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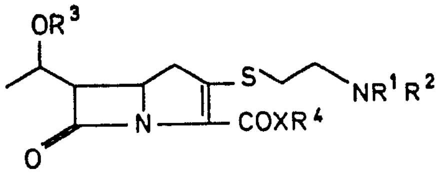
(54) THIENAMYCIN DERIVATIVES

(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:-

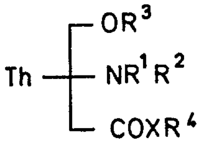
This invention relates to antibiotics, their production and compositions containing them. There is a continuing need for new antibiotics, for there is unfortunately no static effectiveness of a given antibiotic because continued wide-scale usage of any such antibiotic selectively gives rise to resistant 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 provides certain novel derivatives (I) of the antibiotic thienamycin (formula II below). Such compounds, including their O− and carboxyl derivatives and their pharmaceutically acceptable salts, are useful as antibiotics. The compounds of the present invention are generically represented by the following structural formula (I):



I

or, more conveniently, by the symbol:



$$\mathrm{Th}\left[\begin{array}{l}\mathrm{OR^3}\\ \mathrm{NR^1R^2}\\ \mathrm{COXR^4}\end{array}\right.$$

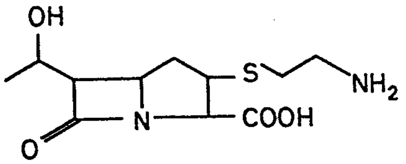
where "Th" symbolizes the bicyclic nucleus of thienamycin and the OH, amino, and carboxyl groups of thienamycin are illustrated; R^2 is acyl (the term "acyl" is by definition inclusive of the alkanoyls including derivatives and analogues thereof such as thio analogues in which the carbonyl oxygen is replaced by sulfur, as well as the sulfur and phosphorus acyl analogues such as substituted sulfonyl, sulfinyl and sulfenyl radicals and substituted P (III and V) radicals such as the substituted phosphorous, phosphoric, phosphonous and phosphonic radicals, respectively; such acyl radicals of the present invention are further defined below); X is oxygen, sulfur or NR' (R' = H or C_{1-6} alkyl); and R^4 is a hydrogen atom, a conventional carboxyl-protecting group (when X is oxygen) such as trialkylsilyl, a pharmaceutically acceptable cation, an acyl radical or a C_{1-10} alkyl, substituted carbonylmethyl, substituted or unsubstituted aminoalkyl, (C_{1-10} straight, branched or cyclic alkoxy)-(C_{1-6} alkyl), (C_{1-6} alkanoyloxy)-(C_{1-6} alkyl), halogenated C_{1-6} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-14} akoxycarbonyloxyalkyl, C_{4-21} dialkylaminoacetoxyalkyl, C_{2-13} alkanamidoalkyl, C_{1-10} alkanoyl, aralkyl in which the alkyl residue is C_{1-3} alkyl, aromatic or cycloaliphatic heterocyclylalkyl in which the alkyl residue is C_{1-3} alkyl and there are from 6 to 10 ring atoms, including from 1 to 4 hetero atoms that are O, S and/or N, arylthioalkyl, aryloxyalkyl, substituted aryloxyalkyl having up to 3 substituents, aryl, e.g. 5-indanyl or phenyl, substituted aryl having up to 3 substituents, phenyl-(C_{2-6} alkenyl), benzyloxy-(C_{1-3} alkyl), (C_{1-10} straight, branched or cyclic alkylthio)-(C_{1-6} alkyl), or (C_{2-10} acylthio)-(C_{1-6} alkyl) radical;

R^3 is hydrogen; or

R^3 is 1.) acyl (generically the group OR^3 is classifiable as an ester); or 2.) R^3 is a univalent hydrocarbon or substituted hydrocarbon radical, e.g. alkyl, aryl, aralkyl, alkenyl or alkynyl, such that the group OR^3 is generically classifiable as an ether; the term "acyl" is by definition inclusive of the alkanoyls including derivatives and analogues thereof such as thio analogues wherein the carbonyl oxygen is replaced by sulfur; as well as sulfur and phosphorus acyl analogues such as substituted sulfonyl, sulfinyl and sulfenyl radicals, and substituted P (III and V) radicals such as substituted phosphorous, phosphoric, phosphonous and phosphonic radicals, respectively; such acyl radicals of the present invention are further defined below, as are the radicals (2., above) which make up the ethers of the present invention; and

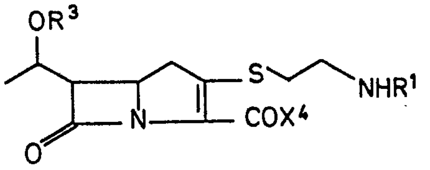
R^1 is substituted or unsubstituted C_{1-10} alkyl, C_{2-10} alkenyl or C_{2-10} alkynyl, ring substituted or unsubstituted cycloalkyl, cycloalkenyl, cycloalkenylalkyl or cycloalkylalkyl having 3-6 ring carbon atoms and 1-6 carbon atoms in the alkyl chain if any; C_{6-10} aryl; aralkyl having 6-10 ring carbon atoms and 1-6 carbon atoms in the alkyl chain; monocyclic or bicyclic heteroaryl or heteroaralkyl comprising 4-10 ring atoms, one or more of which is oxygen, nitrogen and/or sulfur, and 1-6 carbon atoms in the alkyl chain; and in which the ring or chain substituent (or substituents) in the aforementioned radicals is chloro, bromo, iodo, fluoro, azido, cyano, amino, alkylamino, dialkylamino, or a trialkylamino salt in which the or each alkyl has 1-6 carbon atoms, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkylthioalkyl, carboxyl, oxo, (C_{1-6} alkoxy)carbonyl, C_{2-10} acyloxy, carbamoyl, alkylcarbamoyl or dialkylcarbamoyl in which the alkyl groups have 1-4 carbon atoms, cyanothio (−SCN), or nitro; preferred values of R^1 are set forth below.

Thienamycin, a convenient starting material for the preparation of the compounds of the present invention, is disclosed and claimed in US Patent 3,950,375. Thienamycin is known to have the following structural formula (II):



II

Starting material II (including all isomers and mixtures of isomers thereof) is also available by the total synthesis which is described and claimed in the specification of our copending application No. 47326/77 Serial No 1589896. This application discloses the production of all isomers, pure and as mixtures, of II which are suitable starting materials for the preparation of the compounds of the present invention. Another convenient starting material for preparation of the compounds of the present invention is N-alkylated thienamycin and its O– and carboxyl derivatives (III):



III

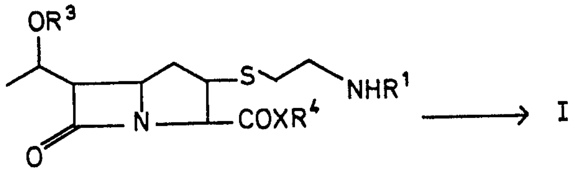
in which R^3, X, R^4 and R^1 are as defined above. The N-alkylated thienamycins (III) are disclosed and claimed in the specification of our copending application No. 48238/76. (1570988).

It has been unexpectedly found that the compounds of the present invention are broad-spectrum antibiotics, which are useful in animal and human therapy and in inanimate systems.

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

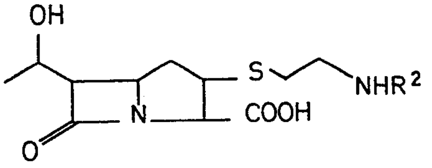
With respect to the generic description of the present invention (formula I, above) the preferred compounds are those in which R^1 is alkyl or alkenyl having up to 6 carbon atoms, such as methyl, ethyl, propyl and allyl; benzyl and nuclear-substituted benzyl such as *p-t*-butyl-benzyl; or heteroaralkyl such as 4-pyridyl-methyl, 2-furyl-methyl or 2-thienyl-methyl; and R^3, R^2, X and R^4 are as defined above and further exemplified below. Especially preferred compounds of the present invention are those in which R^1 and R^2 are as defined in this paragraph; X is oxygen, R^3 is hydrogen, and R^4 is hydrogen or a pharmaceutically acceptable cation.

The compounds of the present invention are most conveniently prepared by the N-acylation of an N–R^1 thienamycin:



III

Appropriate N-acylation procedures (III→I) are fully disclosed in the specification of our copending application No. 48236/76 (1570986) which application discloses and claims N-acyl-thienamycins (IV) and methods for their preparation from thienamycin (II):



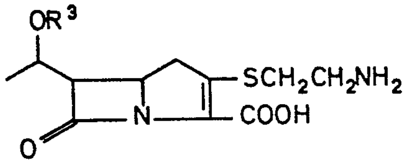
IV

where R^2 is acyl. The N-acylation procedures of the said application are strictly analogous to the above-defined acylation (III→I).

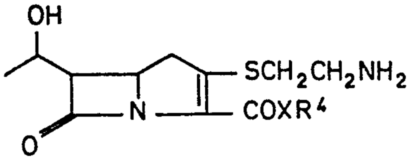
The starting material III is fully disclosed and claimed in the specification of our copending application No. 48238/76 (1570988).

The N-monoalkyl-thienamycin derivatives (III) are prepared by reacting thienamycin or a suitable derivative thereof or a suitably protected thienamycin with an N-alkylating agent, other values of R^1, e.g. benzyl, being introduced in an analogous manner. The process is not unduly critical and any of a variety of well-known N-alkylation procedures may be used. The identity of the N-alkylating agent is a matter of choice within the limits set by the definition of R^1. The N-alkylation may be conducted in any of a variety of solvent systems which are inert or substantially inert to the desired course of reaction. Suitable solvents include polar solvents such as water, lower alkanols such as ethanol, dioxane, tetrahydrofuran (THF), acetonitrile, hexamethylphosphoramide (HMPA), dimethylformamide (DMF) and mixtures (particularly aqueous mixtures) of the above; and non-polar solvents such as benzene and halohydrocarbons such as methylene chloride and chloroform. Typically the reaction is conducted at a temperature of from −40°C to 50°C for from 15 minutes to 5 hours. Usually, the reaction is conducted in the presence of an acid acceptor such as propylene oxide, magnesium oxide or potassium carbonate. The preferred N-alkylating agents include active halides, sulfate esters, and Michael addition reagents. The following reagents are representative of such alkylating agents: methyl iodide, allyl bromide, bromoacetone, phenacyl bromide, benzyl bromide, ethyl chloroacetate, propargyl bromide, 2-bromoethyl ethylether, dimethyl sulfate, ethyl fluorosulfonate, methyl fluorosulfonate, chloromethyl thiocyanate, 2-chloroethyl methyl sulfide, bromomethylcyclopropane, 2,4-dinitrofluorobenzene, 2-chloromethylpyridine, acrylonitrile, methyl methacrylate and nitroethylene.

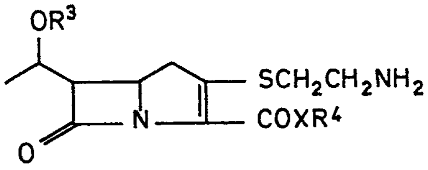
The starting material III may be prepared in any of a variety of ways. One convenient starting material is *tris*-trimethylsilyl thienamycin [Th(TMS)$_3$] (see below). When it is desired for R^3, R^4 or R^3 and R^4 to be other than hydrogen, suitably derivatized starting materials such as Ia, Ib and Ic (below), may be used:



Ia



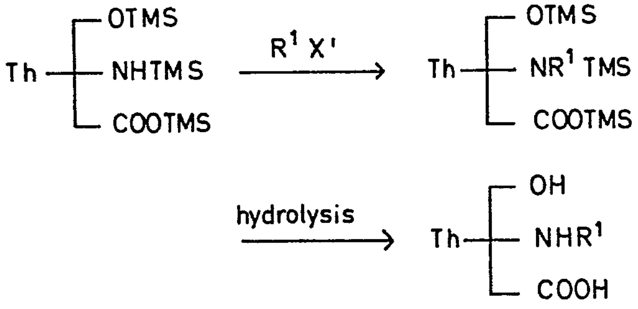
Ib



Ic

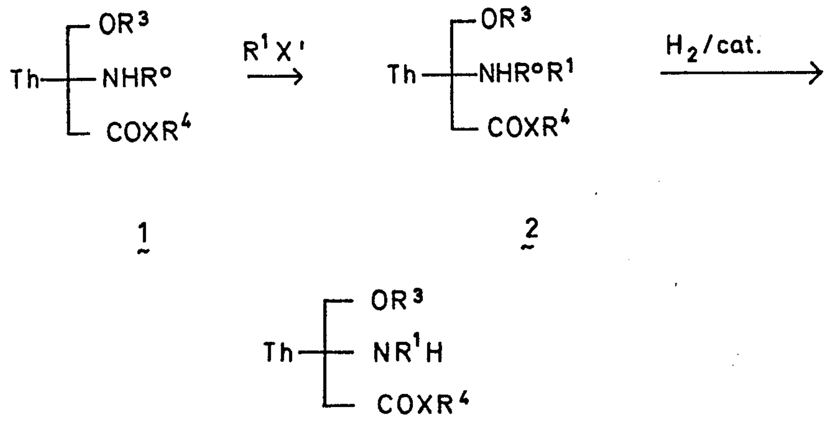
where R^3, X and R^4 are as defined above and further exemplified below. Starting materials Ia, Ib and Ic, which are also useful as antibiotics, are disclosed and claimed in the specifications of our copending applications Nos 7667/77 (1569234) and 48237/76 (1570987). These applications are incorporated herein by reference since they describe useful starting materials for preparing III, and, additionally, analogous processes for converting the N,N-disubstituted thienamycins of the present invention to carboxyl-, O—; and carboxyl- and O-derivatized forms which are also embraced by the present invention and are useful as antibiotics.

