°C. until no further evolution of gas is evident (2 hours). The viscous product is then cooled and held at a vacuum of 0.2 mm for 2 hours to remove all volatile materials.

Example 19.

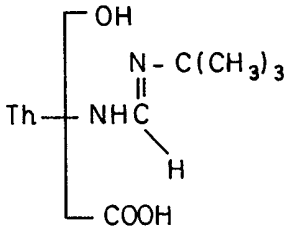
Preparation of N′ (2-Methylthioethyl)-N-formimidoyl thienamycin



Thienamycin (105 mg.) is dissolved in pH 7 0.1*N* phosphate buffer (5 ml.) and to this is added a solution of ethyl N-2-methylthioethyl formimidate (300 μl) in tetrahydrofuran (2 ml.). The pH of the solution is adjusted to and maintained at 8.5 using an autoburette dispensing 1*N* NaOH. After 30 minutes the pH is adjusted to 7.0 with 2.5*N* HCl. The solution is chromatographed on an ice water jacketed column of Dowex 50—X4 resin (53 cc, Na^+ cycle, 200—400 mesh) eluted with deionized water. The N′ [2-methylthioethyl]N-formimidoyl derivative elutes in 2—4 column volumes and is lyophilized to give a white solid.

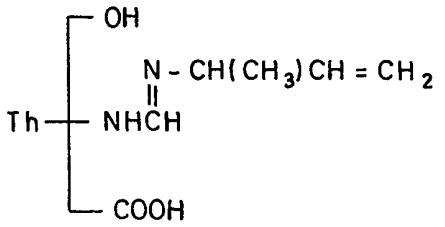
U.V. (pH 7 0.1N phosphate bufer) λ max 298 nm (ε 7,760)
i.r. (Nujol mull) 1760 cm^{-1} (β-lactam).

Example 20.
Preparation of N'-*Tert*-Butyl-N-formimidoyl thienamycin



Thienamycin (105 mg.) is dissolved in pH 7 0.1*N* phosphate buffer (5 ml.) and to this is added a solution of ethyl N-*tert*-butyl formimidate (290 mg.) in tetrahydrofuran (1 ml.). The pH of the solution is adjusted to and maintained at 8.5 using an autoburette dispensing 1*N* NaOH. After 30 minutes, the pH is adjusted to 7.0 with 2.5*N* HCl. The solution is chromatographed on an ice-water-jacketed column of Dowex 50—X4 resin (53 cc, Na^+ cycle, 200—400 mesh) eluted with deionized water. The fractions containing the title product are combined and lyophilized.

Example 21.
Preparation of N' [1-Methyl-2-Propenyl]N-Formimidoyl thienamycin



Thienamycin (126 mg.) is dissolved in pH 7 0.1*N* phosphate buffer (6 ml.) and the pH of the solution is adjusted to 8.5 using an automatic burette dispensing 1*N* NaOH. To this stirred solution is added ethyl N-1-methyl-2-propenyl-formimidate hydrochloride (300 μl) while the pH is maintained at 8.5. After 30 minutes, the pH of the solution is adjusted to 7.0 with 2.5*N* HCl and the solution is chromatographed on an ice-water-jacketed column of Dowex 50—X4 resin (49 cc, Na^+ cycle 200—400 mesh) eluted with deionized water. The N' [1-methyl-2-propenyl]-N-formimidoyl derivative elutes in 2—4 column volumes and is lyophilized to a white solid (59 mg.). U.V. (pH 7 0.1N phosphate buffer) wavelength of maximum absorption = 299 nm (absorptivity = 7,820) i.r. (Nujol mull) 1760 cm^{-1} (β-lactam).

Example 22.
Preparation of N-(1-Buten-3-yl)formamide

A solution of 3.5 g. (0.05 mole) 3-amino-1-butene in 12 ml. of methyl formate is kept at 25°C. for 20 hours; the solution is then concentrated under reduced pressure to remove excess methylformate. The residual N-(1-buten-3-yl)formamide is distilled under reduced pressure. A fraction amounting to 3 g. (b.p. 58—60°C./0.5 mm.) of N-(1-buten-3-yl)formamide is obtained.

Example 23.
Preparation of Ethyl-N-(1-Buten-3-yl)formamide

A mixture of 1.0 g. of N-(1-buten-3-yl)formamide and one equivalent of ethyl chloroformate is stirred under N_2 for 4 hours during which time CO_2 is evolved. The solution is stirred under reduced pressure for 3 hours to remove any unreacted ethyl chloroformate, and a residue of ethyl-N-(1-buten-3-yl)formimidate is obtained.

Example 24.
Preparation of Methyl N-Dimethylaminoformimidate

To a stirred solution of N,N-dimethylformhydrazide (0.22 g) in 2.0 ml of

chloroform, under nitrogen, is added methylchloroformate (0.5 ml.). The mixture is heated at 40°C. for three hours then evaporated under nitrogen. The mixture is triturated with anhydrous ether. The supernatant solution is decanted and the residue dried in a stream of nitrogen.
Yield: 284 mg. nmr $CDCl_3$ δ, 9.13 (CH); 3.80 (OCH_3), 3.01 ($N(CH_3)_2$).

Example 25.

Preparation of Cyclopropyl formamide

A mixture of cyclopropylamine (5.00 g, 87.6 mmole) and methylformate (5.26 g, 87.6 mmole) is stirred at 25°C., for 2 hours (an initial exotherm is noted). The mixture is then placed on the rotary evaporator to remove the MeOH formed in the reaction. The remaining material is distilled through a short path head to yield 6.92 g (93%) of the desired N-cyclopropyl formamide as a colorless oil, n.m.r. ($CDCl_3$) δ 8.1 (1H, br S), 6.8—8.5 (1H, br), δ 2.4—3.0 (1H, m), δ 0.4—1.0 (4H, m).

Example 26.

Preparation of Ethyl N-Cyclopropyl formimidate

Ethyl chloroformate (4.078 g, 37.58 mmole) is added by syringe to N-cyclopropylformamide (3.194 g, 37.58 mmole) in a dry flask under N_2. After an induction period of 30 sec., a rapid evolution of gas begins. The resulting reaction mixture is stirred at 25°C until no further evolution of gas can be detected (~4 hr.), then the viscous product is subjected to a vacuum of 0.5 mm. for 1 hr. to remove any unreacted ethyl chloroformate. NMR analysis of the product shows the formyl proton at δ 9.37 as a broad singlet. ($CDCl_3$ solution).

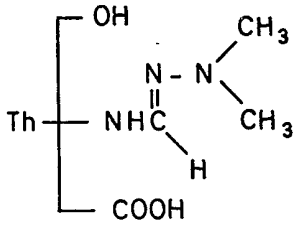
Example 27.

Preparation of Ethyl N-(Methylthioethyl)formimidate

To a 60-ml. separatory funnel are added ethyl formimidate hydrochloride (0.97 g., 8.8 mmole) a solution of β-methylthioethylamine (0.80 g., 8.8 mmole) in CH_2Cl_2 (35 ml.), and H_2O (35 ml.). The mixture is shaken vigorously for 5 minutes. The CH_2Cl_2 layer is separated, washed with brine, dried with $MgSO_4$, filtered, and evaporated under reduced pressure to give the crude imidate (0.59 g.) as a hazy, pale, yellow, liquid.
i.r. 1660, 1230 cm^{-1}.

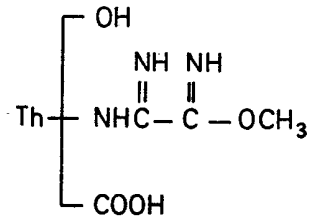
Example 28.

Preparation of N'-Dimethylamino-N-formimidoyl thienamycin



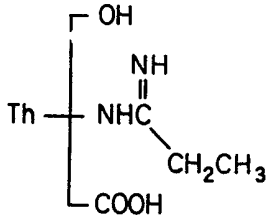
Thienamycin (115 mg.) is dissolved in pH 7 0.1*N* phosphate buffer (7 ml.) and the pH of the solution is adjusted to 8.5 using an automatic burette dispensing 1*N* NaOH. To this stirred solution is added methyl N-dimethylamino formimidate hydrochloride (284 mg.) while the pH is maintained at 8.5. After 20 minutes the pH of the solution is adjusted to 7.0 using 2.5*N* HCl and the solution is chromatographed on Dowex 50—X4 resin (53 cc, Na^+ cycle, 200—400 mesh) eluted with deionized water. The chromatography is carried out with deionized water. The chromatography is carried out in a water-jacketed column at 3°. The N'-dimethylamino-N-formimidoyl derivative elutes in 2 column volumes and is lyophilized to a white solid (40) mg.) UV (pH 7, 0.1*N* phosphate buffer) λ max 298 nm (ε 6, 910), ir (Nujol mull) 1760 cm^{-1} (β-lactam) nmr (D_2O) δ 1.29 (d, J = 6 Hz, CH_3—CH), 2.59 (s, N (CH_3)$_2$), 7.76 (s, NCH).

Example 29.
Preparation of Methyl oxalimidoyl thienamycin



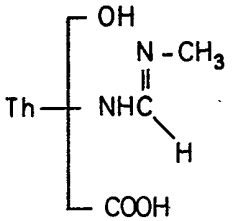
Thienamycin (105 mg.) is dissolved in pH 7 0.1*N* phosphate buffer (5 ml.) and the pH of the solution is adjusted to 8.5 using an automatic burette dispensing 1*N* NaOH. To this solution is added methyl oxalimidate (200 μl) while the pH is maintained at 8.5. After 30 minutes the pH is adjusted to 7.0 using 2.5*N* HCl and the solution is chromatographed on Dowex 50—X4 resin (53 cc, Na^+ cycle, 200—400 mesh) eluted with deionized water. The chromatography is carried out in water jacketed column at 3°. The methyl oxalimidoyl derivative elutes in 2 column volumes and is lyophilized to a white solid (44 mg.) uv (pH 7 0.1N phosphate buffer) λ max 298 nm (ε 6, 230) ir (Nujol mull) 1760 cm^{-1} (β-lactam); nmr (D_2O) δ 1.27 (d, J = 6 Hz, CH_3—CH), 3.87 (s, —OCH_3).

Example 30.
Preparation of N-Propionimidoyl thienamycin



Thienamycin (114 mg.) is dissolved in pH 7 0.1*N* phosphate buffer (10 ml.) and the pH of the solution is adjusted to 8.5 using an automatic burette dispensing 1*N* NaOH. Solid ethyl propionimidate hydrochloride (231 mg.) is added portionwise as rapidly as possible allowing the pH to be maintained near 8.5. After 30 minutes the pH is adjusted to 7.0 using 2.5*N* HCl and the solution is chromatographed on Dowex 30—X4 resin (72 cc, Na^+ cycle, 200—400 mesh) eluted with deionized water. The N-propionimidoyl derivative elutes in 2 column volumes and is lyophilized to a white solid (76 mg.), uv (pH 7 0.1*N* phosphate buffer) λ max 298 nm (ε 7,830) nmr (D_2O) δ 1.28 (d, J = 6 Hz, CH_3CH(OH)), 1.23 (t, J = 8 Hz, —CH_2—CH_3), 2.50 (q, J = 8 Hz, CH_2CH_3).

Example 31.
Preparation of N'-Methyl-N-formimidoyl thienamycin

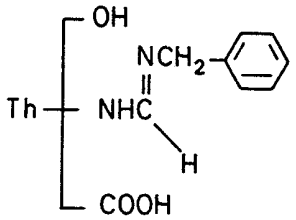


Thienamycin (140 mg.) is dissolved in pH 7 0.1*N* phosphate buffer (10 ml.) and the pH of the solution is adjusted to 8.5 using an automatic burette dispensing 1*N* NaOH. To this solution is added methyl N-methyl formimidate hydrochloride (200 μl) while the pH is maintained at 8.5. After 40 minutes the pH is adjusted to 7.0 using 2.5*N* HCl and the solution is chromatographed on Dowex 50—X4 resin (72 cc, Na^+ cycle, 200—400 mesh) eluted with deionized water. The N'-methyl-N-formimidoyl derivative elutes in 2 column volumes and is lyophilized to a white

solid (43 mg.), uv (pH 7 0.1N phosphate buffer) λ max 298 nm (ε 7,250) ir (Nujol mull) 1765 cm^{-1} (β-lactam). nmr (D_2O) δ 1.29 (d, J = 6 Hz, CH_3—CH), 2.92 (s, N—CH_3) 7.80 (s, N—CH).

Example 32.

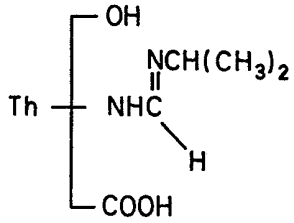
Preparation of N'-Benzyl-N-formimidoyl thienamycin



Thienamycin (110 mg.) is dissolved in pH 7 0.1*N* phosphate buffer (7 ml.) and the pH of the solution is adjusted to 8.5 using an automatic burette dispensing 1*N* NaOH. A solution of ethyl N-benzyl formimidate fluroborate (572 mg.) in *p*-dioxane (2 ml.) is added to the buffered solution while the pH is maintained at 8.5. After 20 minutes the pH of the solution is addjusted to 7.0 using 2.5*N* HCl and chromatographed on Dowex 50—X4 resin (53 cc, Na^+ cycle, 200—400 mesh) eluted with deionized water. The chromatography is carried out in a water-jacketed column at 3°. The N'-benzyl-N-formimidoyl derivative elutes in 2 column volumes and is lyophilized to a white solid (5 mg.). uv (pH 7 0.1*N* phosphate buffer) λ max 295 nm (ε 3,980) ir (Nujol mull) 1765 cm^{-1} (β-lactam) nmr (D_2O) δ 1.29 (d, J = 6 Hz, CH_3CH), 4.44 (s CH_2—Ar), 7.37 (s, Aryl), 8.14 (s, NCH).

Example 33.

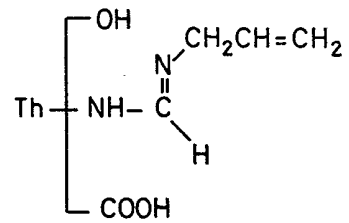
Preparation of N'-Isopropyl-N-formimidoyl thienamycin



Thienamycin (110 mg.) is dissolved in pH 7 0.1N phosphate buffer (7 ml.) and the Ph of the solution is adjusted to 8.5 using an automatic burette dispensing 1N NaOH. A solution of methyl N-isopropyl formimidate hydrochloride (300 mg.) in *p*-dioxane (1 ml.) is added to the magnetically stirred buffered solution while the pH is maintained at 8.5. After 25 minutes the pH off the solution is adjusted to 7.0 using 2.5N NaOH and chromatographed on Dowex 50—X4 resin (53 cc, Na^+ cycle, 200—400 mesh) eluted with deionized water. The chromatography is carried out in a water jacketed column at 3°C. The N'-isopropyl-N-formimidoyl derivative elutes in 2 column volumes and is lyophilized to a white solid (12 mg.). UV (pH 7 0.1N phosphate buffer) λ max 299 nm (ε 8,130) ir (Nujol mull) 1760 cm^{-1} (β-lactam) nmr (D_2O) δ 1.26 (d, J = 6Hz, CH_3CH(OH)), 1.29 (d, J = 6Hz, CH(CH_3)$_3$), 7.89 (s, NHCH), 7.96 (s, NHCH).

Example 34.

Preparation of N(N'-Allyl-formimidoyl)thienamycin

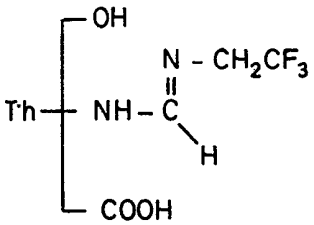


To a prechilled sample of Thienamycin (123 mg., 0.452 mmols) is added 13 ml.

of cold 0.1*N* phosphate buffer. The solution is adjusted to pH 9 with *N* sodium hydroxide. To this basic solution at 2°C. is added all at once ethyl N-allyl-formimidate hydrochloride (0.3 g.). The pH dropped to 7.3 and is brought back to 8.5 with additional sodium hydroxide. The reaction mixture is stirred at 2°C. for an additional 30 min. and the pH is adjusted to 7 with cold 0.1*N* sulfuric acid. The reaction mixture is assayed using high pressure liquid chromatography on a C_{18}-Porosil column, developed with 10% aqueous tetrahydrofuran and is found to show only trace amounts of thienamycin (retention time, 5 min.) and substantially pure product (retention time, 10.5 min.). The reaction mixture is chromatographed on a Dowex—50 x 4 column (60 ml., Na cycle 200—400 mesh) eluting with water at a flow rate of 0.5 ml/min/cm² of resin bed. After discarding the first 400 ml. of eluate, the next 150 ml. is lyophilized to give the product. Yield 96 mg. (63%). U.V. λmax 301 nm, 24.60 Du/mg. (NH_2OH extinguished) 90% purity. IR Nujol exhibits C = O at 5.67 μ and 5.90 μ. NMR 100 MHz D_2O shows its a 1:1 mixture of *syn-* and *anti-*N(N'-allylformimidoyl)thienamycin.

Example 35.

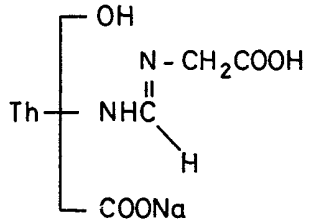
Preparation of N(N'-Trifluoroethyl-formimidoyl)thienamycin



To a prechilled sample of thienamycin (123 mg., 0.452 mmoles) is added 15 ml. of cold 0.1*N* phosphate buffer. The solution is adjusted to pH 9 with *N* sodium hydroxide. To this basic solution at 0—2°C. is added ethyl N-trifluoroethyl-formimidate (0.3 ml.) in dioxane (2 ml.) portionwise over 30 min. The pH of the reaction is maintained at 8.5—9 during the addition. The reaction mixture is stired for a few minutes. After the addition of imidate is completed and the pH is brought to 7 with cold 0.1*N* H_2SO_4·HPLC, C_{18} Porosil reverse phase, using 10% aqueous tetrahydrofuran exhibits a new peak at 12.2 min. assayed to the desired product. The mixture is chromatographed on a Dowex 50 x 4 column (60 ml. 200—400 mesh). The column is eluted with water at a flow rate of 0.5 ml./min./cm² of resin bed. The forerun is discarded and fractions containing the product are combined and lyophilized to give a hygroscopic solid, 10.2 mg. λ max 302 nm.