As stated above the N-alkylation is carried out in any of the above-named solvents in the presence of the N-alkylating agent of choice, such as R^{1}X', where X' is a leaving group such as halogen atom or a sulfate ester. When using, for example, the above mentioned Th(TMS)$_3$ then the desired product is obtained by aqueous hydrolysis following the N-alkylation step. The following reaction diagram summarizes the process:



where TMS is trimethylsilyl and R^1 and X' are as defined above.

A second scheme for the preparation of monoalkyl thienamycins (III) involves the N-alkylation of an N-substituted thienamycin in which the substituent is an easily removable bulky group (R°) such as an aralkyl group, for example substituted and unsubstituted benzyl, benzhydryl ($-CH(C_6H_5)_3$) and trityl ($-C(C_6H_5)_3$) in which the ring substituent may be halo, nitro, C_{1-6} alkyl or C_{1-6} alkoxyl. The following reaction diagram summarizes this scheme:



1

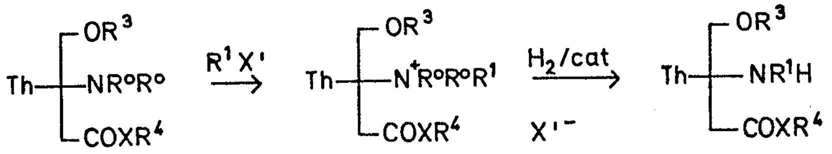
2

3 or III

where all symbolism is as defined above.

In words relative to the above diagram, starting material 1, prepared, for example, from the reaction of thienamycin or a derivative thereof with an aralkyl halide, is reacted with the N-alkylating agent of choice R^1X', as above described, to provide the N,N-dialkyl intermediate 2. The aralkyl N-substituent R° is readily removable to provide 3 by hydrogenolysis. Suitable conditions for this final cleavage step involve hydrogenating 2 in a solvent such as ethanol under hydrogen (1 to 4 atmospheres) in the presence of a catalyst such as platinum, palladium, or oxides thereof. The ultimate product of this reaction is primarily 3, the N-monoalkyl species. However, there is some co-presence of N,N-dialkyl thienamycin. Such contaminating by-products may be separated by chromatographic methods and the magnitude of contamination may be minimized by using one equivalent or less of the alkylating agent R^1X'.

A third method for the preparation of the N-monoalkyl compounds III, particularly N-(C_{1-10} alkyl) compounds, is similar to the above described procedure except that the starting material 1a is an N,N-diaralkyl-thienamycin. The preparation of such starting materials is described in the specification of our copending application No. 48238/76 (1570988). The following reaction diagram summarizes this process:



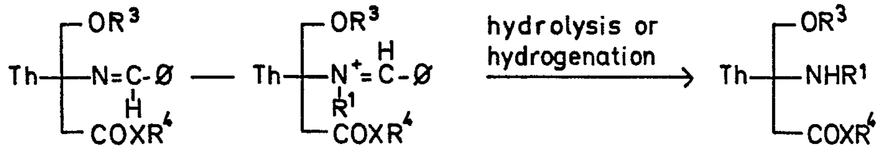
1a

III

where all symbolism is as described above.

It is to be noted that this scheme for the preparation of N-(C_{1-10} alkyl) thienamycins is not complicated by the co-preparation of N,N-di-(C_{1-10} alkyl)-thienamycins.

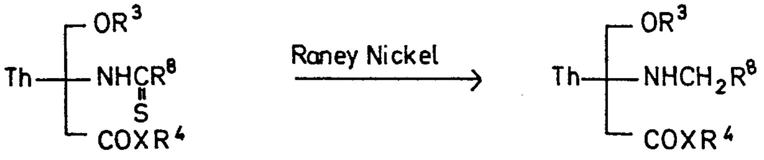
A fourth method which is particularly suitable for the preparation of N-(C_{1-10} alkyl)-thienamycins species (III) involves the N-alkylation of a Schiff's Base of thienamycin. The following diagram illustrates and summarizes the reaction.



4 5 6 or III

where all symbolism is as previously defined and in addition Ø is phenyl, R^4 and R^3 are trimethylsilyl (TMS) and X is oxygen. The preferred Schiff's base is that obtained by reacting thienamycin with benzaldehyde or a nuclear substituted benzaldehyde. In the latter case, Ø is substituted phenyl in the foregoing scheme. The process for preparing such Schiff's bases is not critical. The reaction of 4 with the alkylating reagent R^1X' provides intermediate compound 5 which upon aqueous hydrolysis or catalytic hydrogenolysis provides the desired N-(C_{1-10} alkyl)-thienamycin 6.

A fifth method for preparing N-(C_{1-10} alkyl)-thienamycins (III) involves the desulfurization of an N-thioacyl-thienamycin in the presence of a hydrogenation catalyst such as Raney Nickel:



where X is oxygen, R^3 and R^4 are as previously defined but are preferably hydrogen, and R^8 is hydrogen, aryl or C_{1-5} alkyl. The N-thioacyl-thienamycin starting materials are fully disclosed in the specification of our copending application No. 48236/76 (1570986). The above desulfurization is typically conducted in polar protic solvents such as water, C_{1-6} alkanols such as ethanol, and aqueous mixtures thereof at a temperature of from 0-50°C for from 2 minutes to 5 hours.

Identification of the Radical $-COXR^4$

In the generic representation of the compounds of the present invention (I, above), the radical represented by $-COXR^4$, is, *inter alia*, $-COOH$ (X is oxygen and R^4 is hydrogen) or a radical (as defined) known to be a pharmaceutically acceptable salt, ester, anhydride (R^4 is acyl) or amide radical in bicyclic β-lactam antibiotics, such as the cephalosporins and penicillins and their nuclear analogues.

Suitable radicals (R^4) include conventional protecting or carboxyl blocking groups. The term "blocking group" 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, wherein X=O and R^4 is given:

(i) $R^4 = CR^aR^bR^c$ where at least one of R^a, R^b and R^c is an electron-doner, e.g., *p*-methoxyphenyl, 2,4,6-tri-methylphenyl,9-anthryl, methoxy, CH_2SCH_3, tetrahydrofur-2-yl, tetrahydropyran-2-yl of 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) $R^4 = CR^aR^bR^c$ 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, cyanomethyl, ethoxycarbonylmethyl, arylsulphonylmethyl, 2-dimethylsulphoniummethyl, *o*-nitrophenyl or cyano. Suitable esters of this type include benzoylmethoxycarbonyl, *p*-nitrobenzyloxy-carbonyl, 4-pyridylmethoxycarbonyl, 2,2,2-trichloroethoxy-carbonyl and 2,2,2-tribromoethoxycarbonyl.

(iii) $R^4=CR^aR^bR^c$ 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 and R^c group, if there is one, is hydrogen. Suitable esters of this type include *t*-butyloxycarbonyl, *t*-amyloxycarbonyl, diphenylmethoxy-carbonyl and triphenylmethoxycarbonyl.

(iv) $R^4=R^d$, where R^d is adamantyl, 2-benzyloxy-phenyl, 4-methylthiophenyl or tetrahydropyran-2-yl.

Silyl esters, under this category or blocking groups, may conveniently be prepared from a halosilane or a silazane of the formula:
$R^{4'}{}_3SiX'$; $R^{4'}{}_2SiX'_2$; $R^{4'}{}_3Si.NR^{4'}{}_2$; $R^{4'}{}_3Si.NH.COR^{4'}$;
$R^{4'}{}_3Si.NH.CO.NH.SiR^{4'}{}_3$; $R^{4'}NH.CO.NH\ .SiR^{4'}{}_3$; or $R^{4'}C(OSiR^{4'}{}_3)$;
$HN(SiR^{4'}{}_3)_2$ where X′ is a halogen such as chloro or bromo and the various groups $R^{4'}$, which can be the same or different, represent hydrogen atoms or alkyl, e.g., methyl, ethyl, n-propyl or iso-propyl; aryl, e.g., phenyl; or aralkyl, e.g. benzyl groups.

More generally stated, pharmaceutically acceptable carboxyl derivatives of the present invention are those derived by reacting thienamycin or an N-protected thienamycin such as III or an N-acylated thienamycin, or a compound of the present invention I with such compounds as alcohols, phenols, thiols, thiophenols and acylating reagents. Such starting materials or compounds of the present invention may be derivatized to establish the R^3 group of the compounds of the present invention (I, above). For example, esters and amides of interest are the compounds of the formula I (above) having the following group at the 2-position: $-COXR^4$ where X is oxygen, sulfur, or NR′ (R′ is H, alkyl or aryl) and R^4 is alkyl having 1-10 carbon atoms, straight or branched, such as methyl, ethyl, *t*-butyl, pentyl or decyl; substituted carbonylmethyl, including phenacyl, nuclear substituted phenacyl in which the substituent is chloro, bromo, fluoro or C_{1-6} alkyl such as *p*-bromo-phenacyl and *p*-*t*-butylphenacyl, acetoxyacetylmethyl, pivaloyloxyacetylmethyl, carboxymethyl and its alkyl and aryl ester, and α-carboxy-α-isopropyl; aminoalkyl including 2-methylaminoethyl, 2-diethylaminoethyl, 2-acetamidoethyl, phthalimidomethyl and succinimidomethyl; alkoxyalkyl where the alkoxy portion has 1-10 and preferably 1-6 carbon atoms, but can be branched, straight or cyclic, and the alkyl portion has 1-6 carbon atoms, such as methoxymethyl, ethoxymethyl, isopropoxymethyl, decyloxymethyl, ethoxypropyl, decyloxypentyl or cyclohexyloxymethyl; alkanoyloxyalkyl where the alkanoyloxy portion is straight or branched and has 1-6 carbon atoms and the alkyl portion has 1-6 carbon atoms, such as acetoxymethyl, pivaloyloxymethyl, acetoxyethyl, propionyloxyethyl or acetoxypropyl; halogenated alkyl where halo is chloro, bromo, fluoro or iodo, and the alkyl portion is straight or branched having 1-6 carbon atoms, e.g. 2,2,2-trichloroethyl, trifluoroethyl,2-bromopropyl, diiodomethyl, 2-chloroethyl or 2-bromoethyl; 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, 3-methyl-2-butenyl, 2-methyl-2-propenyl, methallyl or 1,4-cyclohexadien-1-ylmethyl; alkynyl having 2-10 carbon atoms, either straight or branched e.g. 3-pentenyl, propargyl, ethynyl or 3-butyn-1-yl; C_{3-14} alkoxycarbonyloxyalkyl, C_{4-21} dialkylaminoacetoxyalkyl, C_{2-13} alkanamidoalkyl, alkanoyl, either straight or branched, having 1-10 carbon atoms, such as pivaloyl, acetyl or propionyl; substituted or unsubstituted aralkyl or heterocyclylalkyl where the aryl residue has 6 to 10 carbon atoms, the alkyl has 1-3 carbon atoms (e.g. benzyl or benzhydryl), and the heterocycle can be monocyclic or bicyclic aromatic or cycloaliphatic and has 6 to 10 ring atoms, of which 1 to 4 are hetero atoms selected from O, S and N, such substituted aralkyl or heterocyclylalkyl radicals having 1-3 nuclear substituents such as benzyl, phenoxy, halogen (chlorine, fluorine, bromine, iodine) 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-trimethylbenzyl, *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 the cyclic analogue thereof; *p*-trimethylsilylbenzyl, 3,5-*bis*-*t*-butoxy-4-hydroxybenzyl, phenylethyl and 2-(*p*-methylphenyl)-ethyl; and such heterocyclyl-alkyl radicals including 2,2-dimethyl-5-cownaranmethyl, 5-indanylmethyl, 2-thienylmethyl, 2-furylmethyl, 3-*t*-butyl-5-isothiazolmethyl, 6-pivaloyloxy-3-pyridazinylethyl and 5-phenylthio-1-tetrazolylmethyl; phthalidyl; arylthioalkyl; aryloxyalkyl (where aryl is preferably a phenyl ring) having 0, 1, 2 or 3 substituents, particularly unsubstituted phenyl or *ortho* or *para* monosubstituted phenyl, and the alkyl residues contain 1-6 carbon atoms, 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, phenylthioethyl; aryl having 6-10 ring atoms or nuclear substituted aryl having up to 3 substituents, preferably hydroxy, C_{1-6} alkyl, chlorine, fluorine or bromine, and is particularly unsubstituted phenyl or 5-indanyl or *ortho* or *para* monosubstituted phenyl, e.g. 4-methyl-phenyl, 4-hydroxy-phenyl, 4-*t*-butylphenyl, *p*-nitrophenyl, 3,5-dinitrophenyl, or *p*-carboxyphenyl, the latter having either the free acid or the sodium salt form; phenylalkenyl where alkenyl has 2-6 carbon atoms, such as 3-phenyl-2-propenyl; benzyloxyalkyl, either substituted or unsubstituted, where alkyl has 1-3 carbon atoms, such as benzyloxymethyl, 4-nitrobenzyloxymethyl or 4-chlorobenzyloxymethyl; alkylthioalkyl where the alkylthio residue has 1-10 and preferably 1-6 carbon atoms and can be branched, straight or cyclic and the alkyl residue has 1-6 carbon atoms, such as methylthiomethyl, methylthioethyl, ethylthioethyl, cyclohexylthiomethyl, decylthiobutyl, methylthiopropyl, isopropylthioethyl or methylthiobutyl.

In addition to the esters and thio esters listed above, amides, i.e. compounds in which X is an

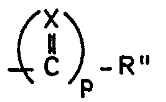
$$\overset{R'}{-N-}$$

group, are also embraced by the present invention. Representative of such amides are those in which R′ is hydrogen, methyl, ethyl, phenyl, *p*-methoxyphenyl, benzyl, carboxymethyl, methylthioethyl or heteroacyl; also embraced by $-COXR^4$ are anhydrides in which R^4 is benzyloxycarbonyl, ethoxycarbonyl, benzoyl or pivaloyl.

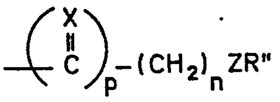
The especially preferred $-COXR^4$ radicals of the present invention are those in which (relative to Structure I above) X is oxygen, sulfur or NR′ (R′ is hydrogen or lower alkyl); and R^4 is C_{1-6} alkyl, C_{2-6} alkenyl, such as methallyl, 3-methylbutenyl or 3-butenyl; methylthioethyl; benzyl; substituted benzyl such as *p*-*t*-butylbenzyl, *m*-phenoxybenzyl, *p*-pivaloyloxybenzyl or *p*-nitrobenzyl; pivaloyloxymethyl, 3-phthalidyl, acetoxymethyl, propionyloxymethyl, acetylthiomethyl, pivaloythiomethyl, allyl, 4-butenyl, 2-butenyl, 3-methyl-2-butenyl, phenacyl, acetoxyacetylmethyl, methoxymethyl, *p*-acetoxybenzyl, *p*-pivaloyloxybenzyl, *p*-isopropoxybenzyl, 5-indanyl-methyl, 5-indanyl, benzyloxymethyl, ethylthioethyl, methylthiopropyl, methoxycarbonyloxymethyl, ethoxycarbonyloxymethyl, dimethylamino-acetoxymethyl, crotonolacton-3-yl or acetamidomethyl.

Identification of R^3 and R^2

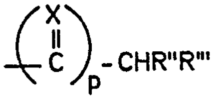
In the generic representation of the compounds of the present invention, (formula I above), the radical R^3 can be, in addition to hydrogen, 1) acyl, e.g. a substituted or unsubstituted aliphatic, aromatic or heterocyclic, araliphatic or heterocyclyl-aliphatic carboxylic acid radical, a substituted or unsubstituted carbamoyl radical or a carbothioic acid radical; (generically the group $-OR^3$ is classifiable as an ester); or 2) the group $-OR^3$ is classifiable as an ether, e.g. R^3 is alkyl, aryl or aralkyl. For the preferred esters, (1) R^3 is one of the following radicals in which $p = 1$, and in the preferred ethers (2) R^3 is one of the following radicals in which $p = 0$. The radical R^2, which can be any one of those types of acyl radical mentioned above for R^3, is preferably also of one of these formulae when $p = 1$:



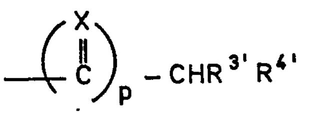
$$-\left(\overset{X}{\overset{\|}{C}}\right)_p-R''$$



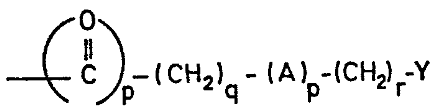
$$-\left(\overset{X}{\overset{\|}{C}}\right)_p-(CH_2)_nZR''$$



$$-\left(\overset{X}{\overset{\|}{C}}\right)_p-CHR''R'''$$



$$-\left(\overset{X}{\overset{\|}{C}}\right)_p-CHR^{3'}R^{4'}$$



$$-\left(\overset{O}{\overset{\|}{C}}\right)_p-(CH_2)_q-(A)_p-(CH_2)_r-Y$$

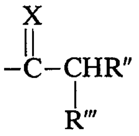
in which R‴, $R^{3'}$ and $R^{4'}$ are as defined below, *n* is 0, 1, 2, 3 or 4; *p* is 0 or 1, *q* is 0, 1, 2, 3, 4 or 5; *r* is 0, 1, 2, 3, 4 or 5; Z is O, S, −CO− or −NH; A is O, S, −NH− or −N($C_{1\text{-}6}$ alkyl)−; X is O or S; R″ is hydrogen; amino; substituted amino such as $C_{1\text{-}6}$ alkylamino or di ($C_{1\text{-}6}$ alkyl) amino; substituted or unsubstituted $C_{1\text{-}6}$ straight or branched 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 (monocyclic or bicyclic) where the alkyl residue typically comprises 1 to 3 carbon atoms, the heterocyclic ring comprises typically 4 to 10 atoms and the hetero atom or atoms are O, N and/or S; such above-listed groups can be unsubstituted or can be substituted by radicals such as OH, SH, SR (R is $C_{1\text{-}6}$ alkyl or aryl such as phenyl), $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkoxy, Cl, Br, F, I, cyano, carboxy, sulfamino, carbamoyl sulfonyl, azido, amino, substituted amino, such as alkylamino including quaternary ammonium salts, wherein the alkyl group(s) comprise(s) 1 to 6 carbon atoms, $C_{1\text{-}6}$ halogenated alkyl such as trifluoromethyl carboxy-($C_{1\text{-}6}$ alkyl), carbamoyl-($C_{1\text{-}6}$ alkyl), N-substituted carbamoyl-($C_{1\text{-}6}$ alkyl), amidino, guanidino, N-substituted guanidino or guanidino-($C_{1\text{-}6}$) alkyl). Representative examples of acyl groups −CX−R″ that might be mentioned are those where 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*-4N-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- guanidino, *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-imidazolylmethyl, 2-benzofuranylmethyl, 2-indolylmethyl, 2-phenylvinyl, 2-phenylethynyl, 1-amino-cyclohexyl, 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-(5-methoxythienyl)methyl, 2- or 3-(4-chlorothienyl)methyl, 2- or 3-(5-sulfothienyl)-methyl, 2- or 3-(5-carboxythienyl)methyl, 3-(1,2,5-thiadiazolyl)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.

Representative members of the substituent

$$-(CH_2)_nZR''$$

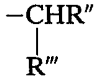
that might be mentioned are allylthiomethyl, phenylthiomethyl, butylmercaptomethyl, α-chlorocrotylmercaptomethyl, phenoxymethyl, phenoxyethyl, phenoxybutyl, phenoxybenzyl, diphenoxymethyl, dimethylmethoxyethyl, dimethylbutoxymethyl, dimethylphenoxymethyl, 4-guanidininophenoxymethyl, 4-pyridylthiomethyl, *p*-(carboxymethyl)phenoxymethyl, *p*-(carboxymethyl-phenylthiomethyl, 2-thiazolylthiomethyl, *p*-(sulfo)phenoxymethyl, *p*-(carboxymethyl)phenylthiomethyl, 2-pyrimidinyl-thiomethyl, phenethylthiomethyl, 1-(5,6,7,8-tetrahydronaphthyl)oxomethyl, N-methyl-4-pyridylthio, benzyloxy, methoxy, ethoxy, phenoxy, phenylthio, amino, methylamino, dimethylamino, a pyridinium-methyl or trimethylammonium-methyl salt, cyanomethylthiomethyl, trifluoromethylthiomethyl, 4-pyridylethyl, 4-pyridylpropyl, 4-pyridylbutyl, 3-imidazolylethyl, 3-imidazolylpropyl, 3-imidazolylbutyl, 1-pyrroloethyl, 1-pyrrolopropyl, and 1-pyrrolobutyl.

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



$$-\overset{\overset{\large X}{\|}}{C}-\underset{\underset{\large R'''}{|}}{C}HR''$$

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



$$-\underset{\underset{\large R'''}{|}}{C}HR''$$

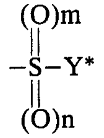
that might be mentioned are α-aminobenzyl, α-amino-(2-thienyl)methyl, α-(methylamino)benzyl, α-amino-methylmercaptopropyl, α-amino-3- or 4-chlorobenzyl, α-amino-3- or 4-hydroxybenzyl, α-amino-2,4-dichlorobenzyl, α-amino-3,4-dichlorobenzyl, *D*(-)-α-hydroxybenzyl, α-carboxybenzyl, α-amino-(3-thienyl)methyl *D*(-)-α-amino-3-chloro-4-hydroxy-benzyl, 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-1,2,3-thiadiazolyl)-hydroxymethyl, 4-(5-chlorothienyl)-aminomethyl, 2-(5-chlorothienyl)-hydroxymethyl, 2-(5-chlorothienyl)-carboxy-methyl, 3-(isothiazolyl)-aminomethyl, 3-(isothiazolyl)-hydroxymethyl, 3-(isothiazolyl)-carboxymethyl, 2-(thiazolyl)-aminomethyl, 2-(thiazolyl)-hydroxymethyl, 2-(thiazolyl)carboxymethyl, 2-benzothienylaminomethyl, 2-benzothienylhydroxymethyl, 2-benzothienylcarboxymethyl, α-sulfobenzyl, α-phosphonobenzyl, α-diethylphosphono, and α-monoethylphosphono. Further acyl radicals of interest in this class when X = oxygen are:

$$-\overset{\overset{\large O}{\|}}{C}CHR^{3'}R^{4'}$$

where $R^{3'}$ and $R^{4'}$ are as defined below. $R^{3'}$ is hydrogen, halo, such as chloro, fluoro, bromo or iodo, amino, guanidino, phosphono, hydroxy, tetrazolyl, carboxy, sulfo or sulfamino and $R^{4'}$ is phenyl, substituted phenyl, a monocyclic or bicyclic substituted or unsubstituted heterocycle 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, C_{1-6} alkyl, a heterocyclic-thio or substituted heterocyclic-thio group, or cyano. The substituents on the $R^{3'}$ and $R^{4'}$ residues are halo, carboxymethyl, guanidino, guanidinomethyl, carbamoylmethyl, aminomethyl, nitro, methoxy or methyl. When $R^{3'}$ is hydrogen, hydroxy, amino or carboxy and $R^{4'}$ is phenyl or a 5- or 6-membered heterocyclic ring having one or two sulfur, oxygen or nitrogen hetero atoms, such as tetrazolyl, thienyl or furyl, the following acyl radicals are representative: phenylacetyl, 3-bromophenylacetyl, *p*-aminomethylphenylacetyl, 4-carboxymethylphenylacetyl, 4-carbamoylmethylphenylacetyl, 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-

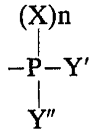
chlorophenylmalonyl, 2-thienylmalonyl, 3-thienylmalonyl; α-phosphonophenylacetyl, α-amino cyclohexadienylacetyl, α-sulfaminophenylacetyl, α-hydroxyphenylacetyl, α-tetrazolylphenylacetyl and α-sulfophenylacetyl.

The acyl radical may also be selected from sulfur (1) and phosphorus (2) radicals:



$$\overset{(O)m}{\overset{\|}{-\underset{\underset{(O)n}{\|}}{S}-Y^*}}$$

1



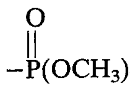
$$\overset{(X)n}{\overset{|}{-\underset{\underset{Y''}{|}}{P}-Y'}}$$

2

where, with respect to (1), each of *m* and *n* is 0 or 1 and $Y^* = O^{\ominus}M^{\oplus}$, $-N(R'')_2$, or R″; where $M^{\oplus}$ is hydrogen, an alkali metal cation or an organic base; and R″ is as defined above, e.g. alkyl, alkenyl, aryl or heteroaryl, and with respect to (2), X = O or S; n = 0 or 1; and each of Y′ and Y″ is $O^{\ominus}M^{\oplus}$,$-N(R'')_2$, R″ or ZR″ where all symbols are as defined above, e.g., R″ and ZR″ are respectively: alkyl, alkenyl, aryl or heteroaryloxy; or Y′ and Y″, including R″ residues, are joined together to form a cyclic ester, ester- amide or amide function. Illustrative examples of radicals (1) are: methylsulfonyl, *p*-nitrophenylsulfonyl, *p*-chlorophenylsulfonyl, *o*-nitrophenylsulfenyl, sulfamoyl, diemthylsulfamoyl, and sulfo; illustrative examples of radicals (2) are: dimethoxyphosphino, dibenzyloxyphosphino, dihydroxyphosphino, dimethoxyphosphinyl, dimethoxyphosphinothioyl, dibenzyloxyphosphinyl, and dihydroxyphosphinyl.