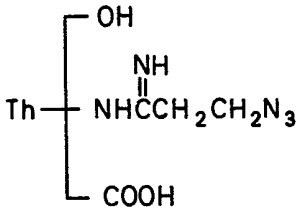
Example 36.

Preparation of N(N'-Carboxymethyl-formimidoyl)thienamycin Sodium Salt



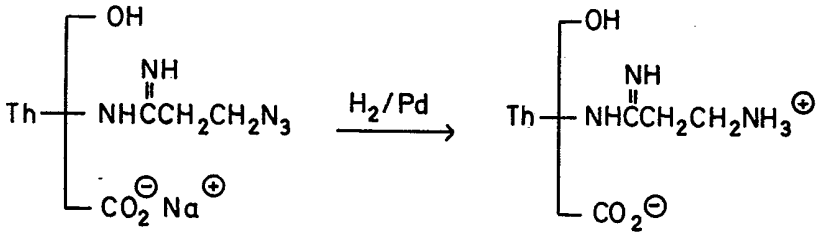
Thienamycin (130 mg.) is dissolved in pH 7 0.1*N* phosphate buffer (4 ml.) and solid sodium ethyl N-carboxymethyl formimidate (500 mg.) is added at once in one portion. The pH of the solution is adjusted to 8.5 using an automatic burette dispensing 1*N* NaOH. After 25 min. at pH 8.5 the solution is adjusted to 7.0 with 2.5*N* HCl. The solution is then chromatographed on an ice-water-jacketed column of Dowex 50— x 4 resin (51 cc, Na^+ cycle, 200—400 mesh) eluted with deionized water. The eluate of the first column volume was combined and concentrated to 7 ml. This solution was then chromatographed on an ice-water-jacketed column of XAD—2 resin (53 cc) eluted with deionized water. The second through fourth column volumes were collected and combined and lyophilized to give sodium N, (N'-carboxymethylformimidoyl)thienamycin (25 mg.). uv (pH 7 0.1*N* phosphate buffer) λ max 300 nm (ϵ 6, 390) ir (Nujol mull) 1755 cm^{-1} (β-lactam) nmr (D_2O) δ 1.29 (d, J = 6Hz, CH_3CH), 7.85 (s, NCH).

Example 37.
Preparation of N-(3-Azidopropionimidoyl)thienamycin



To a solution of thienamycin (133 mg.) in 10 ml. 0.1*M* pH 7.0 phosphate buffer is added 1.2 g. of O-ethyl-3-azidopropionimidate·HCl while the solution is maintained at pH 8.5 with 2.5N NaOH. The mixture is stirred at 0°C. for 0.5 hr., then is neutralized with 2.5*N.* HCl to pH 7.0, concentrated to 5 ml. and chromatographed on a Dowex 50W × 8 (Na form) column (1.5″ × 12″) which is eluted with water to give 30 mg. of the desired product. The product shows UV $\lambda_{max}^{H_2O}$ 300 nm; high-pressure liquid chromatography (HPLC) retention time of 10 min. with comparison to that of 4.8 min. of the starting material under the same conditions (⅛″ × 2′, Bondapak C_{18} reverse phase column eluted with 10% THF in water at flow rate of 1.5 ml./min.); Electrophoretic mobility 5 mm toward cathode at 50V/CM for 20 min. in 0.05M pH 7.0 phosphate buffer.

Example 38.
Preparation of N-(3-aminopropionimidoyl)thienamycin



N-(3-azidopropionimidoyl)thienamycin (I) (43 mg in 40 ml water) is hydrogenated under 1 atm of H_2 in the presence of 0.1 g catalyst (10% palladium on charcoal) for 30 minutes. Electrophoresis of the resulting mixture shows a new bioactive product which moves 30 mm. toward cathode (50V/CM for 20 min. in 0.05M pH 7.0 phosphate buffer) in addition to the starting material (I) which moves 5 mm. toward cathode. The electrophoretic mobility of the product is consistent with that of the expected product (II). The resulting reaction mixture from the hydrogenation reaction is neutralized with 2.5 NHCl and filtered from the catalyst. The filtrate is concentrated to 10 ml. and chromatographed on XAD—2 resin (2.3 × 16 cm. column). The column is eluted with water to provide the desired product II as the hydrochloride after lyophilization (23 mg. N-(3-aminopropionimidoyl) thienamycin hydrochloride). U.V. Absorbance maximum in water equals 301 nm (absorptivity equals 7080),
I.R.: Nujol Mull 1765 cm^{-1}
NMR 60 mHz (D_2O) δ 1.30 ppm, (doublet, 3) δ 2.60—3.72 ppm (multiplet, 11) and δ 4.18 ppm (multiplet, 2).

Example 39.
Preparation of N-Nitroguanyl thienamycin

Thienamycin (131 mg.) is dissolved in a solution of dimethyl sulfoxide (10 ml.), tri-*n*-butylamine (0.30 mole) and 2-methyl-1-nitro-2-thiopseudourea (0.3 g.). The solution is heated in a water bath at 45°C. while a stream of nitrogen is vigorously bubbled into the solution. After 50 min. the solution is concentrated under high vacuum to 1.0 ml. and dissolved in 0.05*N* ph 7 phosphate buffer (7 ml.). The unreacted thiopseudourea is precipitated and removed by filtration. The solution is then chromatographed on Dowex 50—X4 resin (53 cm^3, 200—400 mesh, Na^+ cycle) and eluted with water. The N-nitroguanyl derivative elutes in the first column volume and is lyophilized to a solid (23%).

UV (pH 7 0.1N phosphate buffer) λ_{max} 269 nm (ε 11,000)
Electrophoresis (40 v/cm., pH 7 0.1N phosphate buffer, 20 min.) 3.0 cm. toward cathode.

Example 40.

Preparation of the N-Isobutyrimidoyl thienamycin

Following the procedure of Example 12 but replacing ethyl acetimidate hydrochloride with isobutyrimidate hydrochloride and allowing the reaction to proceed at 20°C. and ph 8.2 there is obtained N-isobutyrimidoyl thienamycin (14%).

UV (pH 7 0.1N phosphate buffer) λ_{max} 298 nm (ε 8,290)
NMR (D_2O S 1.27 (d, J = 7H_z, $CH(CH_3)_2$, 1.29 (d, J = 6H_z, $CH_3CH(OH)$, 2.79 (heptet, J = 7H_z, $CH(CH_3)_2$).

Example 41.

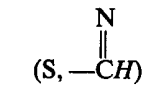
Preparation of N'-Methyl-N-acetimidoyl thienamycin

Following the procedure of Example 12, but replacing ethyl acetimide hydrochloride with methyl-N-methyl acetimidate, there is obtained N-methyl-N'-acetimidoyl thienamycin (10%).
UV (pH 7 0.1*N* phosphate buffer) λ_{max} 298 nm (ε 6,700)
IR (Nujol mull) 1750 cm^{-1} (β-lactam), 1660 cm^{-1} (C = NCH_3)
NMR (D_2O) δ 1.27 (d, J = 6H_z, $CH_3CH(OH)$, 2.22 and 2.25 (S, N—CCH_3), 2.97 (S, NCH_3).

Example 42.

Preparation of N'-Methyl-N-formimidoyl thienamycin

Following the procedure of Example 12, but replacing ethyl acetimidate hydrochloridde with ethyl N-methyl formimidate hydrochloride there is obtained N'-methyl-N-formimidoyl thienamycin (10%).
UV (pH 7 0.1N phosphate buffer) λ_{max} 298 nm
NMR (D_2O) δ 1.30 (d, J = 6H_z, $CH_3CH(OH)$, 2.92 (S, N—CH_3), 7.78



(S, —C*H*)

Example 43.

Following the procedure of Example 12, but replacing the reagent with an equivalent amount of methyl methoxyacetimidate, there is obtained: N(methoxyacetimidoyl)thienamycin (34%);

UV $\lambda_{max}^{H_2O}$ 198, 301 nm (ε 16,180, 8,700);
IR (Nujol mull) 1760 cm^{-1} (β-lactam);
NMR (60 MHz, D_2O) δ 1.28, 3H, (d, J = 6Hz, CH_3·CH(OH);
δ 3.50, 3H, (S, CH_3·O·CH_2) δ 4.35, 2H, (S, CH_3·O·CH_2);
HPLC, 1.50 × retention time of thienamycin.

Example 44.

Preparation of Ethyl N-Methoxyformimidate

A mixture of methoxylamine hydrochloride (0.020 mole, 1.6700 g.) and anhydrous potassium carbonate (0.010 mole, 1.3821 g.) is dissolved in 7.0 ml. water. Ether 80 ml. is added and the reaction mixture is treated with ethyl formimidate hydrochloride (0.02 mole, 2.1900 g.). The mixture is shaken for 15 minutes. The ethereal layer is separated and the aqueous layer is extracted with two portions of ether (30 ml.). The combined and dried ethereal solution is evaporated to give 0.8433 g of ethyl N-methoxyformimidate.
nmr δ 1.36 (triplet)
δ 3.83 (singlet)
δ 4.13 (quartet)
δ 6.56 (singlet)

Example 45.

Ethyl N-(2,2,2-trifluoroethyl)formimidate

Ethyl formimidate hydrochloride (0.555 g., 5 mmole), 2,2,2-trifluoroethylamine hydrochloride (0.677 g., 5 mmole) and potassium carbonate (0.345 g., 2.5

mmole) are suspended in 20 ml CH_2Cl_2 and treated with 2 ml. H_2O. The mixture is shaken vigorously for 3 minutes. The organic phase is separated and the aqueous extracted twice with 10 ml portions of CH_2Cl_2. The combined organic phase is dried and the CH_2Cl_2 distilled through a Vigreaux column to give ethyl N-(2,2,2-trifluoroethyl)formimidate. n.m.r. δ 1.33 t (CH_3CH_2); 3.8 q (j = 10 c.p.s., CF_3CH_2) 4.23 q (j = 7.5, CH_3CH_2O); 7.6 S (H—C = N).

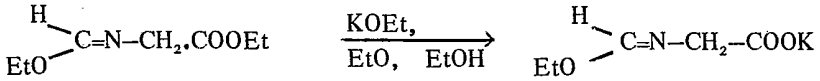
Example 46.

Preparation of Ethyl N-ethoxycarbonylethyl-formimidate

Ethyl formimidate hydrochloride (0.55 g., 5 mmole), ethyl glycinate hydrochloride (0.697 g., 5 mmole) and potassium carbonate (0.345 g., 2.5 mmole) are suspended in 20 ml CH_2Cl_2 and treated with 2 ml H_2O. The mixture is shaken vigorously for 4 minutes. The organic phase is separated, the aqueous phase is extracted twice with CH_2Cl_2 (10 ml.) and the combined organic phase is dried and evaporated to give ethyl N-ethoxycarbonylmethyl-formimidate. n.m.r. δ: 126 t (CH_2—CH_2); 4.06 S (N—CH_2—C); 4.23 g (CH_3CH_2—O); 7.5 S (N = CH).

Example 47.

Preparation of Potassium N-ethoxycarbonylmethyl-formimidate



Potassium (0.18 g.) is dissolved in a mixture of 0.6 g. EtOH and 4 ml. Et_2O under N_2. The solution is diluted with 50 ml. of Et_2O and ethyl N-ethoxycarbonyl-methyl-formimidate (0.79 g.) in 2 ml. Et_2O is added, followed by 0.1 ml. H_2O. Rapid crystallization of the salt takes place. The solid is filtered, washed with ether and dried under vacuum to give Potassium N-ethoxycarbonylmethylformimidate. n.m.r. (D_2O) 1.13 t (CH_3CH_2); 3.63 g (CH_3—CH_2O); 3.8 S (N—CH_2—C); 8.06 S N = CH.

Example 48.

Preparation of Ethyl N-Benzylformimidate

A solution of 690 mg. (5.1 mmoles) of N-benzylformamide in 5 ml. of methylene chloride is cooled in an ice-water bath and put under an argon blanket. The solution is stirred while 4.9 ml. (4.9 mmoles) of 1M triethyloxonium fluoroborate in methylene chloride is added dropwise. After a 45 minute reaction time, the mixture is concentrated to dryness under reduced pressure at room temperature, and the residue is dried under reduced pressure over P_2O_5. The nuclear magnetic resonance spectrum of the product in deuterochloroform is fully in accord with the product being a fluoroborate etherate complex of ethyl N-benzylformimidate.

Example 49.

Preparation of N-isopropyl formamide

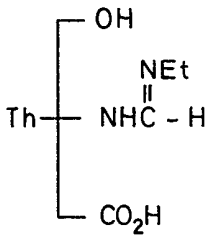
Formamide (1.13 g., 0.98 ml.) is dissolved in 10 ml. of toluene, containing toluenesulfonic acid (4.7 g.). To the above mixture is added isopropylamine (2.95 g., 4.25 ml.). The mixture is refluxed overnight under a gentle stream of N_2. The solution is filtered and the toluene is evaporated under reduced pressure. The residual oil is distilled at 59—62°C/0.7 mm. to give 1.0 g. of the desired product.

Example 50.

Preparation of Methyl N-isopropyl formimidate

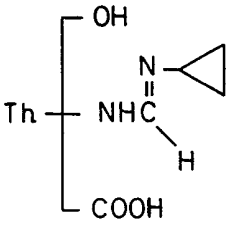
Isopropyl formamide (535 mg.) is treated with an equivalent amount of ethyl chloroformate (440 μl) for 2—3 hours under N_2 at 40—45°C. The mixture is washed successively with petroleum ether anhydrous ether and benzene leaving the product as an oil.

Example 51.
Preparation of N-[N'-Ethylformimidoyl]thienamycin



Thienamycin (100 mg.) in 10 ml. 0.1*M* pH 7.0 phosphate buffer is adjusted and maintained at pH 8.5—9.0 with 2.5*N* sodium hydroxide. To the solution is added 300 mg. of ethyl N-ethylformimidate hydrochloride. The mixture is stirred at 23°C. for 20 minutes, then is neutralized to pH 7.0 with 2.5*N* HCl and chromatographed on a Dowex 50—X8 (Na form) ion-exchange column (1.5″ × 10″). The column is eluted with water taking 6.7 ml. fractions. Fractions 40—90 are combined, concentrated and freeze-dried to give 15 mg. of the solid product. Electrophoresis of the product at 50 v/cm. for 20 minutes in 0.1 M, pH 7.0 phosphate buffer shows a single bioactive zone which moves 2 mm. toward the cathode. uv$\lambda_{max}^{H_2O}$ 301 nm.; nmr (100 MH_2, D_2O); δ 7.77 (S) and 7.82 (S) (formimidoyl CH).

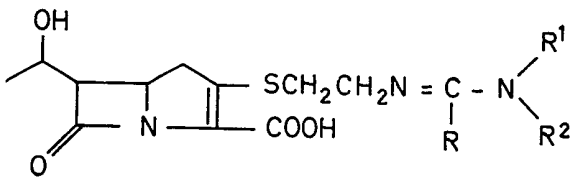
Example 52.
Preparation of N-[N'-cyclopropylformimidoyl]thienamycin



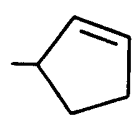
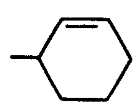
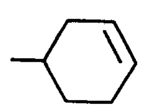
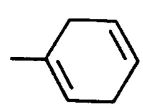
Thienamycin (100 mg.) in 10 ml. 0.1*M* pH 7.0 phosphate buffer is adjusted and maintained at pH 8.5—9.0 while 300 mg. of ethyl N-cyclopropylformimidate hydrochloride is added dropwise to the solution. The mixture is stirred at 23° for 40 minutes, then is neutralized, and chromatographed on a Dowex — 50 × 8 (Na form) ion-exchange column (1.5″ × 10″). The column is eluted with water, collecting 6.5 ml. fractions. Fractions 43—95 are combined, concentrated and freeze-dried to give 54 mg. of the solid product. Electrophoresis of the product shows a single bioactive zone which moves 10 mm. toward the cathode (50 V/CM, 1 hour in 0.05*M* pH 7.0 phosphate buffer).

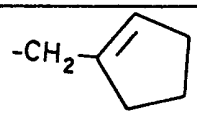
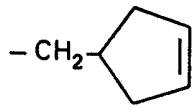
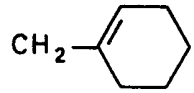
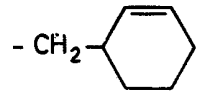
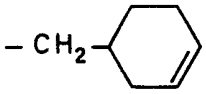
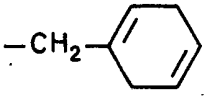
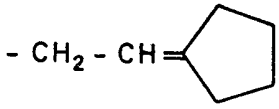
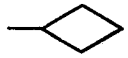
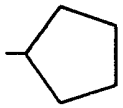
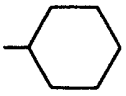
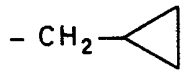
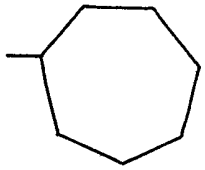
uv$\lambda_{max}^{H_2O}$301 nm; Nmr (100 MHz, D_2O): 0.60—1.30 ppm (m, cyclopropyl) and 7.80 ppm (formimidoyl CH).