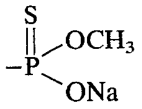
An acyl class of particular interest consists of those known N-acyl blocking or protective groups such as carbobenzyloxy, ring substituted carbobenzyloxy such as *o*- and *p*-nitrocarbobenzyloxy, *p*-methoxycarbobenzyloxy, chloroacetyl, bromoacetyl, phenylacetyl, *t*-butyoxycarbonyl, trifluoroacetyl, bromoethoxycarbonyl, 9-fluorenylmethoxycarbonyl, dichloroacetyl, *o*-nitrophenylsulfenyl, 2,2,2-trichloroethoxycarbonyl, bromo-*t*-butoxycarbonyl and phenoxyacetyl; non-acyl protective groups such as tri(lower alkyl) silyl, for example trimethylsilyl and *t*-butyldimethylsilyl, are also of interest.

Compounds in which R^3 is hydrogen or one of the following radicals and R^2 is one of the following radicals are preferred: 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)ammoniumpropionyl 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, a 3-methyl-1-imidazoliumacetyl salt, 3-sydnonylacetyl, *o*-aminomethylbenzoyl, *o*-aminobenzoyl,

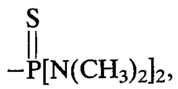


$$\overset{O}{\overset{\|}{-P}}(OCH_3)_2,$$

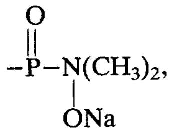
$$\overset{S}{\overset{\|}{-P}}(OCH_3)_2,$$



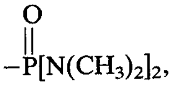
$$\overset{S}{\overset{\|}{-P}}\genfrac{}{}{0pt}{}{OCH_3}{ONa}$$



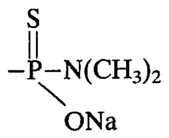
$$\overset{S}{\overset{\|}{-P}}[N(CH_3)_2]_2,$$



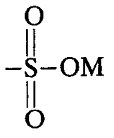
$$\overset{O}{\overset{\|}{-\underset{\underset{ONa}{|}}{P}}}-N(CH_3)_2,$$



$$\overset{O}{\overset{\|}{-P}}[N(CH_3)_2]_2,$$

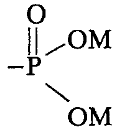


$$\overset{S}{\overset{\|}{-P}}\genfrac{}{}{0pt}{}{-N(CH_3)_2}{ONa}$$



$$\overset{O}{\overset{\|}{-\underset{\underset{O}{\|}}{S}-OM}}$$

or

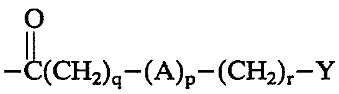


$$\overset{O}{\overset{\|}{-P}}\genfrac{}{}{0pt}{}{OM}{OM}$$

where M is hydrogen or an alkali metal or alkaline-earth metal cation; as well as sulfo, phosphono, carbamoyl, methylsulfonyl, sulfamoyl, dimethylsulfamoyl, bromacetyl, dimethylaminoacetyl, amidinoacetyl, methoxyacetyl, guanylacetyl, phosphamoyl, phosphonothioyl and thiocarbamoyl and, for R^3 only, methoxymethyl, hydroxyethyl, methoxyethyl, dimethylaminomethyl, dimethylaminoethyl, methylthiomethyl, amidinomethyl and guanidinoethyl.

Where trisubstituted ammonium salts are formed, they may be with a pharmaceutical non-toxic anion or may be internal salts with the carboxy group.

An especially preferred class of acyl radicals are terminally substituted acyls in which the substituent is a basic group such as substituted or unsubstituted amino, amidino, guanidino, guanyl and nitrogen-containing monocyclic and bicyclic heterocycles (aromatic and non-aromatic) where the hetero atom or atoms, in addition to nitrogen, can be oxygen and/or sulfur. Such preferred substituted acyls may be represented by the following formula:

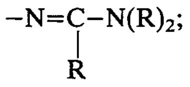


$$-\overset{\overset{\displaystyle O}{\|}}{C}(CH_2)_q-(A)_p-(CH_2)_r-Y$$

where each of *q* and *r* is 0, 1, 2, 3, 4, or 5; *p* is 0 or 1; A is $-O-$, $-NH-$, $N(C_{1\text{-}6}\text{ alkyl})-$ or $-S-$ and Y is (1) substituted or unsubstituted amino or ammonium group of formula

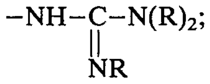
$$-N(R)_2 \qquad \text{or} \quad -\overset{+}{N}(R)_3Q^-,$$

where Q^- is an anion;
an amidino or substituted amidino radical of formula



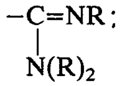
$$-N=\underset{\underset{\displaystyle R}{|}}{C}-N(R)_2;$$

a guanidino or substituted guanidino radical of formula



$$-NH-\underset{\underset{\displaystyle NR}{\|}}{C}-N(R)_2;$$

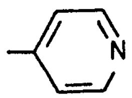
or a guanyl and substituted gyanyl radical of formula

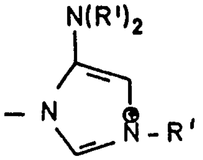


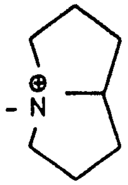
$$-\underset{\underset{\displaystyle N(R)_2}{|}}{C}=NR;$$

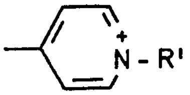
where each R, independently of the others, is hydrogen; $N(R')_2$ (R' is hydrogen or $C_{1\text{-}6}$ alkyl); $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkoxyl, ($C_{1\text{-}6}$ alkoxy)-($C_{2\text{-}6}$ alkyl), $C_{3\text{-}6}$ cycloalkyl, ($C_{3\text{-}6}$ cycloalkyl)-($C_{1\text{-}3}$ alkyl), or (but only when R is attached to carbon), ($C_{1\text{-}6}$ alkoxy)-methyl; or two R groups are joined to form, together with the atom(s) to which they are attached, a ring having 3-6 atoms;

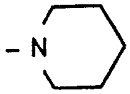
or (2) a nitrogen-containing monocyclic or bicyclic aromatic or non-aromatic heterocycle having 4 to 10 nuclear atoms in which the hetero atom(s), in addition to nitrogen, if any, is/are oxygen and/or sulfur. Such heterocycles are representatively illustrated by the following list of radicals, where R' is H or $C_{1\text{-}6}$ alkyl having 1-6 carbon atoms:

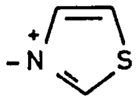


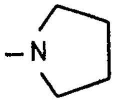


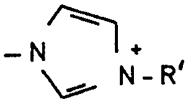


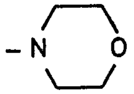


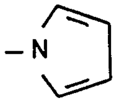


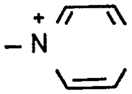


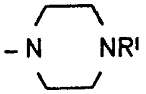


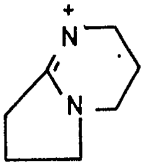




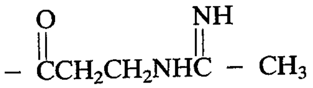




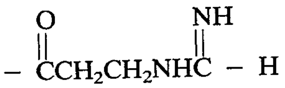




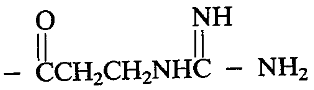
The following specific acyl radicals, in the formulae of which $Q^{\ominus}$ is an anion, which fall within this class, are additionally representative and are preferred:



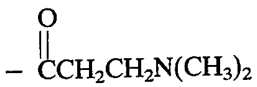
$$-\overset{O}{\overset{\|}{C}}CH_2CH_2NH\overset{NH}{\overset{\|}{C}}-CH_3$$



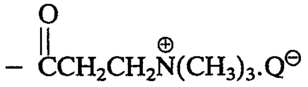
$$-\overset{O}{\overset{\|}{C}}CH_2CH_2NH\overset{NH}{\overset{\|}{C}}-H$$

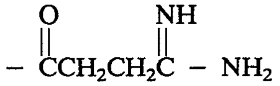


$$-\overset{O}{\overset{\|}{C}}CH_2CH_2NH\overset{NH}{\overset{\|}{C}}-NH_2$$

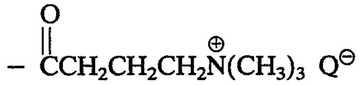


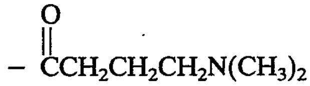
$$-\overset{O}{\overset{\|}{C}}CH_2CH_2N(CH_3)_2$$

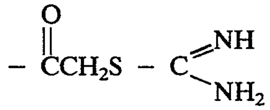

$$-\overset{O}{\overset{\|}{C}}CH_2CH_2\overset{\oplus}{N}(CH_3)_3.Q^{\ominus}$$

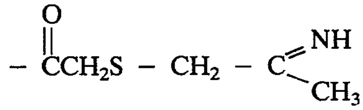

$$-\overset{O}{\overset{\|}{C}}CH_2CH_2\overset{NH}{\overset{\|}{C}}-NH_2$$

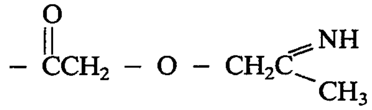

$$-\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2NH\overset{NH}{\overset{\|}{C}}-CH_3$$


$$-\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3\ Q^{\ominus}$$


$$-\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2N(CH_3)_2$$


$$-\overset{O}{\overset{\|}{C}}CH_2S-C\begin{matrix}{=}NH\\ \diagdown NH_2\end{matrix}$$


$$-\overset{O}{\overset{\|}{C}}CH_2S-CH_2-C\begin{matrix}{=}NH\\ \diagdown CH_3\end{matrix}$$


$$-\overset{O}{\overset{\|}{C}}CH_2-O-CH_2C\begin{matrix}{=}NH\\ \diagdown CH_3\end{matrix}$$

However, it is to be understood that any acyl radical may be used in the practice of the invention and is to be considered within the scope of the invention.

In another preferred group of compounds in accordance with the present invention,

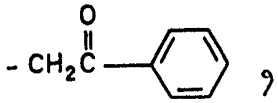
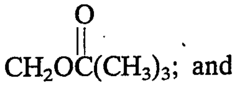
X is oxygen;

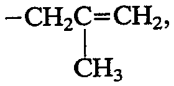
R^3 is hydrogen, CH_3, SO_3H, CH_2OCH_3, $\overset{O}{\overset{\|}{C}}OCH_3$, or $\overset{O}{\overset{\|}{C}}CH_2NH_2$;

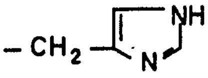
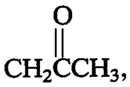
R^4 is hydrogen, $-CH_2O\overset{O}{\overset{\|}{C}}CH_3$, $-CH_2OCH_2C(CH_3)_3$, $-CH_2CH=CH_2$, $-CH_2\overset{CH_3}{\overset{|}{C}}=CH_2$,

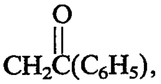
– $CH_2CH_2N(C_2H_5)_2$, , – $CH_2CH_2CH_3$,

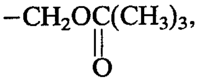
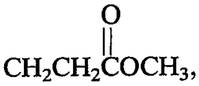
$-CH_2CH_2N(CH_3)_2$,

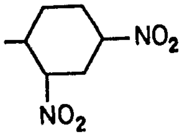
, $-CH_2SCH_3$, or  $-CH_2OC(=O)C(CH_3)_3$; and

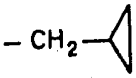
R^1 is CH_3, – CH_2CH_3, – $CH_2CH=CH_2$, – $CH_2CH_2CH_3$, – $CH_2(C_6H_5)$, – $CH(C_6H_5)_2$, $-C(C_6H_5)_3$,  $-CH_2C(CH_3)=CH_2$, $-CH_2OCH_3$, $-CH_2CH=CH-CH_3$, $-CH_2CH_2CH=CH_2$,

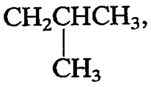
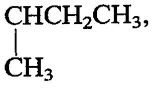
, a salt of – $CH_2CH_2\overset{\oplus}{N}(CH_3)_3$,  – $CH_2C(=O)CH_3$,

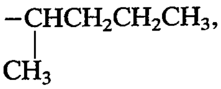
– $CH_2CH_2(OCH_3)_2$, – $CH_2 - C \equiv CH$,  – $CH_2C(=O)(C_6H_5)$, – CH_2SCH_3,

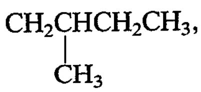
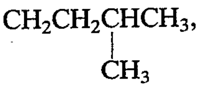
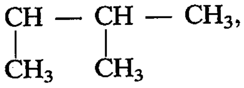
 $-CH_2OC(=O)C(CH_3)_3$, – $CH_2CH_2C \equiv N$,  – $CH_2CH_2C(=O)OCH_3$,

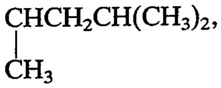
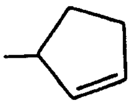
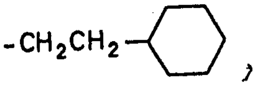


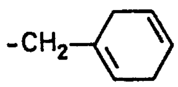


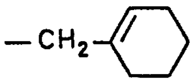
– $CH(CH_3)_2$, – $CH_2CH_2CH_2CH_3$,  – $CH_2CH(CH_3)CH_3$,  – $CH(CH_3)CH_2CH_3$,

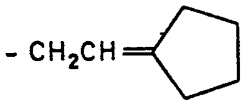
 $-CH(CH_3)CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_2CH_3$,

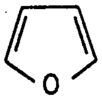
 – $CH_2CH(CH_3)CH_2CH_3$,  – $CH_2CH_2CH(CH_3)CH_3$,  – $CH(CH_3)-CH(CH_3)-CH_3$, – $CH_2C(CH_3)_3$,

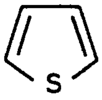
 – $CH(CH_3)CH_2CH(CH_3)_2$,   

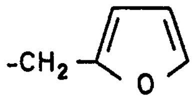


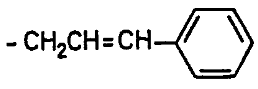


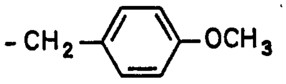






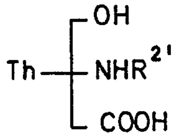




or  .