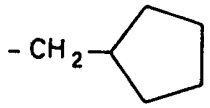
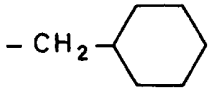
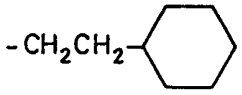
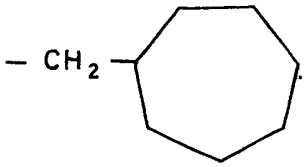
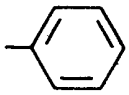
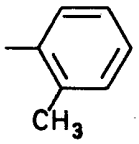
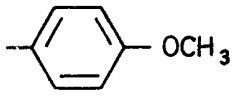
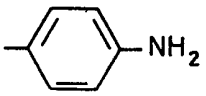
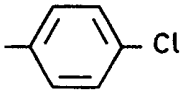
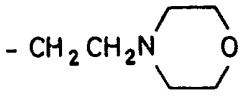
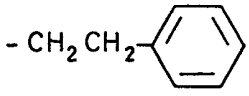
Example 53.
Following the procedure set forth in the foregoing text and Examples, the following compounds of the present invention are obtained. The reagents, imido ethers and imido halides, utilized in the reaction with thienamycin, or a derivative thereof, to provide the following compounds are either known, or may be prepared as described above.

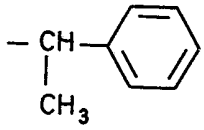
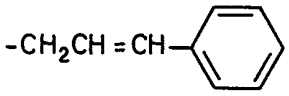
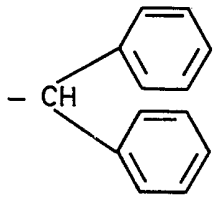
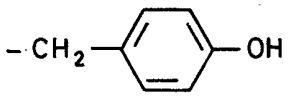
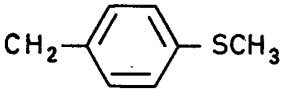
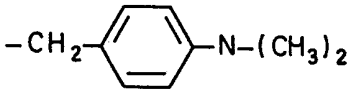
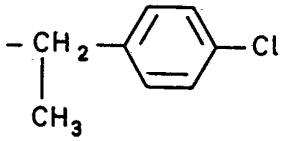


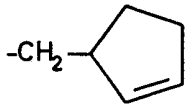
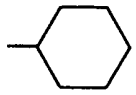
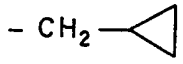
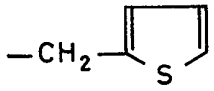
Compound	R	R^1	R^2
1.)	H	$-CH_2CH_2CH_2CH_3$	H
2.)	H	$-CH_2-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CH_3$	H
3.)	H	$-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}CH_2CH_3$	H
4.)	H	$-CH_2CH_2CH_2CH_2CH_3$	H
5.)	H	$-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CH_2CH_2CH_3$	H
6.)	H	$-CH_2\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CH_2CH_3$	H
7.)	H	$-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CH_3$	H
8.)	H	$-\underset{\displaystyle CH_3}{\underset{\vert}{\overset{\displaystyle CH_3}{\overset{\vert}{C}}}}-CH_2-CH_3$	H
9.)	H	$-CH_2-C(CH_3)_3$	H
10.)	H	$-CH_2CH_2CH_2CH_2CHCH_3$	H
11.)	H	$-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CH_2CH(CH_3)_2$	H
12.)	H	$-CH_2-\underset{\displaystyle CH_3}{\underset{\vert}{C}}=CH_2$	H
13.)	H	$-CH_2-CH=CH-CH_3$	H
14.)	H	$-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CH=CH_2$	H
15.)	H	$-CH_2CH_2CH=CH_2$	H
16.)	H	$-CH_2CH_2-CH=CH-CH_3$	H

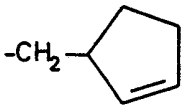
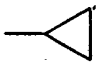
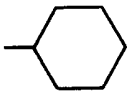
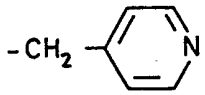
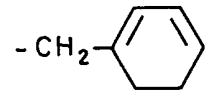
Compound	R	R^1	R^2
17.)	H	$-\underset{CH_3}{\underset{\mid}{CH_2}}-CH_2-CH=CH_2$	H
18.)	H	$-CH_2-\underset{CH_3}{\underset{\mid}{CH}}-CH=CH_2$	H
19.)	H	$-\underset{CH_3}{\underset{\mid}{CH}}-\underset{CH_3}{\underset{\mid}{C}}=CH_2$	H
20.)	H	$-\underset{C_2H_5}{\underset{\mid}{CH}}-CH=CH_2$	H
21.)	H	$-CH_2-CH=CH-CH_2CH_2CH_3$	H
22.)	H	$-CH_2-CH_2-CH=CH-CH_2CH_3$	H
23.)	H	$-\underset{CH_3}{\underset{\mid}{CH}}-CH=CH-CH_2CH_3$	H
24.)	H	$-\underset{CH_3}{\underset{\mid}{CH_2}}-CH_2-CH=CH_2-CH_3$	H
25.)	H	$-\underset{CH_3}{\underset{\mid}{CH}}CH_2-CH_2CH_2=CH_2$	H
26.)	H		H
27.)	H		H
28.)	H		H
29.)	H		H

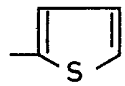
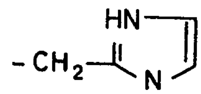
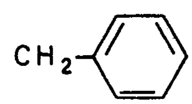
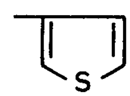
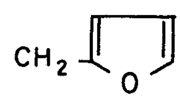
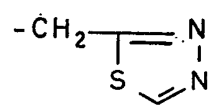
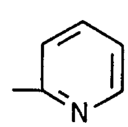
Compound	R	R^1	R^2
30.)	H		H
31.)	H		H
32.)	H		H
33.)	H		H
34.)	H		H
35.)	H		H
36.)	H		H
37.)	H		H
38.)	H		H
39.)	H		H
40.)	H		H
41.)	H		H

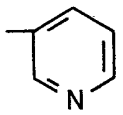
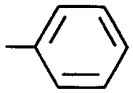
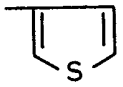
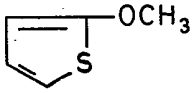
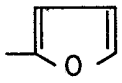
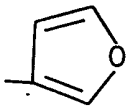
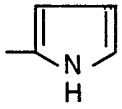
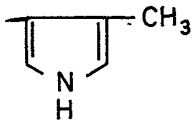
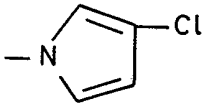
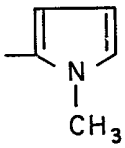
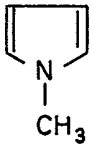
Compound	R	R^1	R^2
42.)	H		H
43.)	H		H
44.)	H		H
45.)	H	1-adamantyl	
46.)	H		H
47.)	H		H
48.)	H		H
49.)	H		H
50.)	H		H
51.)	H		H
52.)	H		H
53.)	H		H

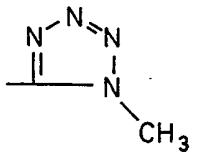
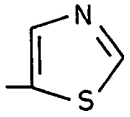
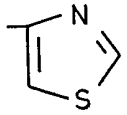
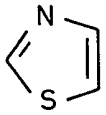
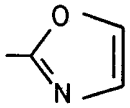
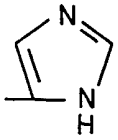
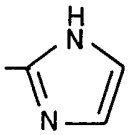
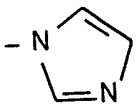
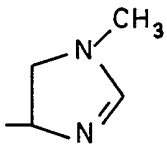
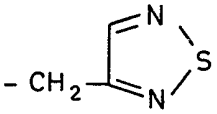
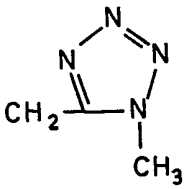
Compound	R	R^1	R^2
54.)	H		H
55.)	H		H
56.)	H		H
57.)	H		H
58.)	H		H
59.)	H		H
60.)	H		H
61.)	H	$-C_2H_5$	$-C_2H_5$
62.)	H	$-CH(CH_3)_2$	$-CH(CH_3)_2$
63.)	H	$-CH_2CH_2CH_3$	$-CH_2CH_2CH_3$
64.)	H	$-CH_3$	$-C_2H_5$
65.)	H	$-CH_3$	$-CH(CH_3)_2$
66.)	H	$-CH_3$	$-CH_2CH=CH_2$
67.)	H	$-CH_2CH=CH_2$	$-CH_2CH=CH_2$

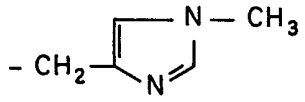
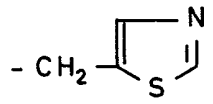
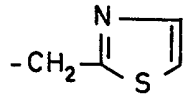
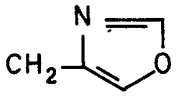
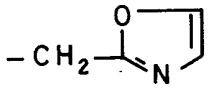
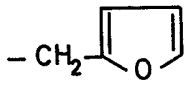
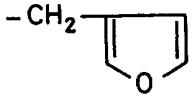
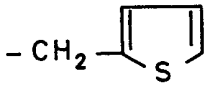
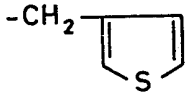
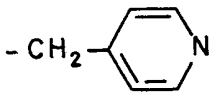
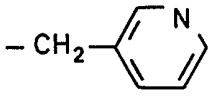
Compound	R	R^1	R^2
68.)	H	$-C(CH_3)_3$	$-CH_3$
69.)	H	$-CH_3$	$-\underset{\displaystyle CH_3}{\overset{\displaystyle |}{CH}}-C_2H_5$
70.)	H	$-C_2H_5$	$-CH(CH_3)_2$
71.)	H	$-CH_3$	$-\underset{\displaystyle CH_3}{\overset{\displaystyle |}{CH}}-CH=CH_2$
72.)	H	$-CH_3$	$-CH_2-CH(CH_3)_2$
73.)	H	$-CH_3$	$-CH_2CH_2CH_3$
74.)	H	$-CH_3$	$-CH_2C_6H_5$
75.)	H	$-CH_3$	$-C_6H_5$
76.)	H	$-CH_3$	
77.)	H	$-CH_3$	$-\underset{\displaystyle CH_3}{\overset{\displaystyle |}{CH_2}}-CH=CH_2$
78.)	H	$-CH_3$	
79.)	H	$-CH_3$	
80.)	H	$-CH_3$	
81.)	$-CH_3$	$-C_2H_5$	H
81.)	$-CH_3$	$-CH_2CH=CH_2$	H
83.)	$-CH_3$	$-CH(CH_3)_2$	H

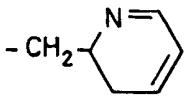
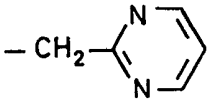
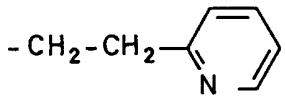
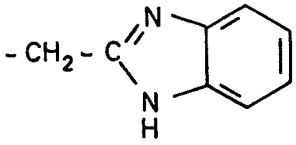
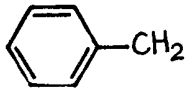
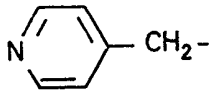
Compound	R	R^1	R^2
84.)	$CH=CH_2$	$-CH_3$	H
85.)	$-CH=CH_2$	$-C_2H_5$	H
86.)	$-CH=CH_2$	$-CH(CH_3)_2$	H
87.)	$-CH_3$	$-C(CH_3)_3$	H
88.)	$-CH_3$		H
89.)	$-CH_3$		H
90.)	$-CH_3$		H
91.)	$-CH_3$	$-CH_2C_6H_5$	H
92.)	$-CH_3$		H
93.)	$-CH_3$	$-\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH=CH_2$	H
94.)	$-CH_3$	$-CH_2-\underset{\displaystyle CH_3}{\underset{\vert}{C}}=CH_2$	H
95.)	$-CH_3$	$-\underset{\displaystyle CH_3}{\underset{\vert}{CH_2}}-CH_2CH_3$	H
96.)	$-CH=CH_2$	H	H
97.)	$-CH_3$		H
98.)	$-CH_3$	$-C_6H_5$	H

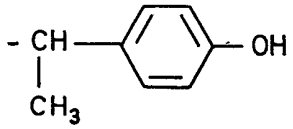
Compound	R	R^1	R^2
99.)	$-CH_3$		H
100.)	$-CH_3$		H
101.)	CH_3	CH_3	CH_3
102.)	CH_3	CH_3	C_2H_5
103.)	CH_3	CH_3	$-CH(CH_3)_2$
104.)	CH_3	CH_3	$CH_2CH=CH_2$
105.)	CH_3	C_2H_5	C_2H_5
106.)	CH_3	CH_3	$-\underset{CH_3}{\underset{\vert}{CH_2}}-CH=CH_2$
107.)	CH_3	CH_3	
108.)	CH_3	$-CH_2CH=CH_3$	
109.)	CH_3	C_2H_5	
110.)	CH_3	CH_3	
111.)	COOH	H	H
112.)	H		H

Compound	R	R^1	R^2
113.)	H		H
114.)	H		H
115.)	H		H
116.)		H	H
117.)	H		H
118.)		H	H
119.)	H		H
120.)	H		H
121.)		H	H
122.)	H		H
123.)		H	H

Compound	R	R^1	R^2
124.)		H	H
125.)	H		H
126.)	H		H
127.)	H		H
128.)	H		H
129.)		H	H
130.)	H		H
131.)	H		H
132.)		H	H
133.)	H		H
134.)	H		H

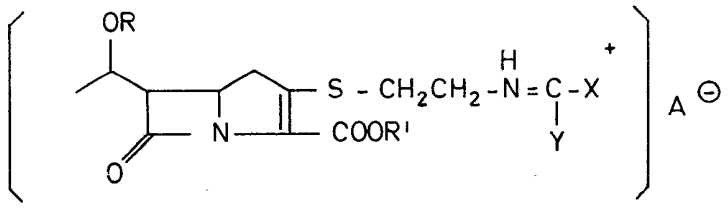
Compound	R	R^1	R^2
135.)	H		H
136.)	H		H
137.)	H		H
138.)	H		H
139.)	H		H
140.)	H		H
141.)	H		H
142.)	H		H
143.)	H		H
144.)	H		H
145.)	H		H

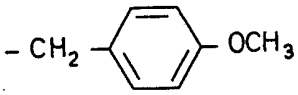
Compound	R	R^1	R^2
146.)	H		H
147.)	H		H
148.)	H		H
149.)	H		H
150.)		H	H
151.)		H	H
152.)	H	$-CH_2-O-CH_3$	H
153.)	H	$-CH_2CH_2-O-CH_3$	H
154.)	CH_3	$-CH_2CH_2-S-CH_3$	H
155.)	H	$-CH_2CH_2-OH$	H
156.)	H	$-CH_2CH(OCH_3)-CH_3$	H
157.)	H	$-CH_2CH_2-CH_2-C\equiv N$	H
158.)	H	$-CH_2CH_2CH-(OCH_3)_2$	H
159.)	H	$-CH_2-C(=O)-Ph$	H

Compound	R	R^1	R^2
160.)	H	$-CH(CH_2OH)-CH_2CH_3$	H
161.)	H	$-CH_2CH_2CONH_2$	H
162.)	H	$-CH_2COOC_2H_5$	H
163.)	H	$-C(CH_3)CH_2CH_2CH_2N(C_2H_5)_2$	H
164.)	H	$-CH_2CH_2-SH$	H
165.)	H		H
166.)	H	$-CH_2CH_2-N(CH_3)_2$	H
167.)	H	$-CH_2CH_2CH_2-Br$	H
168.)	H	$-CH_2CH_2CH-N(CH_3)_2$	H
169.)	H	$-CH_2CH_2-N(CH_3)_3$	H
170.)	NH_2	CH_3	H
171.)	NH_2	CH_3	CH_3
172.)	$NHCH_3$	CH_3	CH_3
173.)	$N(CH_3)_2$	CH_3	CH_3
174.)	NH_2	C_2H_5	H
175.)	NH_2	$-CH(CH_3)_2$	H
176.)	NH_2	$-CHCH=CH_2$	H
177.)	$NHCH_3$	$-CH(CH_3)_2$	H

Compound	R	R^1	R^2
178.)	$NHCH_3$	CH_3	H
179.)	NH_2	$N(CH_3)_2$	H
180.)	NH_2	$NHNH_2$	H
181.)	OCH_3	H	H
182.)	OCH_3	CH_3	H
183.)	OCH_3	CH_3	CH_3
184.)	OCH_3	C_2H_5	H
185.)	OCH_3	$CH(CH_3)_2$	H
186.)	OCH_3	H	H
187.)	SCH_3	CH_3	H
188.)	SCH_3	CH_3	CH_3
189.)	SCH_3	$CH(CH_3)_2$	H
190.)	$S-CH_2-CH=CH_2$	CH_3	H
191.)	$S-CH_2-Ph$	CH_3	H
192.)	$-SCH_2CH=CH_2$	H	H
193.)	SCH_2Ph	H	H
194.)	H	$-OH$	H
195.)	H	$-OCH_3$	H
196.)	CH_3	$-OH$	H
197.)	H	$-C\equiv N$	H
198.)	H	$-NHCH_3$	H

Compound	R	R^1	R^2
199.)	H	NH_2	H
200.)	CH_3	CH_3	NH_2
201.)	H	CH_3	$N(CH_3)_2$
202.)	CH_2Br	H	H
203.)	$-CH_2N(CH_3)_2$	H	H
204.)	$-CH_2S-CH_3$	H	H
205.)	$-\overset{O}{\overset{\|}{C}}-NH_2$	H	H
206.)	$-CH_2N(CH_3)_3$	H	H
207.)	$-C(CH_3)_3$	H	$-C(CH_3)_3$
208.)	$-CH\begin{matrix}CH_3\\ \vert \\ CH_3\end{matrix}$	CH_3	$-CH\begin{matrix}CH_3\\ \vert \\ CH_3\end{matrix}$
209.)	$-CH\begin{matrix}CH_3\\ \vert \\ CH_3\end{matrix}$	$-CH\begin{matrix}CH_3\\ \vert \\ CH_3\end{matrix}$	$-CH\begin{matrix}CH_3\\ \vert \\ CH_3\end{matrix}$
210.)	$-C(CH_3)_3$	$-C(CH_3)_3$	$-C(CH_3)_3$



Compound	R	R′	X	Y	A
211.)	H	$-CH_2CH=C(CH_3)_2$	NH_2	H	Cl
212.)	H		NH_2	H	Cl
213.)	H	$-CH_2-O-\overset{\overset{O}{\|\|}}{C}-C(CH_3)_3$	$NHCH_3$	H	HSO_4
214.)	H	$-CH_2-O-\overset{\overset{O}{\|\|}}{C}-C(CH_3)_3$	NH_2	CH_3	CH_3COO
215.)	H	$-CH_2CH_2-CH=CH_2$	$NHCH(CH_3)_2$	H	Cl
216.)	H	$-CH_2CH_2-S-CH_3$	$NHCH_3$	CH_3	H_2PO_4
217.)	H	$-CH_2-O-\overset{\overset{O}{\|\|}}{C}-CH_3$	$NHCH_3$	CH_3	Cl
218.)	H	$-CH_2-\overset{\overset{O}{\|\|}}{C}-Ph$	NH_2	H	Cl
219.)	H	–5 indanyl	$N(CH_3)_2$	H	Cl
220.)	H	–phthalidyl	$-CH_2CH=CH_2$	H	Cl
221.)	SO_3-	Na	NH_2	H	–
222.)	PO_3H_2-	$-CH_2O\overset{\overset{O}{\|\|}}{C}CH(CH_3)_2$	NH_2	CH_3	–
223.)	SO_3-	$-CH_2-CH=C(CH_3)_2$	$NHCH_3$	H	H
224.)	PO_3H_2-	Na	$NHCH(CH_3)_2$	H	–

Compounds 221 to 224 form internal salt with the imido nitrogen.

Preparation of Pharmaceutical Compositions

Example 54.

One unit dosage form is made by mixing 120 mg. of N-acetimidoyl thienamycin (product of Example 12) with 20 mg. of lactose and 5 mg. of magnesium stearate and placing the 145 mg. mixture into a No. 3 gelatin capsule. Similarly, by using more of the active ingredient and less lactose, other dosage forms can be put up in No. 3 gelatin capsules and should it be necessary to mix more than 145 mg. of ingredients together, larger capsules such as compressed tablets and pills can also be prepared. The following Examples are illustrative of the preparation of pharmaceutical formulations:

Example 55.

TABLET	PER TABLET
N-acetimidoyl thienamycin	125 mg.
Cornstarch, U.S.P.	6 mg.
Dicalcium Phosphate	192 mg.
Lactose, U.S.P.	190 mg.

The active ingredient is blended with the di-calcium phosphate, lactose and about half of the cornstarch. The mixture is then granulated with a 15% cornstarch paste (6 mg.) and rough-screened. It is dried at 45°C. and screened again through No. 16 screens. The balance of the cornstarch and the magnesium stearate is added and the mixture is compressed into tablets, approximately 0.5 inch in diameter each weighing 800 mg.

Example 56.

PARENTERAL SOLUTION

Ampoule:

N-acetimidoyl thienamycin	500 mg.
Sterile water	2 ml.

Example 57.

OPTHALMIC SOLUTION

N-acetimidoyl thienamycin	100 mg.
Hydroxypropylmethyl cellulose	5 mg.
Sterile Water to	1 ml.

Example 58.

OTIC SOLUTION

N-acetimidoyl thienamycin	100 mg.
Benzalkonium chloride	0.1 mg.
Sterile Water to	1 ml.

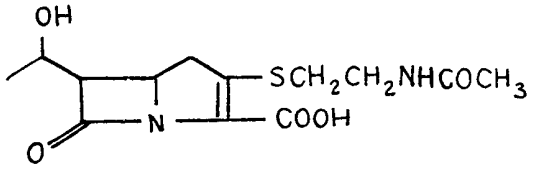
Example 59.

TOPICAL OINTMENT

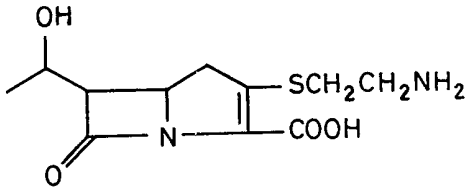
N-acetimidoyl thienamycin	100 mg.
Polyethylene glycol 4000 U.S.P.	400 mg.
Polyethylene glycol 400 U.S.P.	1.0 gram

The active ingredient in the above formulations may be administered alone or in combination with other biologically active ingredients as, for example, with other antibacterial agents such as lincomycin, a penicillin, streptomycin, novobiocin, gentamycin, neomycin, colistin and kanamycin, or with other therapeutic agents such as probenecid.

As already mentioned above, position isomers of thienamycin as well as thienamycin itself, either alone or as mixtures, may serve as starting materials in the preparation of the compounds of the present invention. Some of these isomers are obtainable from natural products of fermentation as described and claimed in the specifications of our copending application No. 48235/76 (Serial No. 1,561,109). See in particular Examples 6 and 7 of that specification, which describes the preparation of Antibiotics $890A_1$ and $890A_3$, which have the formula:



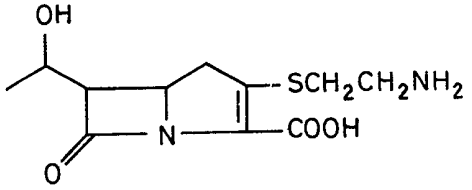
These compounds can be treated to cleave the N-acetyl group to give the corresponding free base of formula:



I

By total synthesis all isomers can be made available (below) as a mixture of 4 diastereoisomers which possess antibacterial activity and which are amenable to resolution by conventional techniques. The 4 diastereoisomers (2 *cis*, 2 *trans*) are separable by chromatography. Resolution of any given *d/l* pair with optically active acids or bases proceeds according to conventional techniques. It should be noted that the absolute configuration of the first-identified starting material (I) is 5R 6S 8R.

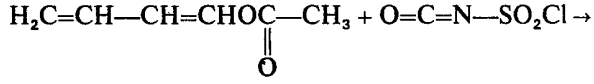
Preparation of Thienamycin by Total Synthesis

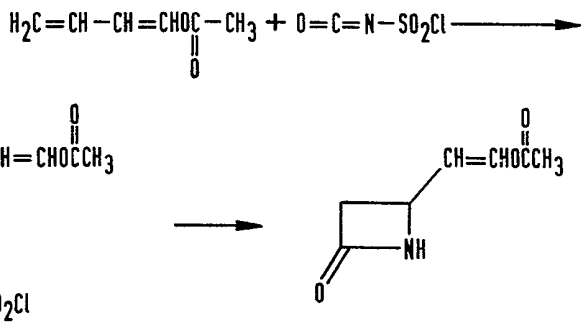


I

Step A:

Preparation of 4-(2-acetoxyvinyl)azetidine-2-one





A solution of 1.0 ml distilled chlorosulfonylisocyanate (1.65 g; 11.7 mmoles) in 2.5 ml anhydrous diethyl ether is cooled under N_2 in a –20°C bath.

A solution of 2.5 g 1-acetoxybutadiene (22 mmoles) in 2.5 ml anhydrous ether is similarly cooled under N_2 in a –20°C bath.

The chlorosulfonylisocyanate solution is added dropwise to the acetoxybutadiene solution by means of a Teflon tube immersed in the CSI solution and pressurized with N_2. The addition takes 10 minutes. Little or no color is seen and the reaction is stirred at –20°C for 0.5 hour. The solution is clear and has a light yellow color.

A solution of 2 g sodium sulfite and 5 g K_2HPO_4 in 20 ml H_2O is prepared during the above 0.5 hour reaction time and is cooled in an ice bath; 20 ml of ether is added and the mixture is vigorously stirred in an ice bath. At the end of the 30 minute reaction time, the reaction mixture is transferred, again using N_2 pressure and the Teflon tube, from the reaction flask which is maintained in the –20°C bath, to the vigorously stirred hydrolysis mixture. Rapid dropwise addition is completed in 5 minutes. The hydrolysis is allowed to continue for 5 additional minutes. the hydrolysis mix has a pH of 6—8, preferably pH 8.

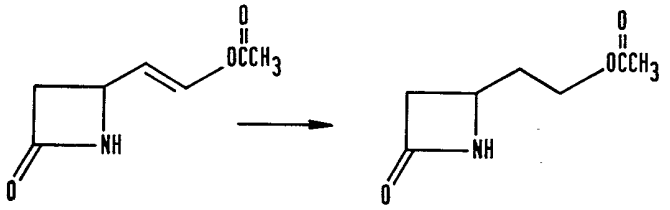
The phases are separated, leaving a yellowish-orange gum with the aqueous phase. The ether phase is dried directly with $MgSO_4$. The aqueous/gum phase is extracted three more times with 50 ml portions of ether, each being added to the initial ether/$MgSO_4$.

The dried extracts are filtered and concentrated under a N_2 stream to 5 ml; a portion of the product is crystalline at this stage.

A column of 10 g Baker silica gel, packed in ether is prepared, and the ether concentrate is applied to the top and run in. The flask/solids are rinsed three times with 2 ml ether, each being pipetted off and run into the column. Elution is then begun with ether. The first 25 ml is primarily void volume. The next five 10 ml fractions are collected followed by three 50 ml fractions, and all are reduced in volume under a N_2 stream. The product crystallizes from fractions 4—6, with traces in 3 and 7. Fractions 1—3 contain a yellowish sharp-smelling material which resinifies on standing. Yield: 100 mg as a mixture of the *cis* and *trans* isomers.

Step B:

Preparation of 4-(2-Acetoxyethyl)-2-Azetidinone

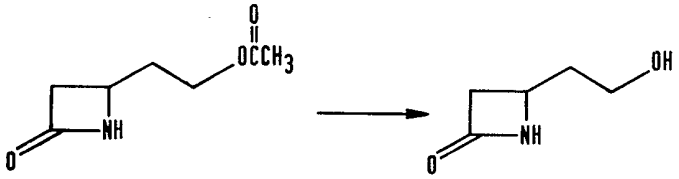


A solution of 4-(2-acetoxyvinyl)-2-azetidinone (10.0 g, 0.065 mole) in 200 ml ethyl acetate containing 100 mg of 10% Pd/C is hydrogenated on a Parr shaker at 25°C under 40 psi hydrogen for 15 minutes. The mixture is filtered through a bed of Supercel and washed with additional ethyl acetate. The combined filtrate is evaporated *in vacuo* to give 4-(2-acetoxyethyl)-2-azetidinone (10.0 g) as a crystalline solid. Recrystallization from ether affords white crystals: M.P. 44—7°; ir $(CHCl_3)_\mu$ 5.66, 5.74; nmr $(CDCl_3)\tau$ 3.44 (broad s, 1, NH), 5.82 (m, 2, CH_2OCOCH_3), 6.29 (m, 1, C—4H), 6.87 (1/2 AB pattern further split in four by C—4H and NH, 1,

J_{gem} = 12.8Hz, J = 4.5H J_{NH} = 1.9 Hz, 7.38 (1/2 AB pattern further split in four by C—4H and NH, 1, J_{gem} = 12.8Hz, J = 2.3Hz, J_{NH} = 1.0Hz), 7.93 and 8.02 (s on m, total 5, $OCOCH_3$ and $CH_2CH_2OCOCH_3$, respectively).

Step C:

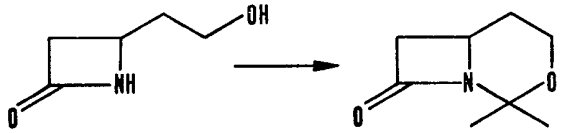
Preparation of 4-(2-Hydroxyethyl)-2-Azetidinone



Under nitrogen at 0°, a solution of 4-(2-acetoxyethyl)-2-azetidinone (2.24 g, .014 mole) in 25 ml anhydrous methanol is treated with a solution of sodium methoxide (77 mg, 1.4 mmoles) in 5 ml anhydrous methanol. After stirring for 1 hour, the solution is neutralized with glacial acetic acid. Removal of the methanol *in vacuo* gives crude 4-(2-hydroxyethyl)-2-azetidinone as an oil. The product is purified by chromatography on silica gel eluting with 10% MeOH/$CHCl_3$ to give 1.55 g of the alcohol: m.p. 50°; ir ($CHCl_3$)μ 5.67; nmr ($CDCl_3$)τ 3.20 (broad s, 1, NH), 6.24 and 6.28 (m on t, total 3, C—4H and CH_2OH respectively), 6.90 (broad s on 1/2 AB pattern further split in four by C—4H and NH, total 2, OH and C—3H respectively, J_{gem} = 13.OHz, J_{vic} = 4.2Hz, J_{NH} = 1.6Hz), 7.42 (1/2 AB pattern further split in four by C—4H and NH, 1, C—3H, J_{gem} = 13.OHz, J_{vic} = 2.2Hz, J_{NH} = 1.1Hz), 8.16 (m, 2, CH_2CH_2OH).

Step D:

Preparation of 8 - Oxo - 2,2 - dimethyl - 3 - oxa - 1 - azabicyclo[4.2.0]octane



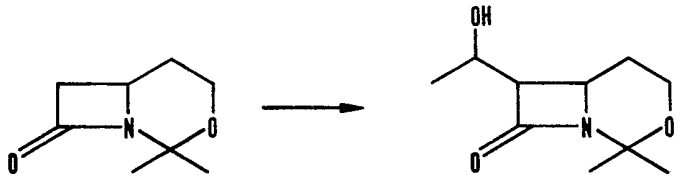
A solution of 4-(2-hydroxyethyl)-2-azetidinone (1.87 g, .016 mole) and 2,2-dimethoxypropane (1.69 g, .016 mole) in 25 ml anhydrous methylene chloride is treated with boron trifluoride etherate (.201 ml, .002 mole) at 25°C. The resulting solution is stirred for ten minutes. Removal of the solvent under reduced pressure gives an oil (2.5 g). Chromatography of the crude product on silica gel using 2:1 ethyl acetate/benzene as eluting solvent gives 8 - oxo - 2,2 - dimethyl - 3 - oxa - 1 - azabicyclo[4.2.0]octane (1.59 g) as a crystalline solid. Recrystallization from ether/hexane gives product of m.p. 60—1°.

ir ($CHCl_3$)μ:
5.73 (β-lactam)

nmr ($CDCl_3$)τ:
6.02—6.28, m, 2H, C—4 methylene
6.22—6.62, m, 1H, C—6 methine
6.90, dd, 1H, $J_{7,7}$ = 14Hz, $J_{6,7}$ = 4.5Hz
C—7 proton *cis* to C—6H
7.47, dd, 1H, $J_{7,7}$ = 14Hz, $J_{6,7}$ = 2Hz
C—7 proton *trans* to C—6H
7.82—8.68, m, 2H, C—5 methylene
8.23, s, 3H } C—2 methyls
8.57, s, 3H }

Step E:

Preparation of 8 - oxo - 2,2 - dimethyl - 7α and β - (1 - hydroxyethyl) - 3 - oxa - 1 - azabicyclo[4.2.0]octane



To a solution of 1.1 equivalents of freshly prepared lithium diisopropylamide in anhydrous tetrahydrofuran under a nitrogen atmosphere at –78° is added a solution of 8 - oxo - 2,2 - dimethyl - 3 - oxa - 1 - azabicyclo[4.2.0]octane in anhydrous tetrahydrofuran which has been cooled to –78°C. After two minutes, the resulting lithium enolate is treated with excess acetaldehyde. The solution is stirred for 30 minutes at –78° and then poured into water. The aqueous phase is saturated with sodium chloride and extracted with ethyl acetate. The combined ethyl acetate solutions are dried over magnesium sulfate and filtered. The filtrate is evaporated under reduced pressure to give the crude product. Purification by chromatography on silica gel using ethyl acetate/benzene gives 8 - oxo - 2,2 - dimethyl - 7α and β - (1 - hydroxyethyl) - 3 - oxa - 1 - azabicyclo[4.2.0]octane.

Data for 8 - oxo - 2,2 - dimethyl - 7β - (1 - hydroxyethyl) - 3 - oxa - 1 - azabicyclo[4.2.0]octane:

ir (CH_2Cl_2)μ:
5.72μ (β-lactam)

nmr ($CDCl_3$)τ:
5.53—6.43, m, 4H, C—4 methylene + C—6 methine + C—9 methine
6.90, dd on broad s, 2H, $J_{7,9} = 9$Hz
$J_{6,7} = 5.5$Hz, C—7 methine + O*H*
7.70—8.83, m, 2H, C—5 methylene
8.27, s, 3H } C—2 methyl
8.60, s, 3H }
8.78, d, 3H, $J_{9,10} = 6.5$Hz, C—10 methyl

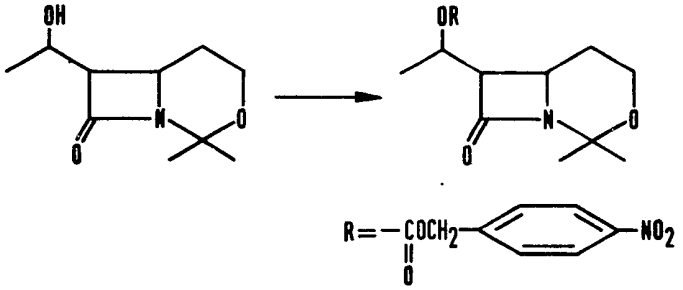
Data for 8 - oxo - 2,2 - dimethyl - 7α - (1 - hydroxyethyl) - 3 - oxa - 1 - azabicyclo[4.2.0]octane:

ir ($CHCl_3$)μ:
2.9 broad O—H
5.73 β-lactam

nmr (acetone—d_6)δ:
4.23—3.33, m, C—9 methine + C—4 methylene + C—6 methine
3.33, broad s, O*H*
2.83, dd, J = 2Hz, 6Hz } C—7 methine
2.67, dd, J = 2Hz, 8Hz }
1.93—1.63, m, C—5 methylene
1.63, s } C—2 methyls
1.40, s }
1.23, d, J = 6.5Hz, C—10 methyl

Step F:

Preparation of 8 - Oxo - 2,2 - dimethyl - 7α - (1 - *p* - nitrobenzylcarbonyldioxyethyl) - 3 - oxa - 1 - azabicyclo[4.2.0]octane



Under anhydrous conditions at 0°C. a solution of 8 - oxo - 2,2 - dimethyl - 7α - (1 - hydroxyethyl) - 3 - oxa - 1 - azabicyclo[4.2.0]octane (60 mg, .302 mmole) in 0.6 ml ether is treated with powdered potassium hydroxide (19 mg, .332 mmole). After a period of 15 minutes, *p*-nitrobenzyl chloroformate (65 mg, .302 mmole) is added to the reaction mixture. Stirring is continued at 25°C for an additional 15 hours. The mixture is partitioned between 1M pH 7 phosphate buffer and more ether. The ether phase is washed with water and brine, dried over magnesium sulfate and filtered. Evaporation of the filtrate under reduced pressure gives 67 mg of a colorless oil. Purification by preparative thick-layer chromatography on silica gel developing with 1:9 ethyl acetate/benzene gives 8 - oxo - 2,2 - dimethyl - 7α - (1 - *p* - nitrobenzylcarbonyldioxyethyl) - 3 - oxa - 1 - azabicyclo[4.2.0]octane (40 mg) as a mixture of diastereomers.