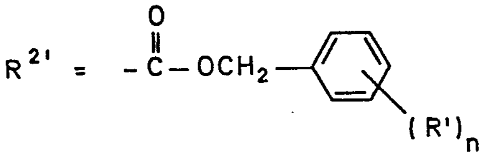
Preparation of Starting Materials Ia, Ib and Ic

The above-described starting materials are conveniently prepared from an N-protected thienamycin species such as an N-acylated thienamycin (1):



1

where $R^{2'}$ 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-fluorenylmethoxycarbonyl, dichloroacetyl, *o*-nitrophenylsulfenyl, 2,2,2-trichloroethoxycarbonyl, bromo-*t*-butoxycarbonyl or phenoxyacetyl; non-acyl protective groups such as tri-(lower alkyl)silyl, for example, trimethylsilyl and *t*-butyldimethylsilyl, are also of interest. The particularly preferred N-blocking groups are substituted and unsubstituted carbobenzyloxy radicals:



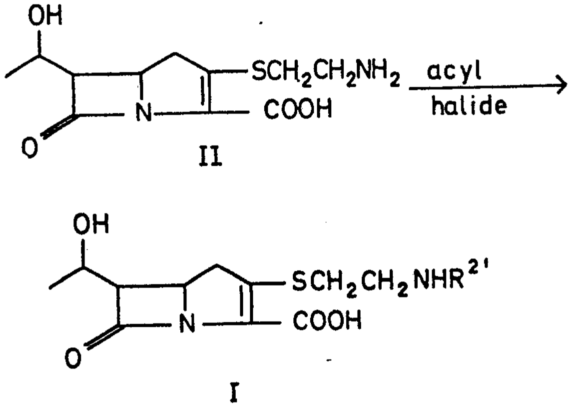
where *n* is 0, 1 or 2 and R′ is lower alkoxy or nitro; and bromo-*t*-butoxycarbonyl.

The ultimate N-deblocking procedure for the preparation of Ia, Ib or Ic is accomplished by any of a variety of well known procedures, which include hydrolysis or hydrogenation; suitable conditions for hydrogenation involve 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 above) is prepared by treating thienamycin (II) 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 lower 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-acylated thienamycin starting materials are fully described in the above-cited specification of copending Application No 48236/76 (1570986).

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 −9° 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), hexamethylphosphoramide (HMPA), acetone, dioxane, tetrahydrofuran

(THF), acetonitrile, heterocyclic amines such as pyridine, ethyl acetate and aqueous mixtures of the above, as well as 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 about 0.5 to about one hour is sufficient. The following formulae illustrate 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.

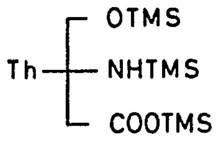


II

I

Generally, when the above-described acylating reaction involves 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.

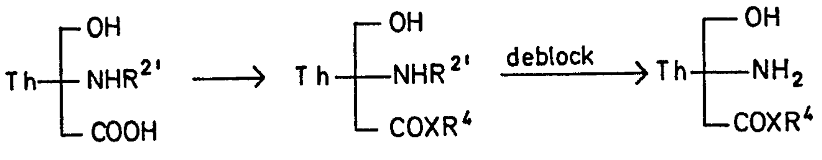
In carrying out these reactions, it is usually not necessary to protect the 2-carboxy group or the $1'$-hydroxy group; however, in cases where the acylating reagent is exceedingly water-sensitive it is sometimes advantageous to perform the acylation in a non-aqueous solvent system. Triorganosilyl (or tin) derivatives of thienamycin proceed, rapidly to give the *tris*-triorganosilyl derivative, for example *tris*-trimethylsilyl thienamycin $Th(TMS)_3$:



$$Th \left[\begin{array}{l} OTMS \\ NHTMS \\ COOTMS \end{array} \right.$$

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



$$Th \left[\begin{array}{l} OH \\ NHR^{2'} \\ COOH \end{array} \right. \longrightarrow Th \left[\begin{array}{l} OH \\ NHR^{2'} \\ COXR^{4} \end{array} \right. \xrightarrow{deblock} Th \left[\begin{array}{l} OH \\ NH_2 \\ COXR^{4} \end{array} \right.$$

1 1b Ib

wherein all symbolism is as previously defined.

In general, the transformation (1 → Ib) is accomplished by conventional procedures known in the art. Such procedures include:

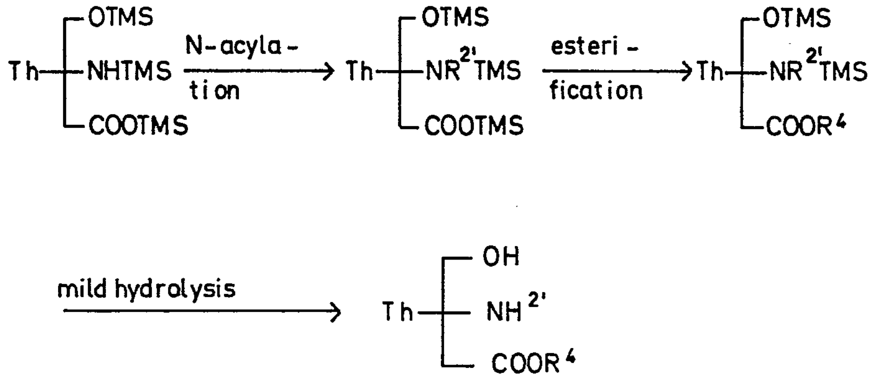
1.) Reaction of 1 (or II, thienamycin) with a diazoalkane such as diazomethane, phenyldiazomethane or diphenyl-diazomethane in a solvent such as dioxane, ethyl acetate or acetonitrile at a temperature of from 0°C to reflux for from a few minutes to 2 hours.

2.) Reaction of an alkali metal salt of 1 with a activated alkyl halide such as methyliodide, benzyl bromide, or *m*-phenoxybenzyl bromide, *p*-*t*-butylbenzyl bromide or pivaloyloxymethyl chloride. Preferred reaction conditions include the use of a solvent such as hexamethylphosphoramide at a temperature of from 0°C to 60°C for from 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 solvents, 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^4X' where X' is halogen such as bromo and chloro and R^4 is as defined with respect to Formula (I) at the beginning of the specification, in a solvent such as THF or CH_2Cl_2 at a temperature of from 0°C to reflux for from 15 minutes to 15 hours, for example according to the following scheme:

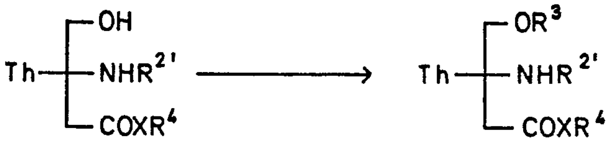


where TMS is triorganosilyl such as trimethylsilyl and all other symbolism is as previously defined.

Amides are most conveniently prepared by reacting the acid anhydride of Ib (X = O, R = 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 all of general organic synthesis and it is to be noted that the reaction parameters are not unduly critical in the preparation of the N-acylated, carboxyl derivatives Ib useful as starting materials in the practice of the present invention.

Starting materials Ia and Ic are conveniently prepared by any of a variety of well-known esterification or etherification reactions upon the secondary alcoholic group of 1b Such procedures include:



1b 2

1.) For the preparation of ethers of the present invention, the acid-catalysed reaction of 1b with a diazoalkane such as diazomethane, phenyldiazomethane or diphenyldiazomethane in an inert solvent such as dioxane, tetrahydrofuran (THF), halohydrocarbons, 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 1b with an alkylating agent such an active halide, for example methyl iodide, benzyl bromide or *m*-phenoxybenzyl bromide; or an alkyl sulfate such as dimethyl sulfate, diethyl sulfate or methyl fluorosulfate 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 hydrous oxides, 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 any inert anhydrous solvent 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.

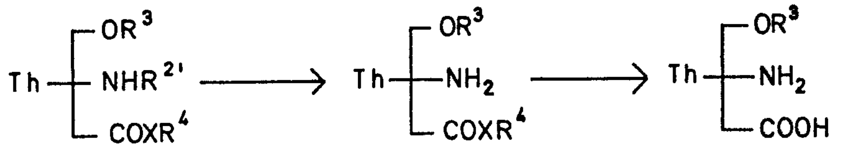
3.) For the preparation of esters of the present invention, the reaction of 1b with any of the above-listed acyl radicals in their acid form. This reaction may be conducted in the presence of a carbodiimide condensing agent such as dicyclohexylcarbodiimide. Suitable solvents include any inert solvent such as $CHCl_3$, CH_2Cl_2, DMF, HMPA, acetone or 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 1b with an acyl halide or an acid anhydride, where the acyl residue is described above. Generally, when the above-described acylating reaction involves an acid halide (suitable halides are chlorides, iodides and bromides) 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, bromoacetic 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-guanidino-phenylacetyl chloride hydrochloride, methanesulfonyl chloride, dibenzylphosphorochloridate, dimethylthiophosphorochloridate, 2-furoyl ethyl carbonates ($Z{-}CO{-}O{-}CO{-}O{-}C_2H_5$, where Z is 2-furyl), methylchloroformate and *bis*-(*p*-nitrobenzyl)phosphorochloridate.

5.) For the preparation of esters of the present invention, the reaction of 1b with a suitably substituted ketene or isocyanate such as ketene, dimethyl ketene, methylisocyanate, methylisothiocyanate, or chlorosulfonyl isocyanate. Suitable solvents include dioxane, tetrahydrofuran and chloroform at a temperature of from −70°C to 60°C from 15 minutes to 18 hours.

The intermediate compound 2 is then N-deblocked as described above to provide starting material Ic. From Ic, Ia is prepared by deblocking the carboxyl group:

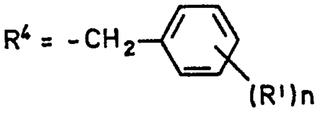


2 Ic Ia

Starting material Ia is conveniently and preferably obtained when X is oxygen and R^4 is a readily removable carboxyl protecting or 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, wherein the intermediate species (Ic or 2) in a solvent such as a lower 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^4 include the sub-generic groups defined above as aralkyl, haloalkyl, alkanoyloxyalkyl, alkoxy-alkyl, alkenyl, substituted alkyl, or aralkoxyalkyl, and also including alkylsilyl, where alkyl has 1-10 carbon atoms. For example, suitable "blocking groups" R^4 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:



wherein n is 0,1 or 2 and R' is lower alkoxyl or nitro.

Normally, the final step in the preparation of the compounds of the present invention is the above described N-acylation reaction, III → I. This N-acylation is exactly as described for the establishment of $R^{2'}$ (structure 1, above) except that $R^{2'}$ is generically the above described acyl radical R^2. Also, the establishment of R^3, $-COXR^4$ or R^3 and $-COXR^4$ may be effected after the establishment of radicals R^1 and R^2 on the amino nitrogen of I to obtain further derivatized embodiments of I; such derivatizations are accomplished exactly as described for the preparation of Ia, Ib and Ic, above.