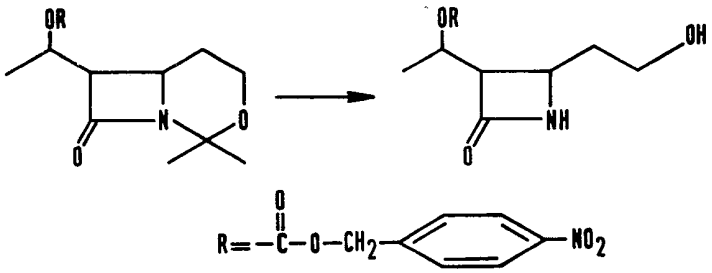
ir (CH_2Cl_2)μ:
5.68 (β-lactam and carbonate), 6.19 and 6.54 (nitro)

nmr($CDCl_3$):
1.67, d, 2H, Ar*H*
2.37, d, 2H, Ar*H*
4.67, s, 2H, ArCH_2
4.67—5.22, m, CH_3CH
5.98—6.25, m, 2H, C—4 methylene
6.25—6.62, m, 1H, C—6 methine
6.75—7.12, m, 1H, C—7 methine
7.75—8.83, m, 2H, C—5 methylene
8.22, s, 3H, C—2 methyl
8.50—8.58, m, 5H, C—2 methyl + CH_3CH

The 7β-diastereoisomers or the 7α and β-mixture are obtained in an analogous manner.

Step G:

Preparation of Cis and Trans - 3 - (1 - p - nitrobenzylcarbonyldioxyethyl) - 4 - (2 - hydroxyethyl) - 2 - azetidinone



8 - Oxo - 3 - oxa - 2,2 - dimethyl - 7α - (1 - *p* - nitrobenzylcarbonyldioxyethyl) - 1 - azabicyclo[4.2.0]octane (1.0 g) is dissolved in 8 ml acetic acid and 2 ml water and heated at 65°C for 1.25 hours. The acetic acid and water are removed under reduced pressure and the residue is taken up in benzene and evaporated to

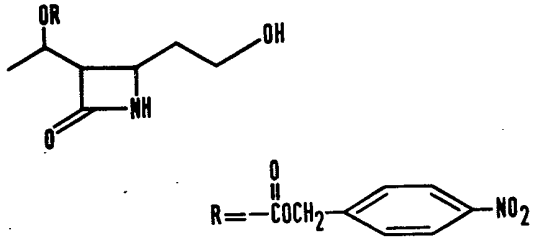
give *trans* - 3 - (1 - *p* - nitrobenzylcarbonyldioxyethyl) - 4 - (2 - hydroxyethyl) - 2 - azetidinone as a mixture of diastereoisomers.

ir (CH_2Cl_2)μ:
5.67 (β-lactam), 5.72 shoulder, 6.20 and 6.57 (nitro)

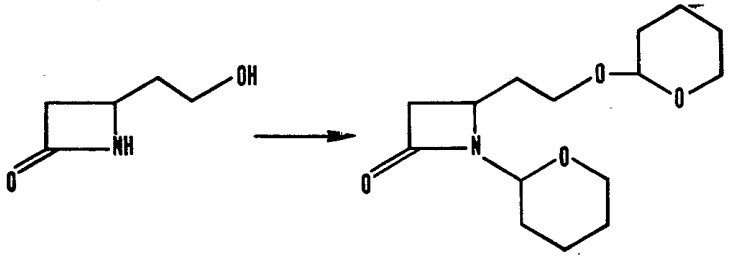
nmr ($CDCl_3$):
1.73, d, 2H, J = 8.5 Hz, Ar*H*
2.43, d, 2H, J = 8.5 Hz, Ar*H*
3.63, broad s, 1H, N*H*
4.73—5.13, m, 1H, CH_3CH
4.72, s, 2H, ArCH_2
6.07—6.53, m, 1H, C—4 methine
6.23, t, 2H, J = 5.5 Hz, CH_2OH
6.73—6.93, m, 1H, C—3 methine
7.63—8.97, m, 3H, CH_2CH_2OH
8.53, d, J = 6.5 Hz, CH_3CH

The *cis* diastereoisomers or the *cis-trans* mixture are obtained in an analogous manner.

Steps D', E', F' and G' as alternative to Steps D, E, F, and G for the preparation of 3 - (1 - *p* - nitrobenzylcarbonyldioxyethyl) - 4 - (2 - hydroxyethyl)azetidinone



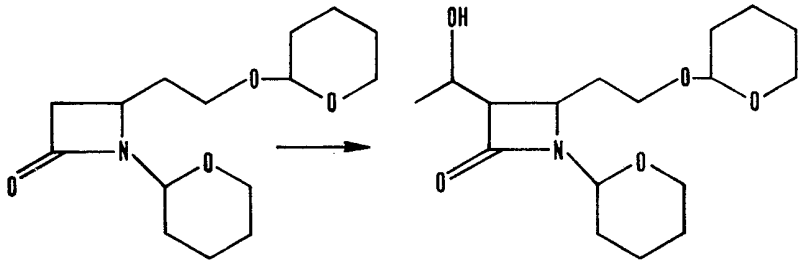
Steps D', E', F' and G'
Preparation of 1 - (2 - Tetrahydropyranyl) - 4 - [2 - (2 - tetrahydropyranyl)-oxyethyl] - 2 - azetidinone



Under nitrogen and at 25°C, a solution of 4 - (2 - hydroxyethyl) - 2 - azetidinone (62 mg, .539 mmole) in .5 ml of anhydrous *p*-dioxane is treated with 2,3-dihydropyran (.98 ml, 1.08 mmoles) and *p*-toluenesulfonic acid monohydrate (19 mg, .10 mmole). The resulting solution is stirred for a period of 60 minutes and then partitioned between 10 ml of .5M pH7 phosphate buffer and 10 ml of ethyl acetate. The aqueous phase is extracted a second time with ethyl acetate. The combined ethyl acetate solutions are washed with brine, dried over magnesium sulfate and filtered. The filtrate is evaporated under reduced pressure to give 216 mg of crude product. Purification by preparative thick-layer chromatography developing with ethyl acetate gives 80 mg of 1 - (2 - tetrahydropyranyl) - 4 - [2 - (2 - tetrahydropyranyl)oxyethyl] - 2 - azetidinone as an oil.

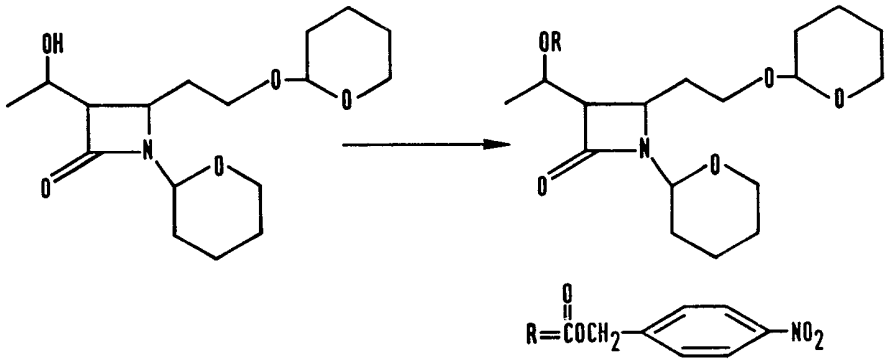
nmr ($CDCl_3$)τ:
5.13—5.60, m, OC*H*
5.83—6.85, m, C—4H + OCH_2
6.95, dd, J = 5Hz and 15 Hz } C—3 methylene
7.35, dd, J = 3Hz and 15 Hz }
7.62—8.95, m, $CHCH_2CH_2CH_2CH_2$ + $CHCH_2CH_2O$

Preparation of *Cis* and *Trans* - 1 - (2 - tetrahydropyranyl) - 3 - (1 - hydroxyethyl) - 4 - [2 - (2 - tetrahydropyranyl)oxyethyl] - 2 - azetidinone



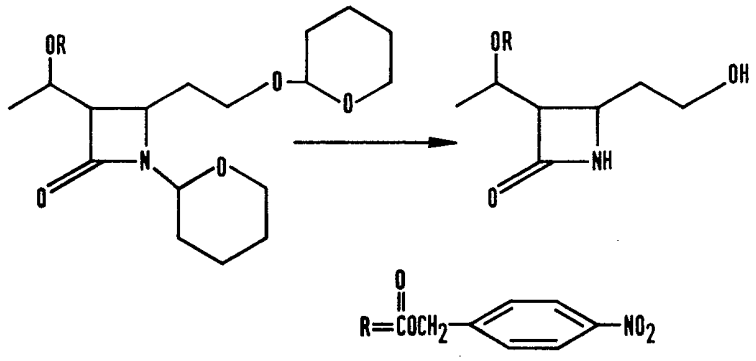
Following the procedure described for the preparation of 8 - oxo - 2,2 - dimethyl - 7α and β - (1 - hydroxyethyl) - 3 - oxa - 1 - azabicyclo[4.2.0]octane from 8 - oxo - 2,2 - dimethyl - 3 - oxa - 1 - azabicyclo[4.2.0]octane and using 1 - (2 - tetrahydropyranyl) - 4 - [2 - (2 - tetrahydropyranyl)oxyethyl] - 2 - azetidinone one obtains a diastereomeric mixture of both *cis* and *trans* - 1 - (2 - tetrahydropyranyl) - 3 - (1 - hydroxyethyl) - 4 - [2 - (2 - tetrahydropyranyl) - oxyethyl] - 2 - azetidinone.

Preparation of *Cis* and *Trans* - 1 - (2 - tetrahydropyranyl) - 3 - (1 - *p* - nitrobenzylcarbonyldioxyethyl) - 4 - [2 - (2 - tetrahydropyranyl)oxyethyl] - 2 - azetidinone



Following the procedure described for the preparation of 8 - oxo - 2,2 - dimethyl - 7α - (1 - *p* - nitrobenzylcarbonyldioxyethyl) - 3 - oxa - 1 - azabicyclo[4.2.0]octane from 8 - oxo - 2,2 - dimethyl - 7α - (1 - hydroxyethyl) - 3 - oxa - 1 - azabicyclo[4.2.0]octane and using *trans* - 1 - (2 - tetrahydropyranyl) - 3 - (1 - hydroxyethyl) - 4 - [2 - (2 - tetrahydropyranyl)oxyethyl] - 2 - azetidinone there is obtained *trans* - 1 - (2 - tetrahydropyranyl) - 3 - (1 - *p* - nitrobenzylcarbonyldioxyethyl) - 4 - [2 - (2 - tetrahydropyranyl)oxyethyl] - 2 - azetidinone. The *cis* diastereoisomers are obtained in an analogous manner.

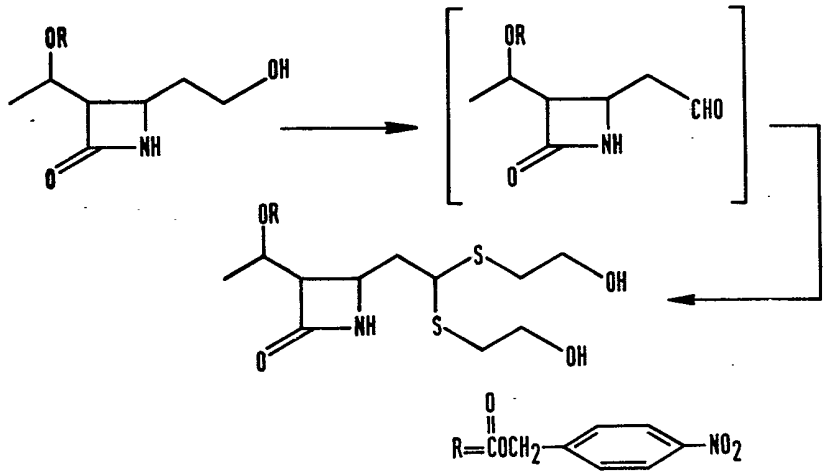
Preparation of *Cis* and *Trans* - 3 - (1 - *p* - nitrobenzylcarbonyldioxyethyl) - 4 - (2 - hydroxyethyl) - 2 - azetidinone



A solution of *trans* - 1 - (2 - tetrahydropyranyl) - 3 - (1 - *p* - nitrobenzylcarbonyldioxyethyl) - 4 - [2 - (2 - tetrahydropyranyl)oxyethyl] - 2 - azetidinone in methanol at 25°C. is treated with .1 molar equivalent of *p*-toluenesulfonic acid monohydrate. The solution is stirred for a period of 2 hours and then neutralized with 1M pH7 phosphate buffer. The product is extracted into ethyl acetate. The ethyl acetate solution is washed with brine, dried over magnesium sulfate and filtered. The filtrate is evaporated under reduced pressure to give *trans* - 3 - (1 - *p* - nitrobenzylcarbonyldioxyethyl) - 4 - (2 - hydroxyethyl) - 2 - azetidinone. The *cis*diastereoisomers are obtained in an analogous manner.

Step H:

Preparation of *Cis* and *Trans* - 3 - (1 - *p* - nitrobenzylcarbonyldioxyethyl) - 4 - [2,2 - bis(2 - hydroxyethyl)thioethyl] - 2 - azetidinone



Under nitrogen at 25°C, a mixture of anhydrous pyridine (.146 ml, 1.81 mmoles) and anhydrous, powdered chromium trioxide (92 mg, .916 mmole) in 8 ml anhydrous acetonitrile is stirred for a period of 30 minutes. To the resulting dark brown solution is added 250 mg of dry Super cel followed by a solution of *trans* - 3 - (1 - *p* - nitrobenzylcarbonyldioxyethyl) - 4 - (2 - hydroxyethyl) - 2 - azetidinone (186 mg, .550 mmole) in 1 ml anhydrous acetonitrile. After stirring for a period of 1 hour, the reaction mixture is filtered through a mixed, packed bed of 2 g each of the silica gel and magnesium sulfate. The bed is washed repeatedly with a total of 30 ml of additional acetonitrile. The filtrate is concentrated under reduced pressure at 25°C. to a volume of 3 ml. By thin-layer chromatography (silica gel; ethyl acetate/benzene 2:1) this solution contains a product ($R_f = .38$) less polar than the starting material ($R_F = .21$).

The acetonitrile solution of *trans* - 3 - (1 - *p* - nitrobenzylcarbonyldioxyethyl) - 4 - (2 - oxoethyl) - 2 - azetidinone prepared above is, under nitrogen and at 0°, treated with 2-mercaptoethanol (0.386 ml, 5.5 mmoles) followed immediately by boron trifluoride etherate (0.176 ml, 1.43 mmoles). After stirring for a period of 15 minutes, this solution is partitioned between aqueous dipotassium hydrogen phosphate (1.5 g. in 4 ml of water) and 12 ml of ethyl acetate. The aqueous phase is extracted a second time with ethyl acetate. The combined ethyl acetate solutions are washed with brine, dried over magnesium sulfate and filtered. The filtrate is evaporated under reduced pressure to give 229 mg of an oil. The product is purified by preparative thick-layer chromatography on silica gel developing with ethyl acetate to give 118 mg of *trans* - 3 - (1 - *p* - nitrobenzylcarbonyldioxyethyl) - 4 - [2,2 - bis(2 - hydroxyethyl)thioethyl] - 2 - azetidinone as a colorless oil.

ir (CH_2Cl_2)μ:
5.75 (5.79 shoulder) β-lactam and carbonate
6.20, 6.55 nitro

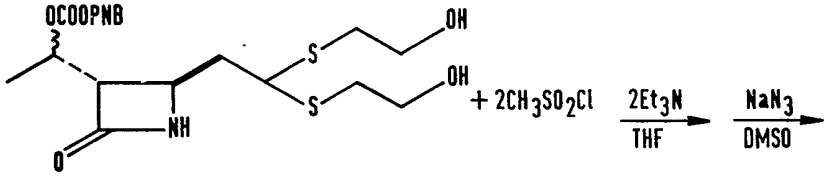
nmr (acetone-d_6)τ:

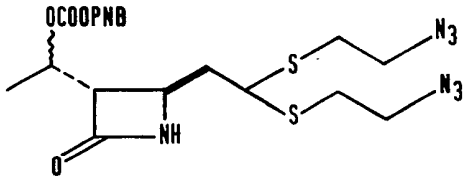
1.70, d, J = 8.5 Hz, 2H, Ar*H*
2.28, d, J = 8.5 Hz, 2H, Ar*H*
2.48—2.88, m, 1H, N*H*
4.63, s, ArCH_2 } 3H
4.63—5.12, m, CH_3CH }
5.80, t, J = 7 Hz, CH_2CH (S, S) } 13H
5.80—7.45, m, C—4H + C—3H + SCH_2CH_2OH }
7.63—8.33, m, 2H, CH_2CH
8.53, d, J = 6.5 Hz 3H, CH_3CH

The *cis* diastereoisomers are obtained in an analogous manner. Alternatively, the mixed diastereoisomers are obtained when the starting materials comprise a mixture of the diastereoisomers.