The products of this invention (I) form a wide variety of pharmacologically acceptable salts with inorganic and organic bases; these include, for example, metal salts derived from alkali or alkaline earth metal hydroxides, carbonates or bicarbonates and salts derived from primary, secondary or tertiary amines such as monoalkylamines, dialkylamines, trialkylamines, lower alkanolamines, di-lower-alkanolamines, lower alkylenediamines, N,N-diaralkyl-substituted lower alkylenediamines, aralkylamines, amino-substituted lower alkanols, N,N-di-lower alkylamino-substituted lower alkanols, amino-substituted polyamino-substituted and guanidino-substituted lower alkanoic acids and nitrogen-containing heterocyclic amines. Representative examples includes salts derived from sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium hydroxide, calcium carbonate, trimethylamine, triethylamine, piperidine, morpholine, quinine, lysine, protamines, arginine, procaine, ethanolamine, morphine, benzylamine, ethylenediamine, N,N'-dibenzylethylenediamine, diethanolamine, piperazine, 2-dimethylaminoethanol, 2-amino-2-methyl-1-propanol, theophylline and N-methylglucamine. Acid-addition salts, e.g. with hydrochloric, hydrobromic, sulfuric, nitric, toluene-*p*-sulfonic and methanesulfonic acids may also be prepared when the acyl radical contains a basic group.

The salts can be mono-salts, such as the monosodium salt obtained by treating one equivalent of sodium hydroxide with one equivalent of the product (I), or mixed di-salts. Such salts may be obtained by treating one equivalent of a base having a divalent cation, such as calcium hydroxide, with one equivalent of the product (I). 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.

The novel thienamycin derivatives of the present invention are valuable antimicrobial substances which are active against various gram-positive and gram-negative pathogens. The present invention provides pharmaceutical compositions containing a compound in accordance with the invention together with a pharmaceutical carrier. These compositions are preferably in unit dosage form, each unit dosage containing a therapeutically effective amount of the compound. They may also contain an antibiotic and/or therapeutic agent that is not a compound in accordance with the invention. Thus, the free acid and especially the salts thereof such as amine and metal salts, particularly the alkali metal and alkaline-earth metal salts, are useful bactericides and can be used for removing susceptible pathogens from dental and medical equipment, for separating micro-organisms, and for therapeutic use in humans and animals. For this latter purpose pharmacologically acceptable salts with inorganic and organic bases such as those known in the art and used for the administration of penicillins and cephalosporins can be utilized. For example, salts such as alkali metal and alkaline earth metal salts, and primary, secondary and tertiary amine salts can be used for this purpose. These salts can be combined with pharmaceutically acceptable liquid and solid vehicles to form suitable dosage unit forms such as pills, tablets, powders, suspensions capsules, suppositories, syrups, or elixirs which can be prepared in accordance with procedures well known in this art.

The novel compounds are valuable antibiotics active against various gram-positive and gram-negative bacteria, and accordingly, find utility in human and veterinary medicine. The compounds of this invention can therefore be used as antibacterial drugs for treating infections caused by gram-positive or gram-negative bacteria, for example against *Staphylococcus aureau, Escherichia coli, Klebsiella pneumoniae, Bacillus substilis, Salmonella typhosa, Pseudomonas* and *Bacterium proteus*. The antibacterials of the invention may further be utilized as additives to animal feeding stuffs, for preserving human foodstuffs and as disinfectants. For example, they may be employed 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 growthof 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 employed 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 tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of aqueous or oily suspensions, solutions, emulsions, syrups or elixirs or may be presented as a dry powder, for reconstitution with water or other suitable liquid before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethyl cellulose, 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 glyceride.

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 dry powder form for reconstitution with a suitable sterile liquid, 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 or throat paints. For medication of the eyes or ears, the preparations may be presented as ophthalmic or otic liquids, e.g. in individual capsules or drops, or in semi-solid form. Topical applications may be formulated in hydrophobic or hydrophilic bases as ointments, creams, lotions, paints and 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 acting 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 15 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 80 to 120 mg of active ingredient per kg of body weight.

The compositions may be administered in several unit dosage forms as, 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% by weight of active material, the preferred range being from about 10-60%. The composition will generally contain from 15 mg to 1500 mg of the active ingredient; however, in general, it is preferable to use a dosage in the range of from 250 mg to 1000 mg. In parenteral administration the unit dosage is usually the pure compound in a slightly acidified sterile water solution or in the form of a soluble powder intended for dissolution.

The following Examples illustrate but do not limit the present invention. In the Examples the words "Dowex", "Nujol" and "Celite" are trade marks, and the XAD resins are manufactured by Rohm & Haas of Philadelphia.

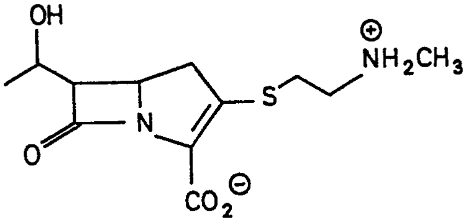
EXAMPLE 1

N-Ethyl-thienamycin

Thienamycin (120 mg) is dissolved in a mixture of 7 ml of 0.1*N* pH 7 phosphate buffer and 3 ml of acetonitrile. The solution is adjusted to pH 9 by the addition of 1*N* sodium hydroxide solution. Ethyl fluorosulfonate $C_2H_5FSO_2$ (0.5 ml) is added dropwise during 8 minutes while the pH is maintained by an automatic titrator. At the end of the reaction the mixture is adjusted to pH 7, diluted with 20 ml of water and then rapidly concentrated under reduced pressure to 10 ml. The dilution and concentration are repeated to further lower the acetonitrile content, then the solution is chromatographed on a column (2 cm × 51 cm) of XAD−2 resin. The column is eluted with water, taking 27 ml fractions. Thienamycin is recovered in fractions 18−30. The combined product fractions are concentrated to 10 ml and freeze dried, yielding 14 mg (12%) of N-ethyl-thienamycin. The 100 MHz NMR spectrum shows NCH_2CH_3 triplet at 1.3 δ superimposed on the CH_3CHOH side chain doublet of equal intensity. The mass spectrum after silylation shows a molecular ion at m/e 444 corresponding to the disilyl derivative of N-ethyl-thienamycin.

EXAMPLE 2

Preparation of N-Methyl-Thienamycin



N-thioformyl-thienamycin (80 mg) is dissolved in pH 7 0.1*N* phosphate buffer (8 ml) and cooled in an ice bath. Deactivated Raney Nickel (Raney Nickel refluxed 1 hr. in acetone, 500 mg) suspended in ethyl acetate is then added to the magnetically stirred solution. The mixture is stirred for 3 min and the catalyst separated from the solution. The product solution is chromatographed on Dowex 50−X4 (Na^+ cycle, 200−400 mesh, 53 cc) and eluted with water. The N-methyl-thienamycin derivative is eluted in 2−3 column volumes and is lyophilized to a white solid (8 mg)

UV (PH 7 0.1N phosphate buffer) λ_{max} 298 nm

IR (Nujol mull) 1755 cm^{-1} (β-lactam)

NMR (100 MHZ, D_2O) δ 1.29 (d, J = 6Hz, CH_3 −CH),
2.68 (S, NCH_3), 3.0−3.3 (m, − CH_2CH_2N, CH_2 − CS)
3.42 (q, C_6H), 4.1−4.5 (m, C_5H, C_7H).

EXAMPLE 3

N-Acetyl-N-ethyl-thienamycin sodium salt

A solution of N-ethyl-thienamycin (8.4 mg) in 7.5 ml of 0.1*N* pH 7 phosphate buffer is adjusted to pH 8.3 with 1*N* sodium hydroxide solution. Acetic anhydride (0.1 ml) is added and the solution is stirred at room temperature for 15 minutes while maintaining the pH at 8.3 by means of an automatic titrator. The reaction mixture is chromatographed on 15 ml of XAD−2 resin, eluting with water. The product peaks at 2 column volumes and the combined product fractions (UV 84 ODU at λ_{max} 302 nm) are concentrated and freeze dried to a white powder, wt 3.4 mg. Electrophoresis (50 V/cm, 20 min, pH 7) gives a single bioactive zone at + 3.5 cm.

EXAMPLE 4

N-Acetyl-N-Methyl-thienamycin sodium salt

Following the procedure of Example 3 except substituting an equivalent amount of N-methyl-thienamycin (Example 2) for the N-ethyl-thienamycin of Example 3 there is obtained N-acetyl-N-methyl-thienamycin.

EXAMPLE 5

N-Methylthienamycin Benzyl Ester

A solution of N-methylthienamycin (50 mg) in 1 ml of water and 1 ml of dioxane is cooled to 0°c and adjusted to pH 5 with 1*N* sulfuric acid. Phenyldiazomethane, (37 mg) in 0.5 ml of dioxane is added during 5 minutes while the pH is maintained at 5 to 5.5 by means of an automatic titrator. The mixture is diluted with water (5 ml) and extracted with ether. The aqueous phase is overlayered with ethyl acetate, cooled and adjusted to pH 2.5. The ethyl acetate is separated by centrifugation and the aqueous phase is adjusted to 0.48 with sodium bicarbonate and extracted twice with ethyl acetate. The extracts are combined and evaporated and the product is isolated by preparative thin-layer chromatography on silica gel using 5:1 (v:v) chloroform-methanol solvent.

EXAMPLE 6

N-Methyl-N-acetyl-thienamycin pivaloyloxymethyl ester

A solution of N-methyl-N-acetylthienamycin sodium salt (30 mg) and pivaloyloxymethyl bromide (25 mg) in 0.2 ml of hexamethylphosphoramide is stirred at 23°C for one hour. Ethyl acetate (5 ml) is added and the mixture is extracted successively with aqueous sodium bicarbonate solution, water and saturated sodium chloride solution. The organic phase is dried and evaporated to a small volume and chromatographed on an 8″ × 8″, 1000 μ silica plate using 5:1 chloroform-methanol solution. The band containing N-methyl-N-acetylthienamycin pivaloyloxymethyl ester is scraped off and eluted with ethyl acetate.

EXAMPLE 7

N-Ethyl-N-acetylthienamycin 3-methyl-2-butenyl ester hydrochloride

To a solution of N-Ethyl-N-acetylthienamycin (30 mg) in 0.5 ml of 3-methyl-2-butenyl alcohol is added 21 mg of dicyclohexyl carbodiimide. The solution is stirred at 23°C for one hour, then filtered from dicyclohexylurea. The filtrate is evaporated and the residue chromatographed on an 8″ × 8″ 500 μ silica gel plate, developed with 1:1 (v:v) ethyl acetate-chloroform.

Following the above procedure but substituting 2-methylthioethanol for 3-methyl-2-butenol there is obtained N-Ethyl-N-acetylthienamycin 2-methylthioethyl ester.

EXAMPLE 8

O, N-Diacetyl-N-ethylthienamycin

N-Ethyl-thienamycin (100 mg) is added to a mixture of 0.3 ml of acetic anhydride in 1 ml of pyridine. The mixture is allowed to react at 23°C for three hours, then pumped to dryness under vacuum. The solid residue is dissolved in water and chromatographed on 100 ml of XAD−2 resin. After eluting with water the product is eluted with 10% THF. The fractions containing O,N-diacetyl-N-Ethyl-thienamycin are combined, evaporated and freeze-dried.

EXAMPLE 9

N-Ethyl-N-acetyl-O-sulfo-Thienamycin benzyl Ester

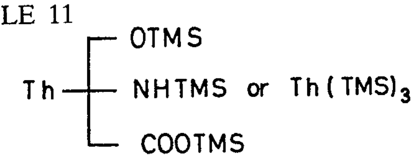
To a solution of N-ethyl-N-acetyl-thienamycin benzyl ester (39 mg) in 0.3 ml of pyridine is added sulfur trioxide-pyridine (17 mg). The mixture is stirred at 25°C. for three hours and the excess of pyridine is evaporated off under reduced pressure. The residue is taken up in 5 ml of water containing 10 mg of sodium bicarbonate and extracted once with ethyl acetate. The aqueous solution is concentrated to 2 ml. and chromatographed on 50 g of XAD−2 resin. The fractions containing N-Ethyl-N-acetyl-O-sulfo-thienamycin benzyl ester are combined, concentrated and freeze dried.

EXAMPLE 10

N-Ethyl-N-Acetyl-O-sulfo-thienamycin sodium salt

A solution of N-Ethyl-N-acetyl-O-sulfo-thienamycin benzyl ester (24 mg) in 1 ml of water containing 5 mg of sodium bicarbonate is hydrogenated in the presence of 20 mg of palladium oxide at 23°C under 1 atm pressure for 2 hours. The catalyst is removed by filtration and the filtrate is chromatographed on 20 g of XAD-2 resin. The fractions containing N-ethyl-N-acetyl-O-sulfo-thienamycin sodium salt are combined, concentrated and freeze-dried.

EXAMPLE 11



$$\mathrm{Th}\left[\begin{array}{l}\mathrm{OTMS}\\ \mathrm{NHTMS}\\ \mathrm{COOTMS}\end{array}\right. \text{ or } \mathrm{Th(TMS)_3}$$

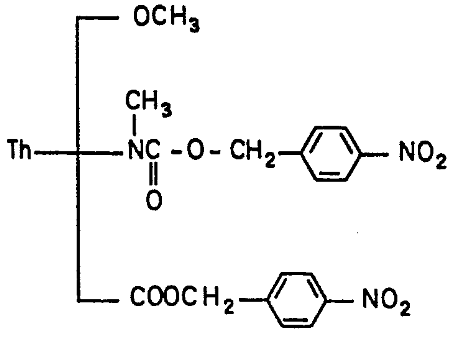
TMS=trimethylsilyl

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 trimethychlorosilane (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 12

Preparation of O,N-Dimethyl-N-(p-Nitrobenzyloxycarbonyl)-Thienamycin-p-Nitrobenzyl Ester



Step A

N-Methyl-N-(p-Nitrobenzyloxycarbonyl) thienamycin Lithium Salt

To N-methyl-thienamycin (220 mg. in 60 ml. water at 0°C) is added successively, 679 mg. $NaHCO_3$, 60 ml dioxane and then with stirring 1.1 equivalents *p*-nitrobenzyl chloroformate over a period of 1.5 minutes. The mixture is allowed to react for 10 minutes, and is then extracted three times with cold ethyl ether. Electrophoresis (0.05 M, pH 7, phosphate buffer, 50V/cm., 20 minutes) shows no free N-methyl-thienamycin present. The aqueous extract is adjusted to pH 2.2 with $1MH_3PO_4$ solution and extracted three times with EtOAc The EtOAc extract is dried over $MgSO_4$, filtered and reextracted 0.1 *N* LiOH, to pH 8.2. The final pH is adjusted to 7.0 with 1*M* H_3PO_4 and the sample lyophilized.

Step B

N-Methyl-N-(p-Nitrobenzyloxycarbonyl)-Thienamycin(p-nitrobenzyl)ester

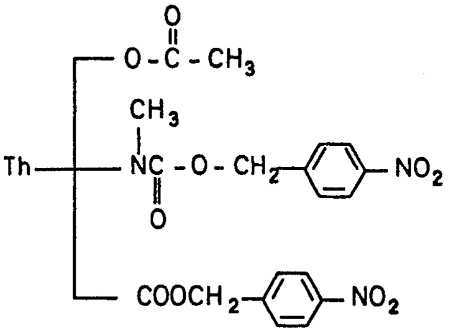
A mixture of *p*-nitrobenzyloxycarbonyl-N-methyl-thienamycin lithium salt (295 mg.) and 0.4 g. of *p*-nitrobenzyl bromide in 3 ml. of hexamethyl phosphoramide is stirred for 3 hours at 25°C. The solution is diluted with 50 ml. of ethyl acetate and extracted successively with water (3 portions), pH 7 phosphate buffer and saturated sodium chloride solution. The organic phase is dried over magnesium sulfate and evaporated to 5 ml., causing the product to crystallize. The crystals are collected and washed with ethyl acetate.

Step C

O, N-Dimethyl-N-p-Nitrobenzyloxycarbonyl)-thienamycin(p-Nitrobenzyl ester

To a solution of 135 mg. of N-methyl-N-*p*-nitrobenzyloxycarbonyl-Thienamycin (p-nitrobenzyl) ester in 50 ml. of methylene chloride at 0°C. is added with vigorous stirring 0.5 ml of 0.006 *M* fluoboric acid in ether-methylene chloride (3:1) (v/v) immediately followed by 10 ml. of a cooled solution of 0.6 *M* diazomethane in methylene chloride. The diazomethane is decolorized in one minute. The solution is extracted with 10 ml of 0.1N pH 7 phosphate buffer, dried and evaporated to a small volume. The solution is applied to two 8″ × 8″ 1000 μ silica gel plates, which are developed with 3:1 ethyl acetate-chloroform. The band containing O,N-dimethyl-N-*p*-nitrobenzyloxycarbonyl-thienamycin *p*-nitrobenzyl ester is eluted with ethyl acetate and the product is recovered by evaporation of the eluate.

EXAMPLE 13

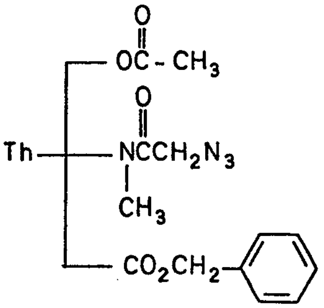


Preparation of O-Acetyl-N-Methyl-N-(p-nitrobenzyloxycarbonyl)-thienamycin(p-nitrobenzyl)ester

To a solution of 50 mg of N-methyl-N-(*p*-nitrobenzyloxycarbonyl)-thienamycin) *p*-nitrobenzyl ester in 0.5 ml. of pyridine is added 0.16 ml. of acetic anhydride. The mixture is allowed to react at 25°C. for three hours, then pumped to dryness under vacuum. The solid residue is dissolved in chloroform and chromatographed on an 8″ × 8″ 1000 μ silica gel plate in 3:1 (v/v) ethyl acetate-chloroform yielding O-acetyl-N-methyl-N-*p*-nitrobenzyloxycarbonyl-thienamycin *p*-nitrobenzyl ester.

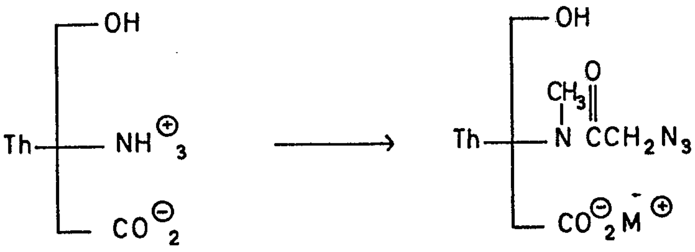
EXAMPLE 14

Preparation of O-Acetyl-N-Methyl-N-Azidoacetyl-thienamycin Benzyl ester



Step A

Preparation of N-Methyl-N-Azidoacetyl-Thienamycin Sodium (I) and Lithium (II) Salts



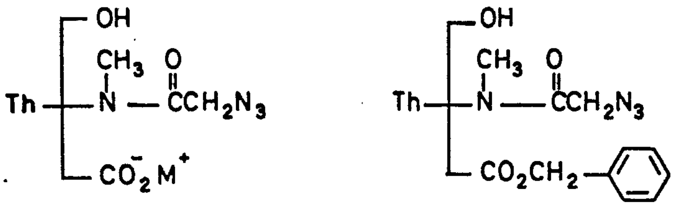
M = Na, Li

(I) N-Methyl-thienamycin (48 mg) is dissolved in 10 ml. cold water and is kept at 0°C. To the solution is added sodium bicarbonate (147 mg., 17.6 mmol) and dioxane (10 ml.). Azidoacetyl chloride (60 mg., 0.50 mmol) is added to the solution during a period of 2 min. The reaction mixture is stirred for 15 min. then is neutralized to pH 7.0 with 30% phosphoric acid and is transferred into a separatory funnel. The solution is extracted with 2

× 50 ml of ether. The aqueous layer is concentrated to 5 ml. and then is charged to a Dowex AG–50×8 (sodium form) ion-exchange column monitored by UV. The desired fractions are combined and lyophilized to give the desired sodium salt.

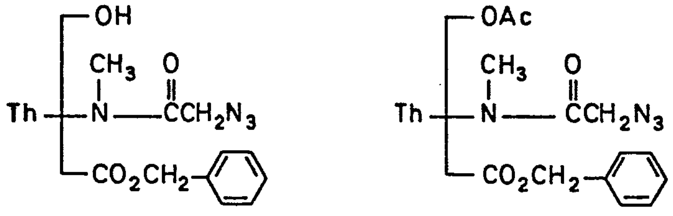
(II) N-Methyl-thienamycin (76.2 mg) is dissolved in 10 ml. of cold water and is kept at 0°C. To the solution is added 0.6 ml. of 1.0 *N* lithium hydroxide solution and 10 ml. dioxane. After stirring for 1 min., azidoacetyl chloride (33.6 mg., 0.28 mmol.) is added during a period of 2 min. The reaction mixture is stirred for additional 1 min. then is neutralized to pH 7.0 with 30% phosphoric acid. After extraction with ether, the aqueous solution is concentrated to 5 ml. and is charged to the Dowex AG-50×8 (lithium form) ion-exchange column. The desired fractions are combined and lyophilized to give the desired lithium salt.

Step B
Preparation of N-Methyl-N-Azidoacetyl-Thienamycin Benzyl Ester



N-Methyl-N-azidoacetyl-thienamycin lithium salt (3.0 mg) is stirred with hexamethylphosphoramide (HMPA) (1.0 ml) and benzyl bromide (30 mg, 0.21 mmol) for 30 min. The reaction mixture is then diluted with ethyl acetate (5 ml) and washed thoroughly with water. The organic layer is separated and dried over sodium sulfate. The product is isolated by silica gel TLC.

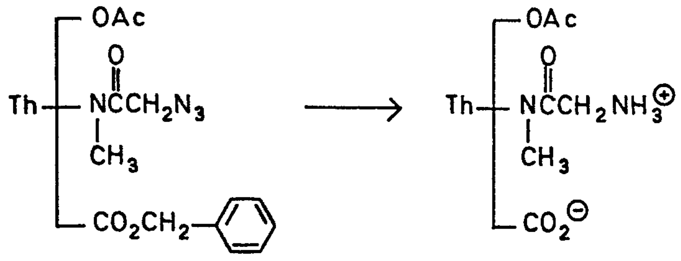
Step C
Preparation of O-Acetyl-N-Methyl-N-Azidoacetyl-ThienamyciN Benzyl Ester



N-Methyl-N-Azidoacetyl-thienamycin benzyl ester (30 mg) is dissolved in 0.5 ml of pyridine. To the solution is added acetic anhydride (0.2 ml). The mixture is kept at room temperature for 40 min. The solution is diluted with 1 ml ethyl acetate and washed with ice-water. The organic layer is separated and dried over sodium sulfate. The desired product is isolated by silica gel TLC.

EXAMPLE 15

Preparation of O-Acetyl-N-Methyl-N-Glycyl-Thienamycin



O-Acetyl-N-Methyl-N-Azidoacetyl-ThienAmycin-benzyl ester (5.0 mg) is dissolved in 0.3 ml dioxane. The solution is added to a hydrogenation flask containing 20 mg of palladium (from palladium oxide) and 0.5 ml 50% dioxane in water and shaken under 45 psi H_2 for 10 mins at 25°C. The catalyst is removed by filtration. After extraction with ether, the solution is lyophilized to give the desired product.

EXAMPLE 16

Preparation of N-methyl-N-(p-Methoxybenzyloxycarbonyl)-thienamycin Sodium Salt

To N-Methyl-thienamycin (20 mg) in 5 ml water at 0°C is added 105 mg $NaHCO_3$, 5 ml. dioxane, and then, dropwise with stirring over 1 min. ten equivalents of *p*-methoxybenzyl chloroformate. After 15 min. the pH is adjusted to 7.5 with 1*M* H_3PO_4 and the solution extracted 3× with ether. The aqueous portion is then adjusted to pH 2.2 at 0°C and extracted 3× with ethyl acetate (EtOAc). The EtOAc is dried quickly with $MgSO_4$, filtered and extracted with a 7.5 ml of an aqueous solution of $NaHCO_3$ (0.01*M*). The extract is lyophilized yielding the product as a light powder.

EXAMPLE 17

Preparation of N-Methyl-N-Bromoacetyl-thienamycin Methyl and Benzyl Esters

Step A: N-methyl-N-Bromoacetyl-thienamycin

To a cooled solution of N-Methyl-thienamycin (28.8 mg.) and sodium bicarbonate (0.3 g.) in 10 ml. of water and 8 ml. of dioxane is added with stirring a solution of 0.25 g. of bromoacetic anhydride in 2 ml. dioxane over a period of 20 minutes. The pH is maintained at 8.0. The mixture is stirred for an additional 5 minutes, then layered with 10 ml. of ether and the pH adjusted to 7 by the addition of 8% phosphoric acid. The ethereal layer is separated and the aqueous layer is extracted twice again with ether. The aqueous layer is evaporated under reduced pressure to 0.5 ml., diluted to 2 ml. with water and put on 50 ml. of XAD-2 resin.

The column is eluted with water. The first 80 ml. is discarded, then the next 100 ml. is collected. The solvent is changed to 10% THF and an additional 100 ml. collected. The combined eluates are adjusted to pH 7, evaporated to 5 ml. under reduced pressure, then freeze-dried to give the sodium salt of N-Methyl-N-bromoacetyl-thienamycin.

Step B

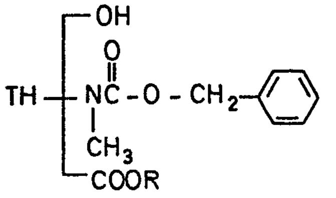
N-methyl-N-Bromoacetyl-thienamycin Methyl and Benzyl Esters

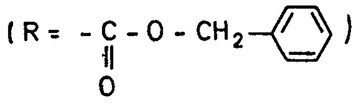
An aqueous solution of the sodium salt is layered with ethyl acetate at 0°C. and adjusted to pH 2. The ethyl acetate phase is separated and the aqueous phase is extracted with ethyl acetate. The combined ethyl acetate solutions are dried over $MgSO_4$ and then treated with a solution of diazomethane. The solvents are evaporated and the residue chromatographed on silica gel plate in 2:1 (v/v) ethyl acetate-chloroform.