Step I:

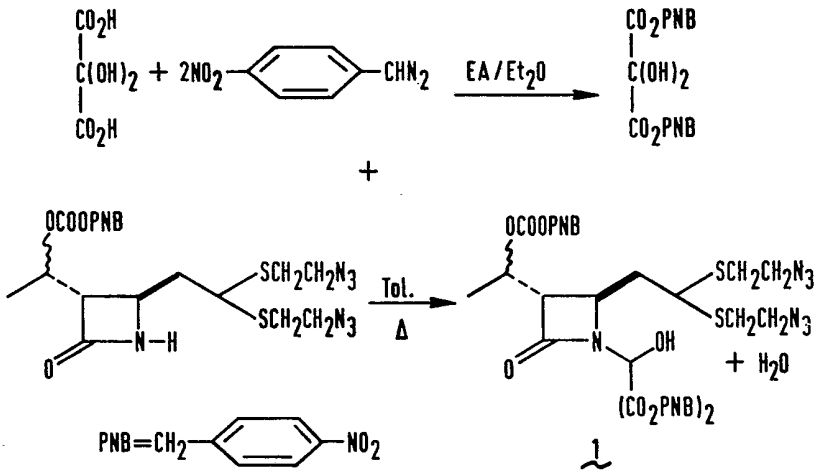
Preparation of Trans - 3 - (1 - p - nitrobenzylcarbonyldioxyethyl) - 4 - [2,2 - bis-(2 - azidoethyl)thioethyl] - 2 - azetidinone





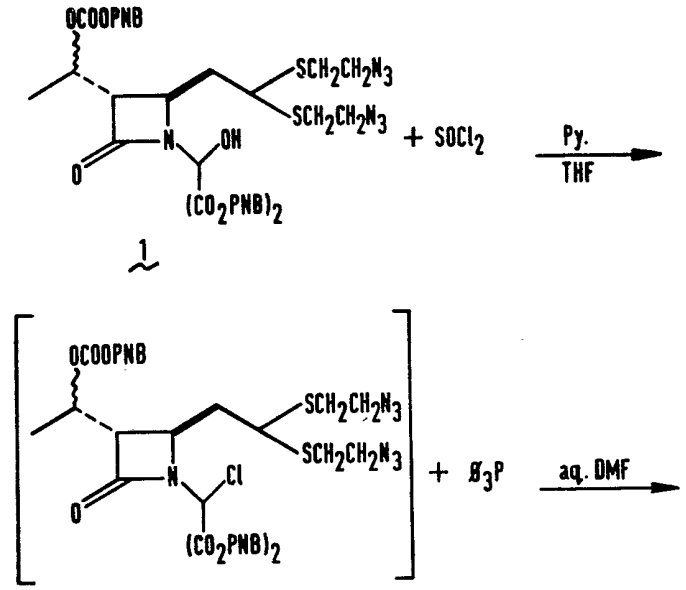
To a solution of 211 mg (mw = 474; 0.445 mmole) *trans* - 3 - (1 - p - nitrobenzylcarbonyldioxyethyl) - 4 - [2,2 - bis(2 - hydroxyethyl)thioethyl] - 2 - azetidinone in 5 ml tetrahydrofuran (THF) (distilled from lithium aluminum hydride) at 0°C is added 103 mg mesyl chloride (mw = 114; 0.904 mmole) in 1 ml THF followed immediately by 134 μl triethylamine (mw = 101; ρ = 0.729; 0.967 mmole). The reaction mixture is stirred for 1 hour under N_2. The triethylamine hydrochloride is filtered under N_2 washing with a few milliliters additional THF. The clear colorless filtrate is concentrated under a stream of N_2 followed by pumping under high vacuum for 10 minutes. The dimesylate is immediately dissolved in 5 ml DMSO (distilled from CaH_2 at 8 mm and stored over 4A Linde Molecular sieves) in the presence of 347 mg NaN_3 (mw = 65; 5.34 mmole). After stirring overnight under N_2, 10 ml H_2O and 20 ml ethyl acetate (EA) are added. The layers are separated, and the aqueous one is washed three times with 10 ml EA, each organic layer then being backwashed with 10 ml H_2O and 10 ml brine. The combined EA layers are dried over anhydrous $MgSO_4$, filtered and concentrated under a N_2 stream to give the crude diazide. Preparative thin layer chromatography on silica gel yields *trans* - 3 - (1 - p - nitrobenzylcarbonyldioxyethyl) - 4 - [2,2 - bis(2 - azidoethyl)thioethyl] - 2 - azetidinone. The *cis* diastereoisomers or the *cis-trans* mixture are obtained in an analogous manner.

Step J:

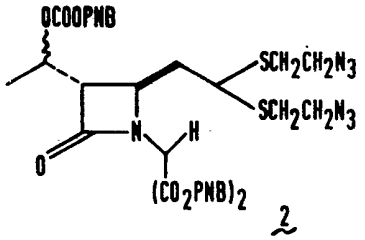


A freshly prepared (H. Davies and M. Schwarz, J.O.C., *30*, 1242 (1965)) solution of *p*-nitrophenyldiazomethane (29 mmole) in 150 ml of ether is added with stirring to a solution of 1.0 g oxomalonic acid, monohydrate (mw = 136; 7.35 mmole) in 50 ml ethylacetate (EA) at 0°C. After 2 1/2 hours the yellow solution is concentrated on a rotary evaporator with mild heating to approximately half the volume, dried over anhydrous sodium sulfate, filtered and concentrated as above to an oil. To the crude p-nitrobenzyl ester in 50 ml toluene (Tol.) is added 3.54 g of *trans* - 3 - (1 - *p* - nitrobenzylcarbonyldioxyethyl) - 4 - [2,2 - bis(2 - azidoethyl)-thioethyl] - 2 - azetidinone (mw = 524; 6.75 mmole). With stirring the reaction mixture is heated in an oil bath allowing approximately 1/3 of the toluene to boil off. Toluene (dried over 3A 1/16" Linde Molecular sieves) is added to again bring the volume to 50 ml, and the azeodrying process is repeated three additional times. The solution is then refluxed under N_2 for one hour, the azeodrying process repeated a final time, and refluxing continued for an additional hour. Concentration of the resulting solution under a stream of N_2 yields crude 1. The crude material is chromatographed on silica gel to give 1. The *cis* diastereoisomers or the *cis-trans* mixture is obtained in an analogous manner.

Step K:



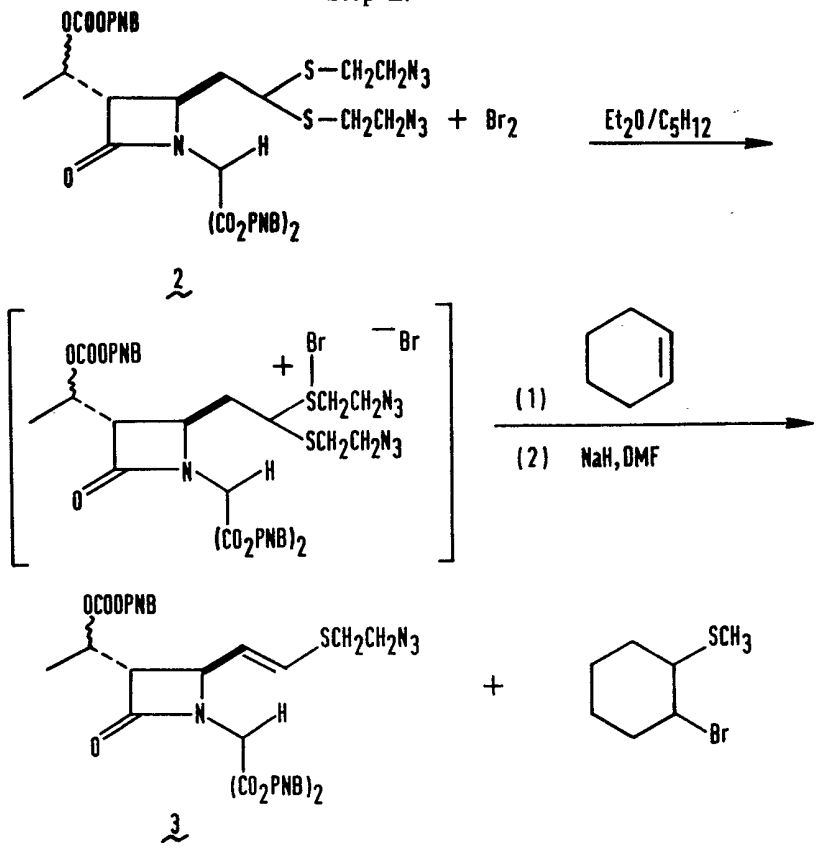
Step K — Continued



2

To a solution of 2.80 g 1 (mw = 912; 3.07 mmole) in 35 ml THF (distilled from lithium aluminum hydride) at –20°C is added 0.3 ml pyridine (mw = 79; ρ = .982; 3.73 mmole) (distilled from NaH and stored over 4A Linde Molecular sieves). With stirring under N_2, 0.438 g thionyl chloride (mw = 119; 3.68 mmole) in 1 ml THF is added dropwise. The reaction mixture is stirred under N_2 for 5 minutes at –20°C, then 1/2 hour at 0°C, and finally 1 hour at 25°C. The pyridine hydrochloride is filtered under N_2 and washed twice with benzene (dried over 3A 1/16″ Linde Molecular sieves). The combined filtrate and washings are concentrated under a N_2 stream, slurried in a small volume of benzene with anhydrous $MgSO_4$, filtered under N_2 and then concentrated under a N_2 stream. Pumping on high vacuum for 1/2 hour yields an oil. To this freshly prepared chloro compound is added with stirring 0.885 g triphenyl phosphine (mw = 262; 3.38 mmole) in 66 ml 9:1 dimethylformamide (DMF)/H_2O followed by 550 mg K_2HPO_4 (mw = 174; 3.16 mmole). The reaction mixture is stirred at 25°C for 35 minutes. After dilution with EA and brine, the layers are separated and the aqueous one extracted three times with EA. The combined EA layers are washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under a stream of N_2 to give crude 2. The material is chromatographed on silica gel to give 2. The *cis* diastereoisomers or the *cis-trans* mixture is obtained in an analogous manner.

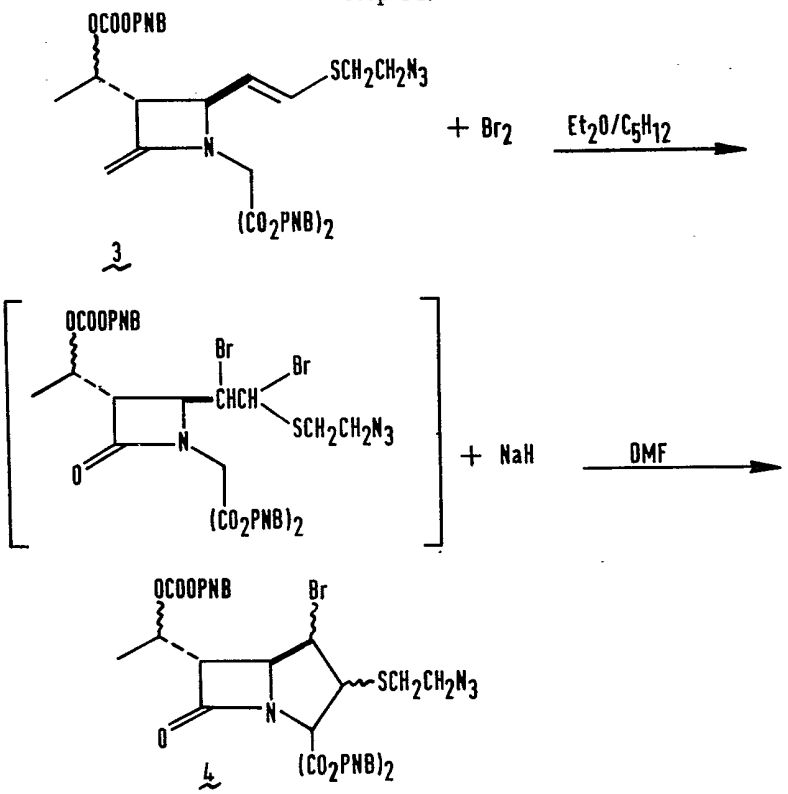
Step L:



3

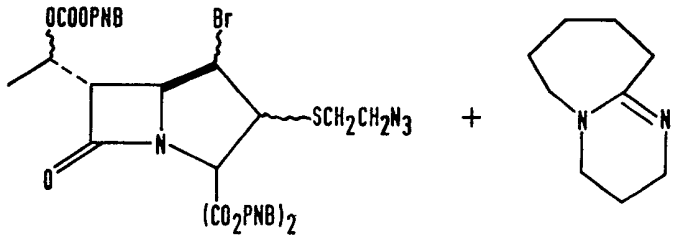
To 7.8 ml pentane (dried over 4A Linde molecular sieves) is added 0.2 ml Br_2 (mw = 160; ρ = 3.12; 3.9 mmole). To a solution of 950 mg 2 (mw = 896; 1.06 mmole) in 15 ml Et_2O (dried over 3A 1/16" Linde molecular sieves) at 0°C. under N_2 with stirring is added dropwise 2.3 ml of the above 0.49 M Br_2 solution (1.13 mmole). After stirring for 10 minutes at 0°C., 114 μl cyclohexene (mw = 82, ρ = .81; 1.13 mmole) is added. After 5 minutes at 0°C, 53 mg 57% NaH (57% of 53 mg = 30.2 mg, mw = 24, 1.26 mmole) in mineral oil is added to the stirred reaction mixture. This is followed immediately by the addition of 14 ml ice cold DMF (distilled from anhydrous $CaSO_4$ at 40 mm and stored over 4A Linde molecular sieves). Stirring at 0°C under N_2 is continued for 3 hours. The reaction mixture is poured into a stirred ice-cold mixture of 2.5 ml 1M KH_2PO_4—40 ml H_2O—75 ml EA. After separation of the layers, the aqueous one is saturated with NaCl and re-extracted with EA. The combined organic layers are extracted once with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under a N_2 stream followed by pumping on a high vacuum pump to provide crude 3. Preparative thin layer chromatography on silica gel yields 3. The *cis* diastereoisomers or the *cis-trans* mixture is obtained in an analogous manner.

Step M:

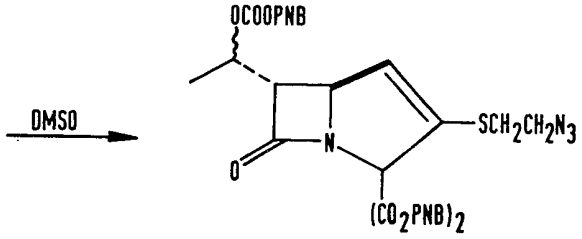


To 9.16 ml pentane (dried over 4A Linde Molecular sieves) is added 0.2 ml Br_2 (mw = 160, 3.9 mmole). To 474 mg 3 (mw = 793; 0.598 mmole) in 13 ml Et_2O (dried over 3A 1/16" Linde Molecular sieves) at 0°C. under N_2 with stirring is added dropwise 1.52 ml of the above 0.42 M Br_2 solution (0.63 mmole). After 15 minutes at 0°C., 33 mg 57% NaH (57% of 33 mg = 18.8 mg; mw = 24; 0.78 mmole) is added followed immediately by the addition of 6.35 ml ice-cold DMF (distilled from anhydrous $CaSO_4$ at 40 mm and stored over 4A Linde Molecular sieves). The reaction mixture is stirred for 1 1/2 hours at 0°C., then poured into a stirred ice-cold mixture of 1.6 ml 1M KH_2PO_4 — 20 ml H_2O, and 20 ml EA. The layers are separated and the aqueous one saturated with NaCl and re-extracted with additional EA. The combined organic layers are washed once with brine, dried over anhydrous $MgSO_4$ and filtered. The filtrate is concentrated under a N_2 stream and then pumped on high vacuum to give crude 4. Preparative thin layer chromatography on silica gel gives 4. The *cis* diastereoisomers or the *cis-trans* mixture is obtained in an analogous manner.

Step N:



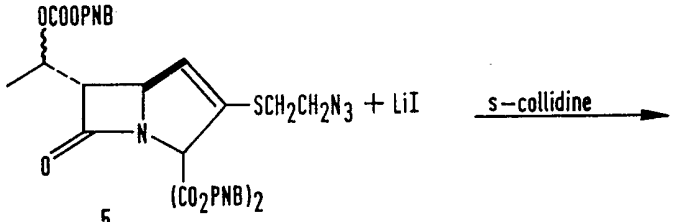
4



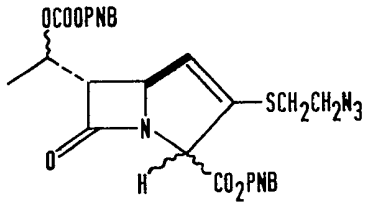
5

To 210 mg 4 (mw = 871; 0.241 mmole) dissolved in 0.5 ml DMSO (distilled from CaH_2 at 8 mm and stored over 4A Linde molecular sieves) is added at 25°C. with stirring 40 mg 1,5 - diazobicyclo[5.4.0]undec - 5 - ene (distilled at 80°C./2 mm) (mw = 152; 0.263 mmole) in 0.7 ml dimethylsulfoxide (DMSO). The solution is stirred under N_2 for 4 hours, and then added to a stirred ice-cold mixture of 0.48 ml 1M KH_2PO_4, 7 ml H_2O, and 10 ml EA. After separation of the layers, the aqueous layer is again extracted with EA. The combined organic layers are washed one time with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under a N_2 stream followed by pumping on high vacuum, to provide crude 5. Preparative thin layer chromatography on silica gel yields 5. The *cis* diastereoisomers or the *cis-trans* mixture is obtained in an analogous manner.

Step O:



5

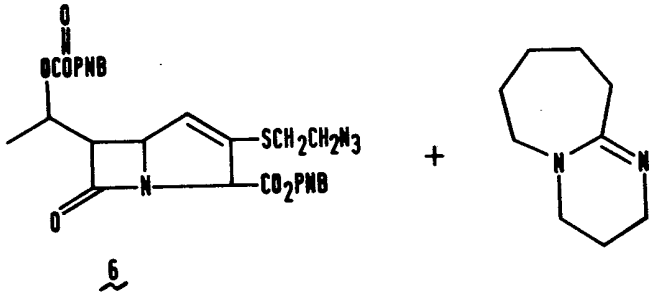


6

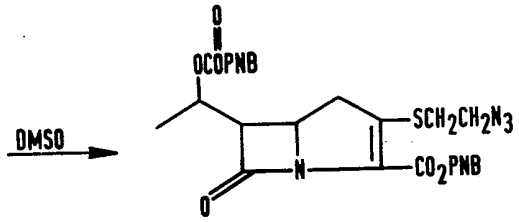
A solution of 187 mg 5 (mw = 791; 0.236 mmole) in 2.5 ml s-collidine (distilled from powdered KOH at 30 mm pressure) is added to 45 mg anhydrous LiI (dried for a few hours at 100°C. over P_2O_5 under vacuum) (mw = 134; 0.336 mmole). With stirring under N_2, the reaction mixture is heated in an oil bath at 120°C. After a total of 25 minutes, the reaction mixture is cooled to 25°C., diluted with CH_2Cl_2 and transferred to a round bottom flask for concentration under a N_2 stream and

then on high vacuum. Partitioning of the residue between 10 ml EA and 1.8 ml 1M KH_2PO_4 in 10 ml H_2O is followed by extraction of the aqueous layer two additional times with EA. The combined organic layers are extracted with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under a stream of N_2 to give crude 6. Preparative thin layer chromatography on silica gel yields 6. The *cis* diastereoisomers or the *cis-trans* mixture is obtained in an analogous manner.

Step P:



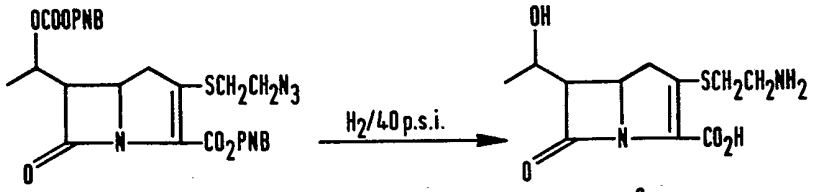
6



7

To a solution of the mixed diastereoisomers, 6, (34 mg; mw = 612; 0.055 mmole) in 0.2 ml DMSO (distilled from CaH_2 at 8 mm and stored over 4A Linde Molecular sieves) with stirring is added 9.5 μl 1,5 - diazobicyclo[5.4.0]undec - 5 - ene (distilled at –80°C./2 mm), (mw = 152; $\rho = 1$; 0.0625 mmole). The solution is stirred under N_2 for 15 minutes diluted to 1 ml total volume with $CHCl_3$ and applied immediately to 2—1000μ silica gel plates. The product band yields 7 as a mixture of *cis* and *trans* diastereoisomers.

Step Q:



7 8

In the presence of 61 mg PtO_2, 61 mg of 7 (mw = 612; 0.1 mmole) in 6 ml dioxane, 6 ml THF, 3 ml H_2O is hydrogenated at 40 p.s.i. —H_2 for 4 hours. The reaction mixture is then filtered through Celite washing with 2 ml 0.1N pH7 phosphate buffer. After concentration *in vacuo* to the cloud point, the aqueous mixture is extracted with ethyl acetate. The water layer is concentrated to a small volume and applied to a column of 100 g XAD—2 resin. Upon elution with H_2O and discarding the initial fractions, those fractions containing product are lyophilized to give *8* as a mixture of *cis* and *trans* diastereoisomers.

The following procedure for the enzymatic N-deacylation of thienamycin, which forms part of the invention claimed in the specification of our copending application No. 48233/76 (Serial No. 1,561,108), is applicable for all isomers of thienamycin — particularly the distinct N-acetyl isomers 890A, and $890A_3$, which are described in our copending application No. 48235/76 (Serial No. 1,561,109).

Deacetylation of N-Acetyl Thienamycin

A 1% (w/v) suspension of fertile lawn soil is prepared by suspending 1 gm. of lawn soil in 100 ml. sterile phosphate buffer-saline solution wherein the phosphate buffer-saline solution has the following composition:

Phosphate Buffer-Saline Solution

NaCl	8.8 g
1M Phosphate Buffer, pH 7.5*	10 ml.
Distilled H_2O	1000 ml.

*1M Phosphate Buffer, pH 7.5

16 ml. 1M KH_2PO_4 are mixed with 84 ml. 1M K_2HPO_4. The pH of the phosphate buffer is adjusted to 7.5 by adding small quantities of either 1M KH_2PO_4 or 1M K_2HPO_4.

Aliquots of this 1% stock soil suspension are used to prepare 10x, 100x and 1,000x dilutions.

One ml. portions of the stock suspension or 1 ml. portions of the 10x, 100x and 1,000x dilutions are added to 2 ml. portions of sterile, 1.0% agar solutions at 48°C. The mixtures are quickly poured over the surface of sterile petri dishes of 85 mm. diameter containing 20 ml. of Medium A. Medium A has the following composition:

Medium A

KH_2PO_4	3.0 g.
K_2HPO_4	7.0 g.
$MgSO_4$	0.1 g.
Distilled H_2O	1000 ml.
N-Acetylethanolamine solution*	8.5 ml.

*N-acetylethanolamine Solution

N-acetylethanolamine is diluted 10x in H_2O and membrane sterilized. This solution is added after autoclaving.

For solid media: Add 20 g. agar

The petri dishes are incubated for 18 days at 28°C. A well-isolated colony is picked and streaked on a petri dish containing Medium B. Medium B has the following composition:

Medium B

Tomato paste	40 g.
Ground oatmeal	15 g.
Distilled H_2O	1000 ml.

pH: adjust to 6 using NaOH

For solid media: Add 20 g. agar

An individual clone is selected and grown for 2 days at 28°C. on a slant of Medium B. A portion of the growth on this slant is streaked on the surface of six slants prepared from Medium B. These slants are incubated for 2 days at 28°C. This culture was identified as *Protaminobacter ruber* and has been designated MB—3528 in the culture collection of Merck & Co., Inc., Rahway, New Jersey, U.S.A. and a sample deposited with the Agricultural Research Service, U.S. Department of Agriculture, Accession No. NRRL B—8143.

A portion of the growth on the slant of *Protaminobacter ruber* MB—3528 is used to inoculate a 250 ml. Erlenmeyer flask containing 50 ml of Medium C. Medium C has the following composition:

Medium C

Dextrose	20 g.
Pharmamedia	8 g.
Corn Steep Liquor (wet basis)	5 g.
Distilled H_2O	1000 ml.

pH: adjust to 7 with NaOH or HCl

N-acetylethanolamine solution	8.5 ml.

*N-acetylethanolamine Solution

N-acetylethanolamine is diluted with 10x in H_2O and membrane sterilized. This solution is added after autoclaving.

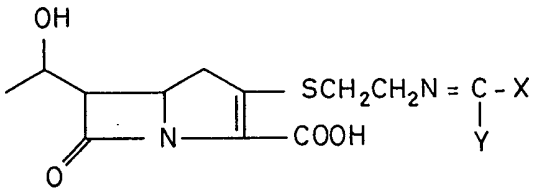
The flask is shaken at 28°C. on a 220 rpm (2" throw) shaker for 4 days. A 25 ml. portion from the flask is centrifuged for 15 minutes at 8,000 rpm. The supernatant is removed and the cells on the surface of the media solids scraped off into 0.5 ml. 0.05M potassium phosphate buffer, pH 7.4. The resulting suspension is subjected to ultrasonic disruption using a Branson Instrument Model LS—75 Sonifier with a 1/2 inch probe at setting 4 for 4, 15 second intervals, while chilling the suspension in ice water during and between disruption. A 10 μl portion of the sonicate is mixed with a 25 μl solution containing 840 μg/ml. of N-acetylthienamycin in 10mM potassium phosphate buffer, pH 7 and incubated overnight at 28°C. Controls containing antibiotic and buffer alone; and sonicated cells and buffer without antibiotic are also run. After incubation overnight at 28°C., 2 μl quantities are applied on cellulose coated TLC plates, which are developed in EtOH:H_2O, 70:30. After air drying, the TLC plate is placed on a *Staphylococcus aureus* ATCC 6538P assay plate for 5 minutes.

The assay plates are prepared as follows: An overnight growth of the assay organism, *Staphylococcus aureus* ATCC 6538P, in nutrient broth plus 0.2% yeast extract is diluted with nutrient broth, plus 0.2% yeast extract to a suspension having 60% transmittance at a wavelength of 660 nm. This suspension is added to Difco nutrient agar supplemented with 2.0 g./l. Difco yeast extract at 37°C. to 48°C., to make a composition containing 33.2 ml. of the suspension per liter of agar. Forty ml. of this suspension is poured into 22.5 cm. × 22.5 cm. petri plates, and these plates are chilled and held at 4°C. until used (5 day maximum).

The TLC plate is removed and the assay plate incubated overnight at 37°C. In addition to the unreacted bioactive N-acetyl thienamycin spot at R_f 0.7—0.89, a bioactive spot is observed at R_f 0.44—0.47 due to thienamycin. Control incubation mixtures of antibiotic plus buffer, cell sonicate plus buffer, and antibiotic plus buffer to which cell sonicate is added just prior to TLC application produce no bioactive material at R_f 0.44—0.47.

WHAT WE CLAIM IS:—

1. A compound having the formula:



II

or a salt, ester, ether, amide or anhydride thereof, in which X is —OR, —SR or —NR^1R^2 and Y, independently of X, is hydrogen, —R, —OR, —SR, or —NR^1R^2; where each of R^1 and R^2, independently of the other, is a hydrogen atom, a radical of the type defined below for R, or a nitro, hydroxyl, C_{1-6} alkoxyl, amino, C_{1-6} monoalkylamino, di(C_{1-6} alkyl)amino, or tri(C_{1-6} alkyl)amino radical, or R^1 and R^2 are joined together to form, together with the nitrogen atom to which they are attached, a substituted or unsubstituted monocyclic or bicyclic heteroaryl or non-aromatic heterocyclic radical comprising 4—10 atoms one or more of which may be an additional oxygen, sulphur or nitrogen hetero atom; R is a cyano or carboxy radical or a substituted or unsubstituted carbamoyl; alkoxycarbonyl; C_{1-10} alkyl; C_{2-10} alkenyl; C_{2-10} alkynyl; C_{3-10} cycloalkyl; C_{4-12} cycloalkylalkyl; C_{4-12} cycloalkylalkenyl; C_{3-10} cycloalkenyl; C_{4-12} cycloalkenylalkenyl; C_{4-12} cycloalkenylalkyl; C_{6-10} aryl; C_{7-16} aralkyl; C_{7-16} aralkenyl or C_{7-16} aralkynyl radical or a substituted or unsubstituted monocyclic or bicyclic heteroar(C_{1-6} alkyl) heteroaryl, non-aromatic heterocyclic-(C_{1-6} alkyl) or non-aromatic heterocyclic radical having 4 to 10 ring atoms one or more of which is an oxygen, sulphur or nitrogen heteroatom; the substitutent(s) on R, R^1, R^2 or the ring formed by joining R^1 and R^2, are halogen; azido; thio; sulpho; phosphono; cyanothio (—SCN); nitro; cyano; amino; hydrazino; C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, tri(C_{1-6} alkyl)amino; C_{1-6} alkylhydrazino, di(C_{1-6} alkyl)hydrazino, tri(C_{1-6} alkyl)hydrazino, hydroxyl; C_{1-4} alkyl; C_{1-6} alkoxyl; C_{1-6} alkylthio; carboxyl; oxo; (C_{1-6} alkoxy)carbonyl; C_{2-10} acyloxy; carbamoyl; (C_{1-4} alkyl)carbamoyl or di(C_{1-4} alkyl)carbamoyl.

2. A compound according to Claim 1 in which R^1 and R^2 are hydrogen or a radical as defined for R and R is a substituted or unsubstituted alkyl, acyl, aralkyl, heteroaryl or heteroaralkyl radical of the type defined in Claim 1.

3. A compound according to Claim 1 in which Y is —NR^1R^2 and X is hydrogen or R.

4. A compound according to Claim 1 in which Y is —NR^1R^2 and X is —NR^1R^2.

5. A compound according to Claim 1 in which Y is —NR^1R^2 and X is —OR or —SR.

6. A compound according to Claim 1 in which Y is hydrogen, R, —OR or —SR, and X is —OR or —SR.

7. A compound according to Claim 3 in which each of R^1 and R^2, independently of the other, is a hydrogen atom; a substituted or unsubstituted C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} cycloalkyl, C_{4-7} cycloalkylalkyl, C_{4-6} cycloalkenyl, C_{4-7} cycloalkenylalkyl, C_{7-10} aralkyl or C_{8-10} aralkenyl radical or a monocyclic heteroar(C_{1-3} alkyl) radical having 5—6 ring atoms, one or more of which is oxygen, sulphur, or nitrogen, the ring or chain substituent(s) of R^1 and R^2 ring chlorine, fluorine, hydroxyl, C_{1-3} alkoxyl, di(C_{1-3} alkyl)amino or C_{1-3} alkylthio, and X is a hydrogen atom or a C_{1-6} alkyl, C_{1-6} aminoalkyl, C_{2-6} alkenyl, C_{2-6} aminoalkenyl, C_{2-6} alkoxyalkyl, C_{2-12} (mono, di or tri)-alkylaminoalkyl, C_{1-6} perhaloalkyl, C_{2-6} alkylthioalkyl, or a substituted or unsubstituted aryl, aralkyl, monocyclic heteroaryl, heteroar(C_{1-6} alkyl), non-aromatic heterocyclic or non-aromatic heterocyclic-(C_{1-6} alkyl) ring in which any substituent(s) are as set out in the definition of R^1 and R^2.

8. A compound according to Claim 4 in which R^1 and R^2 are as defined in Claim 7.

9. A compound according to Claim 3 in which each of R^1 and R^2, independently of the other, is hydrogen, C_{1-6} alkyl, C_{1-6} aminoalkyl, C_{1-6} hydroxyalkyl or C_{2-6} alkenyl and X is hydrogen; alkyl; alkoxyalkyl; alkylaminoalkyl or dialkylaminoalkyl in which the alkyl residues each contain 1 to 6 carbon atoms; aminoalkyl having 1 to 6 carbon atoms; perfluoroalkyl; alkylthioalkyl; or substituted or unsubstituted phenyl, benzyl, phenethyl, monocyclic heteroaryl,

heteroaralkyl, heterocyclyl, and heterocyclylalkyl in which any substituents are as defined in Claim 1.

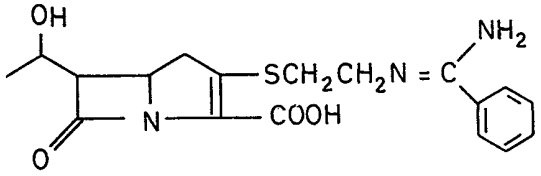
10. A compound according to Claim 4 in which each of R^1 and R^2, independently of the other, is hydrogen; C_{1-6} alkyl; C_{3-6} alkenyl; nitro; amino; or phenyl.

11. A compound according to Claim 9 in which R is hydrogen, methyl, ethyl, propyl, isopropyl, methoxymethyl, hydroxyethyl, hydroxymethyl, aminomethyl, aminoethyl, aminopropyl, dimethylaminomethyl, methylaminomethyl, trifluoromethyl, methylthiomethyl, ethylthiomethyl, phenyl, benzyl, phenethyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiazolyl or 4-thiazolyl; and each of R^1 and R^2, independently of the other, is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, *t*-butyl, allyl, or benzyl.

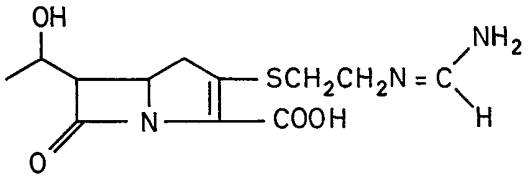
12. A compound according to Claim 9 in which each of R^1, R^2 and R, independently of the other, is hydrogen, C_{1-6} alkyl, C_{1-6} aminoalkyl or C_{2-6} alkenyl.

13. A compound according to Claim 8 in which each of R^1 and R^2, independently of the other, is hydrogen, C_{1-6} alkyl or C_{3-6} alkenyl.

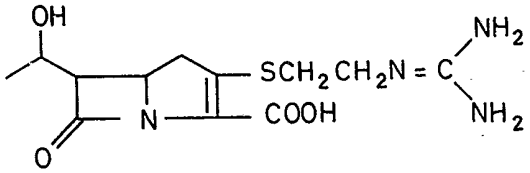
14. A compound having the formula:



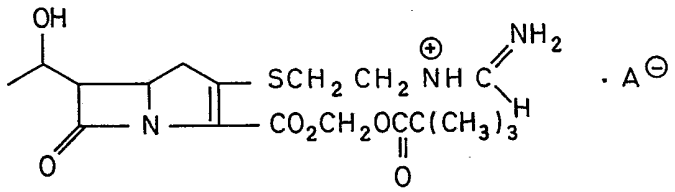
15. A compound having the formula:



16. A compound having the formula:

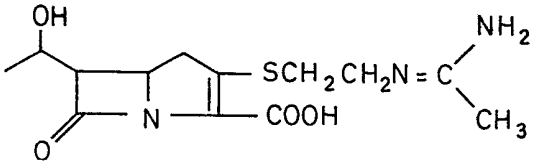


17. A compound having the formula:

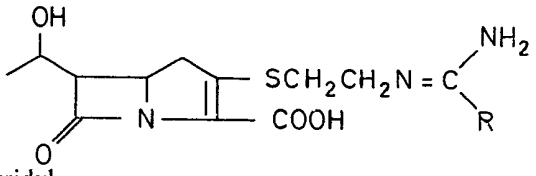


where A is a pharmaceutically acceptable anionic salt residue.

18. A compound having the formula:

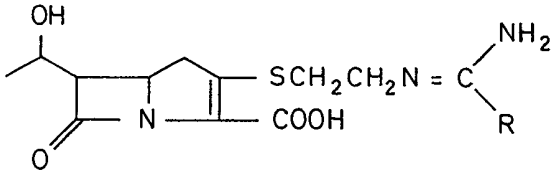


19. A compound having the formula:



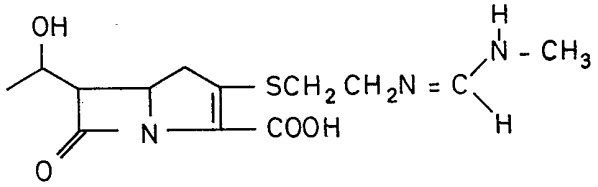
where R is 3-pyridyl.

20. A compound having the formula:

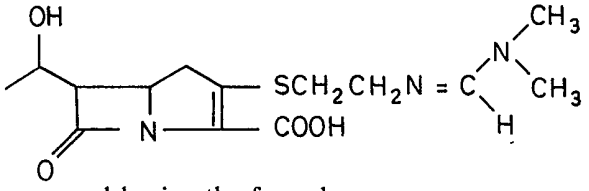


in which R is 4-thiazolyl.

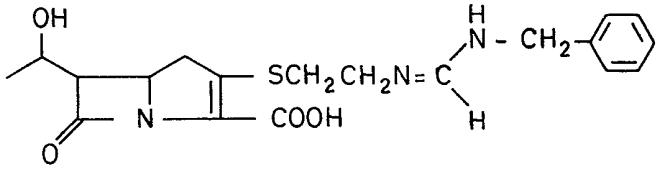
21. A compound having the formula:



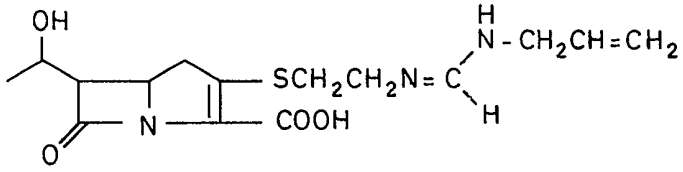
22. A compound having the formula:



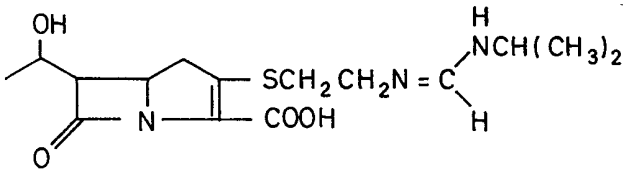
23. A compound having the formula:



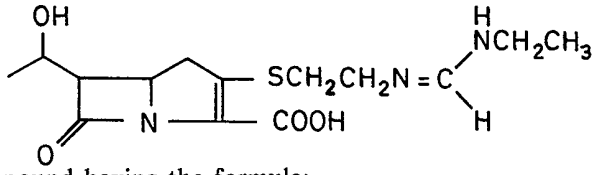
24. A compound having the formula:



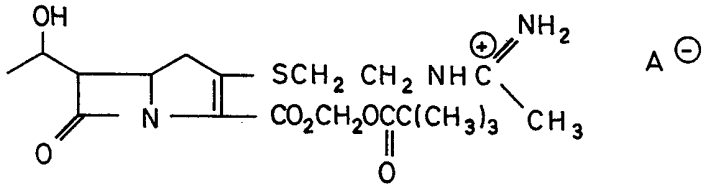
25. A compound having the formula:



26. A compound having the formula:

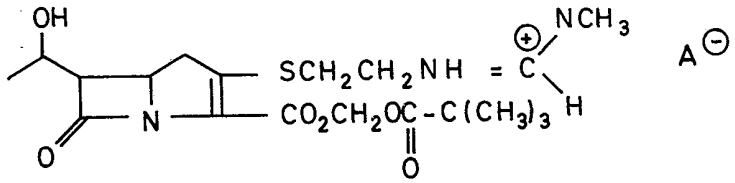


27. A compound having the formula:



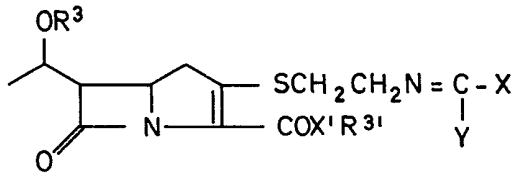
in which A is a pharmaceutically acceptable anionic salt residue.

28. A compound having the formula:



in which A is a pharmaceutically acceptable anionic salt residue.

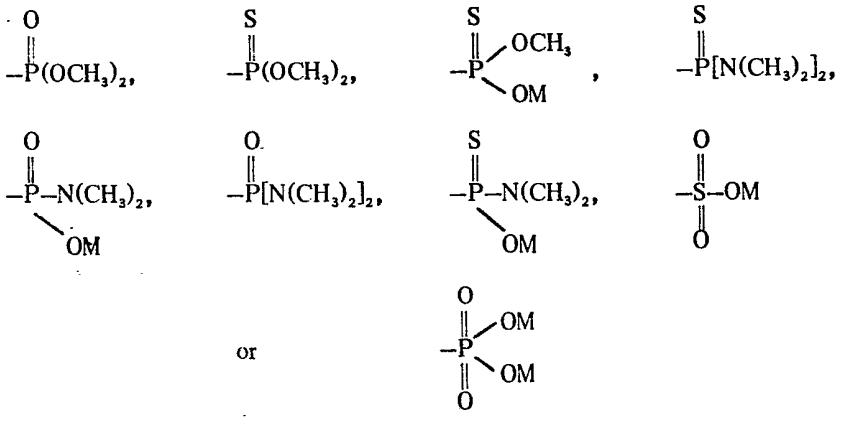
29. A compound having the formula:



in which X and Y are as defined in Claim 1, X′ is oxygen, sulphur, NH or $NR^{3'}$; $R^{3'}$ is a hydrogen atom, a pharmaceutically acceptable cation, or a C_{1-10} alkyl, substituted carbonylmethyl, α-carboxy-α-isopropyl, aminoalkyl, (C_{1-10} alkoxy)-(C_{1-6} alkyl), (C_{1-6} alkanoyloxy)-(C_{1-6} alkyl), halogenated C_{1-6} alkyl, alkenyl having 2—10 carbon atoms, alkynyl having 2—10 carbon atoms, alkanoyl having 1—10 carbon atoms, C_{3-14} alkoxycarbonylalkyl, C_{4-21} dialkylaminoacetoxyalkyl or C_{2-13} alkanamidoalkyl radical; an aralkyl radical in which the alkyl residue has 1—3 carbon atoms and the aryl residue 6—10 carbon atoms, a monocyclic or bicyclic heteroaralkyl in which there are 4 to 10 atoms in the ring, the hetero atom or atoms being oxygen, sulfur and/or nitrogen, and 1 to 6 carbon atoms in the alkyl chain; a phthalidyl radical; a phenylethyl or 2-(*p*-methylphenyl)ethyl radical or an arylthioalkyl analogue thereof; an aryloxy-(C_{1-6} alkyl) radical where aryl is a phenyl ring having 0—3 substituents; or a phenyl, 5-indanyl, substituted phenyl having 1—3 substituents, phenyl-(C_{2-6} alkenyl), benzyloxy-(C_{1-3} alkyl), alkylthioalkyl where the alkylthio residue has 1—10 carbon atoms and the alkyl portion has 1—6 carbon atoms, (C_{1-6} alkoxy)carbonyloxymethyl, di(C_{1-6} alkyl)aminoacetoxymethyl or C_{2-7} alkanamidomethyl radical; and R^3 is a hydrogen atom, an acyl radical or a univalent hydrocarbon or substituted hydrocarbon radical.

30. A compound according to Claim 29 in which R^3 is formyl, acetyl, propionyl, butyryl, chloroacetyl, methoxyacetyl, aminoacetyl, methoxycarbonyl, ethoxycarbonyl, methylcarbamoyl, ethylcarbamoyl, phenylthiocarbonyl, 3-aminopropionyl, 4-aminobutyryl, N-methylaminoacetyl, N,N-dimethylaminoacetyl, an N,N,N-trimethylammoniumacetyl salt, 3-(N,N-dimethyl)aminopropionyl, a 3-(N,N,N-trimethyl)ammonium propionyl salt, an N,N,N-triethylammoniumacetyl salt, a pyridiniumacetyl salt, guanylthioacetyl, guanidinoacetyl, 3-guanidinopropionyl, N^3-methylguanidinopropionyl, hydroxyacetyl, 3-hydroxypropionyl,

acryloyl, propynoyl, malonyl, phenoxycarbonyl, amidinoacetyl, acetamidinoacetyl, amidinopropionyl, acetamidinopropionyl, guanylureidoacetyl, guanylcarbamoyl, carboxymethylaminoacetyl, sulfoacetylaminoacetyl, phosphonoacetylaminoacetyl, N^3-dimethylaminoacetamidinopropionyl, ureidocarbonyl, dimethylaminoguanylthioacetyl, a 3-(1-methyl-4-pyridinium)propionyl salt, 3-(5-aminoimidazol-1-yl)propionyl, 3-methyl-1-imidazoliumacetyl salt, 3-sydnonylacetyl, *o*-aminomethylbenzoyl, *o*-aminobenzoyl,



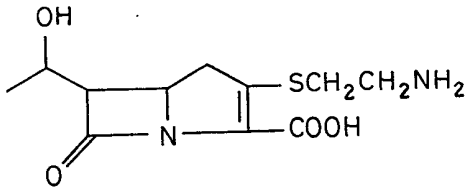
or

X′ is oxygen and $R^{3'}$ is hydrogen, methyl, *t*-butyl, phenacyl, *p*-bromophenacyl, pivaloyloxymethyl, 2,2,2-trichloroethyl, allyl, 3-methyl-2-butenyl, 2-methyl-2-propenyl, benzyl, benzylhydryl, *p*-*t*-butylbenzyl, phthalidyl, phenyl, 5-indanyl, acetylthiomethyl, acetoxymethyl, propionyloxymethyl, methallyl, 3-butenyl, 4-pentenyl, 2-butenyl, acetoxyacetylmethyl, pivaloylacetylmethyl, diethylamino, dimethylaminoethyl, methoxymethyl, *p*-acetoxybenzyl, *p*-pivaloyloxybenzyl, *p*-isopropoxybenzyl, 5-indanylmethyl, benzyloxymethyl, methylthioethyl, dimethylaminoacetoxymethyl, crotonolacton-3-yl, acetamidomethyl, acetylthioethyl, pivaloylthiomethyl or methylthiomethyl.

31. A compound as claimed in Claim 11 in which R^1 and R^2 are hydrogen and R is aminoalkyl.

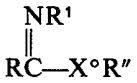
32. A compound as claimed in Claim 31 in which R is aminoethyl.

33. A method of preparing a compound according to Claim 3 comprising treating a compound of formula:

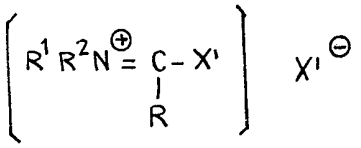


I

or a suitable protected derivative thereof with an imido ester of formula:

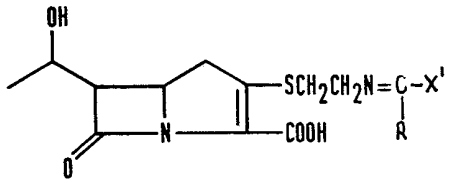


or an imido halide of formula:



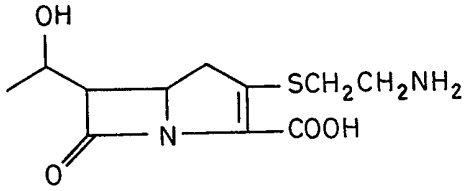
where —X°R″ is a leaving group, X′ is a halogen, X° is O or S, and R, R^1 and R^2 are as defined in Claim 1.

34. A method of preparing a compound according to Claim 3 comprising treating a compound of formula:



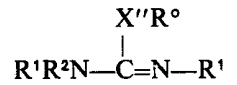
or a suitable protected derivative thereof with an amine of formula NHR^1R^2, where X′ is the leaving group —OR or —SR and R, R^1 and R^2 are as defined in Claim 1.

35. A method of preparing a compound according to Claim 3 comprising treating a compound of formula:



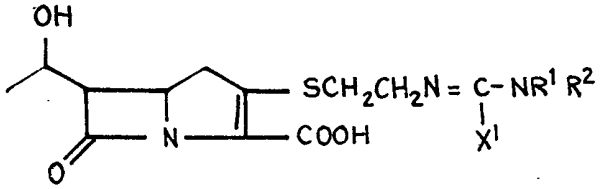
I

or a suitable protected derivative thereof with a compound of formula:



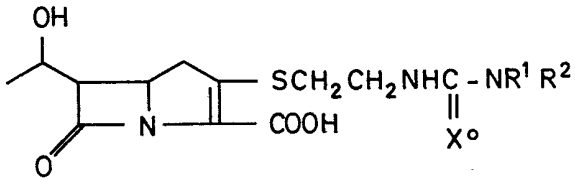
where X″ is O or S, —X″R° is a leaving group and R, R^1 and R^2 are as defined in Claim 1.

36. A method of preparing a compound according to Claim 3 comprising treating a compound of formula:

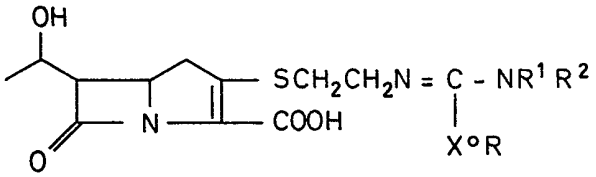


or a suitable protected derivative thereof with an amine NHR^1R^2 where X′ is the leaving group —OR or —SR and R, R^1 and R^2 are as defined in Claim 1.

37. A method of preparing a compound according to Claim 4 comprising treating a compound of formula:

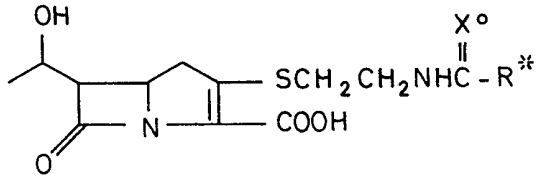


or a suitable protected derivative thereof with an alkylating agent calculated to provide:

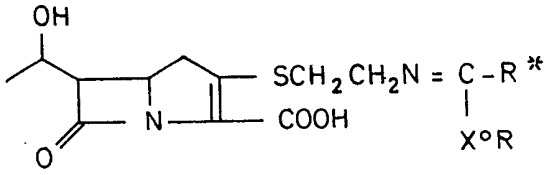


where X° is O or S and R, R^1 and R^2 are as defined in Claim 1.

38. A method of preparing a compound according to Claim 5 comprising treating a compound of formula:



or a suitable protected derivative thereof with an alkylating agent calculated to provide:



where X° is O or S, R* is H, R, OR or SR and R is as defined in Claim 1.

39. A method of preparing a compound according to Claim 1 substantially as hereinbefore described with reference to any one of Examples 3 to 7, 9 to 16, 19, 20, 21, 28 to 43, 51 and 52 or any one of the compounds mentioned in Example 53.

40. A compound according to Claim 1 when prepared by a method as claimed in any one of Claims 33 to 39.

41. A pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutical carrier therefor.

42. A pharmaceutical composition comprising, in unitary dosage form, a therapeutically effective amount of a compound according to Claim 1 and a pharmaceutical carrier therefor.

43. A pharmaceutical composition as claimed in Claim 41 in the form of a capsule, tablet, powder, elixir, aqueous or oily solution or suspension, emulsion or syrup.

44. A composition as claimed in Claim 41 in orally administrable form.

45. A composition as claimed in Claim 41 in intravenously administrable form.

46. A composition as claimed in Claim 41 in intramuscularly administrable form.

47. A composition as claimed in Claim 41 in the form of a suppository.

48. A composition as claimed in Claim 41 in form suitable for absorption through the mucous membranes of the nose and throat or bronchial tissues.

49. A composition as claimed in Claim 48 in the form of a liquid spray or inhalant, a lozenge or a throat paint.

50. A composition as claimed in Claim 41 in aurally or optically administrable form.

51. A composition as claimed in Claim 41 in topically administrable form.

52. A composition as claimed in Claim 51 in the form of an ointment, cream, lotion, paint or powder.

53. An antibacterial composition comprising as active ingredient a compound as claimed in Claim 1 together with a material in respect of which antibacterial action is desired.

54. A disinfectant comprising as active ingredient a compound as claimed in Claim 1 together with a suitable carrier or diluent.

55. A composition as claimed in Claim 53 in which the said material is a human or animal foodstuff.

56. A composition as claimed in Claim 53 in which the said material is a water-based paint.

57. A composition as claimed in Claim 53 in which the said material is the white water of a paper mill.

58. A veterinary composition comprising as active ingredient a compound as claimed in Claim 1 together with a non-toxic base material.

59. A composition as claimed in Claim 53 in the form of an intramammary preparation.

60. A composition as claimed in any one of Claims 41 to 59 in which the said compound is a compound as claimed in any one of Claims 2 to 30.

61. A composition as claimed in any one of Claims 41 to 59 in which the said compound is a compound as claimed in Claim 31.

62. A composition as claimed in any one of Claims 41 to 59 in which the said compound is a compound as claimed in Claim 32.

63. A composition as claimed in any one of Claims 41 to 59 in which the said compound is a compound as claimed in Claim 40.

64. A composition as claimed in Claim 41 substantially as hereinbefore described in any one of Examples 54 to 59.

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