The corresponding benzyl ester is prepared in a similar way from phenyldiazomethane.

EXAMPLE 18

Preparation of N-Methyl-N-benzyloxycarbonyl thienamycin and N-Methyl-N-Benzyloxycarbonyl-Thienamycin Benzyloxycarboxylic Acid Mixed Anydride





A solution of 16.6 mg of N-methyl-thienamycin in 4 ml. of 0.05M pH 7 phosphate buffer and 2 ml. of dioxane in a 3-necked flask fitted with a stirrer, thermometer, pH electrode and the delivery tip of an automatic titrator is cooled to −8°C. in a methanol-ice bath. The pH is brought to 8.2 by the addition of 0.2*N* sodium hydroxide in 50% aqueous dioxane and a solution of 0.015 ml of carbobenzyloxy chloride (benzyl chloroformate, C2—$COOCH_2C_6H_5$) in 2 ml. of chloroform is added. The mixture is stirred at −6°C., pH 8.2, for ten minutes, then layered with ether and the pH is adjusted to 7 by the addition of *N* hydrochloric acid. The layers are separated by centrifugation and the aqueous phase is extracted twice again with ether. The aqueous phase is layered with ethyl acetate and acidified to pH 2. The ethyl acetate is separated and the aqueous layer is extracted again with ethyl acetate. The combined ethyl acetate layer is washed with saturated sodium chloride solution, dried over magnesium sulfate and filtered. The filtrate is stirred with water and the pH brought to 7 by the addition of dilute sodium bicarbonate solution. The aqueous phase is separated and freeze dried giving the sodium salt of N-Methyl-N-benzyloxycarbonyl-thienamycin. The ethereal extracts of the reaction mixture contain the desired product N-methyl-N-benzyloxycarbonyl-thienamycin benzyloxycarboxylic acid mixed anhydride.

EXAMPLE 19

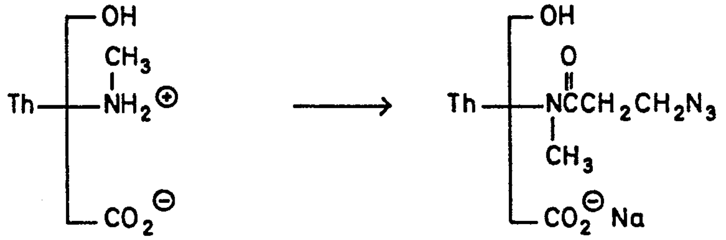
N-Allyl-N-Benzenesulfonyl-thienamycin

N-Allyl-thienamycin (52 mg) is dissolved in pH 7 0.1*N* phosphate buffer (25 ml.) and magnetically stirred in an ice bath. The pH is adjusted to 8.2 with 2.5N NaOH using an automatic dispensing burette and benzenesulfonyl chloride (227 µl, 226 µ-mol) in 500 ml. *p*-dioxane added at once. The pH is maintained at 8.2 (using the automatic burette) for 30 min. and then adjusted to pH 7.0 with dilute aqueous phosphoric acid. The reaction solution is concentrated to 15 ml. and chromatographed on XAD−2 resin (50 cc). The column is eluted with water, then with 10% aqueous tetrahydrofuran which elutes the product. the 10% aqueous tetrahydrofuran eluate is concentrated to 1/3 volume and freeze-dried to give the desired product.

EXAMPLE 20

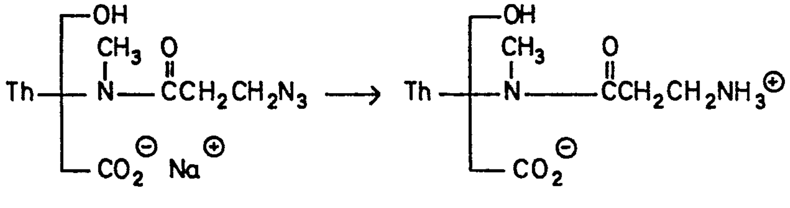
Preparation of N-Methyl-N-[N'-Acetimidoyl-β-alanyl] Thienamycin

Step A: N-[β-Azidopropionyl] Thienamycin

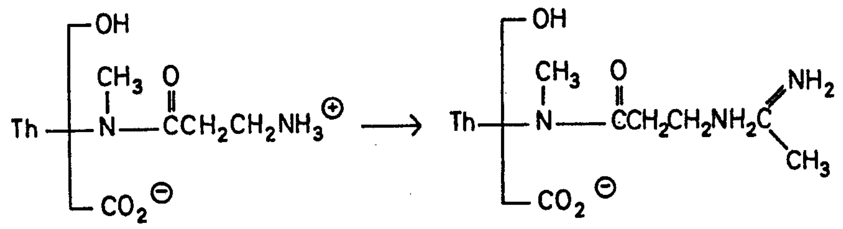


N-Methyl-Thienamycin (184 mg) is dissolved in 30 ml. of water and is kept at 0°C. To the solution is added 0.52 g of $NaHCO_3$, 30 ml of dioxane and 163 mg of β-azidopropionyl chloride. The mixture is stirred for 15 minutes, neutralized with 30% H_3PO_4, and extracted with ether. The aqueous layer is separated and concentrated to 5 ml. The crude product is chromatographed on a Dowex 50W × 8 (Na form) ion-exchange column (1" × 10"). The column is eluted with H_2O to give the desired product.

Step B: N-Methyl-N-(β-Alanyl) Thienamycin



The aqueous solution of N-Methyl-N-(β-azidopropionyl) Thienamycin (40 mg in 20 ml water) is hydrogenated under 1 atm of hydrogen in the presence of 200 mg of palladium at 25°C., for 40 minutes. The resultant solution (pH 9.0) is neutralized with 30% H_3PO_4 and filtered from the catalyst. The mixture is chromatographed on a Dowex 50W × 8 (Na form) ion-exchange column (1" × 10") and the column is eluted with water to give the desired product.



Step C: N-Methyl-N-[N′-Acetimidoyl-β-alanyl] Thienamycin

The aqueous solution of N-Methyl-N-(β-alanyl) thienamycin (125 mg in 15 ml water) is kept at 0°C and maintained at pH 8.5 by adding 2.5*N* NaOH while O-ethylacetimidate hydrochloride (350 mg) is added portionwise to the solution during a period of 10 min. The mixture is stirred for 1 hour then is neutralized with 2.5*N* HCl and concentrated to 15 ml. The solution is chromatographed on a Dowex 50W × 8 (Na form) column (1″ × 10″) eluted with water. The fractions containing the desired product are combined and lyophilized.

EXAMPLE 21

Preparation of N-Methyl-N-(Bromo-t-butyloxycarbonyl) Thienamycin Sodium Salt

N-Methyl-Thienamycin (190 mg) dissolved in 15 ml 0.1*M* pH 7.0 phosphate buffer and 15 ml dioxane is kept at 0°C. The solution is adjusted and maintained between pH 8.5-9.0 with 1*N* NaOH while 480 mg of bromo-*t*-butyl chloroformate is added to the solution during a period of 5 minutes. The mixture is stirred for 30 min., then is neutralized to pH 7.0 with 1*N* HCl and extracted with ether. The aqueous layer is separated, concentrated to 10 ml and chromatographed on a Dowex-50×8 (Na form) column (1.5″ × 10″) which is eluted with H_2O to give the desired product.

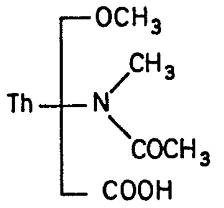
EXAMPLE 22

Preparation of N-Methyl-N-Acetyl-Thienamycin *p*-Nitrobenzyl Ester

N-Methyl-N-acetyl-thienamycin sodium salt (100 mg) is stirred at 25°C., with *p*-nitrobenzyl bromide (300 mg) in 2 ml hexamethylphosphoramide for 1 hour. The mixture is diluted with 10 ml ethyl acetate and then is washed thoroughly with water. the organic layer is separated, dried over Na_2SO_4 and chromatographed on two 250μ silica gel GF TLC plates using ethyl acetate as solvent to give the desired product.

EXAMPLE 23

Preparation of O, N-Dimethyl-N-Acetyl-Thienamycin



Step A: O, N-Dimethyl-N-Acetyl-Thienamycin p-Nitrobenzyl)-Ester

To a solution of 135 mg. of N-Methyl-N-acetyl-Thienamycin *p*-nitrobenzyl ester in 50 ml. of methylene chloride at 0°C. is added with vigorous stirring 0.5 ml of 0.006 *M* fluoboric acid in ether-methylene chloride (3:1 v/v), immediately followed by 10 ml of a cooled solution of 0.6 *M* diazomethane in methylene chloride. The diazomethane is decolorized in one minute. The solution is extracted with 10 m. of 0.1*N* pH 7 phosphate buffer, dried and evaporated to a small volume. The solution is applied to two 8″ × 8″ 1000μ silica gel plates which are developed with 3:1 (v/v) ethyl acetate-chloroform, yielding O,N-dimethyl-N-acetyl-thienamycin (*p*-nitrobenzyl) ester.

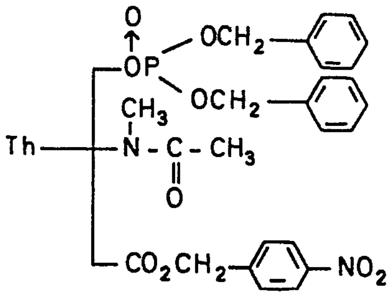
Step B: O, N-Dimethyl-N-acetyl Thienamycin

A solution of 20 mg. of O, N-Dimethyl-N-acetyl-thienamycin *p*-nitrobenzyl ester in 2 ml of tetrahydrofuran and 1 ml of ethanol is hydrogenated at 50 psig, 23°C in the presence of 20 mg of platinum oxide for 2½ hours. The catalyst is filtered and 1 ml of 0.1*N* pH7 phosphate buffer is added to the filtrate. The solution is evaporated under reduced pressure to 2 ml.

and the mixture is taken up in 5 ml of water and 5 ml of ethylacetate and centrifuged. The ethyl acetate layer is removed and the aqueous layer is extracted again with ethyl acetate and with ether and then filtered through Celite. The aqueous solution is applied to a column (20 ml) of XAD-2 resin. The column is first eluted with water and then with 10% tetrahydrofuran. The tetrahydrofuran eluate is concentrated and lyophilized giving substantially pure O, N-dimethyl-N-acetyl-thienamycin sodium salt.

EXAMPLE 24

Preparation of O-Dibenzylphosphoryl-N-Methyl-N-acetyl-Thienamycin p-nitrobenzyl Ester

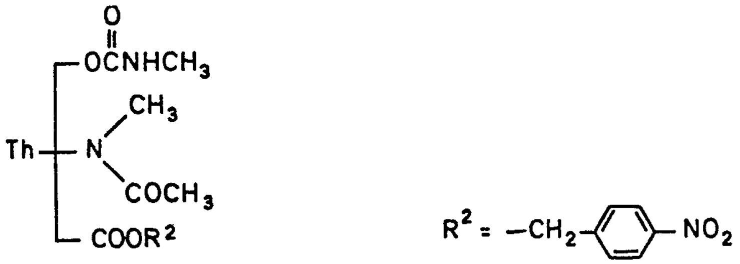


Step A:

To a solution of N-Methyl-N-acetyl-thienamycin (*p*-nitrobenzyl) ester (50 mg) in 5 ml THF at 3°C is added 30 mg of dibenzyl phosphorochloridate followed by 14 μl of triethylamine. The mixture is stirred at 25°C for 2 hours. whereupon the THF is removed *in vacuo*. The residue is taken up in methylene chloride and washed with water. The methylene chloride solution is dried over magnesium sulfate and evaporated. The residue is chromatographed on silica gel yielding O-dibenzylphosphoryl-N-methyl-N-acetyl-thienamycin *p*-nitrobenzyl ester.

EXAMPLE 25

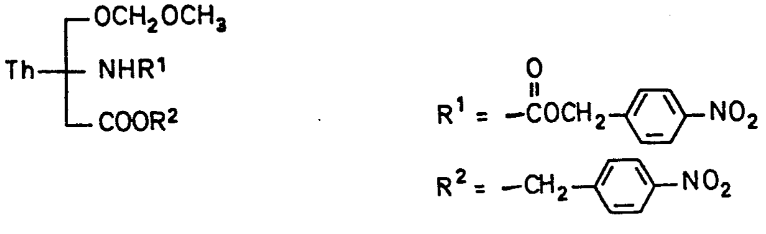
Preparation of O-(Methylcarbamoyl)-N-Methyl-N-acetyl-Thienamycin p-nitrobenzyl ester



A solution of N-Methyl-N-acetyl-thienamycin *p*-nitrobenzyl ester (20 mg) and methyl isocyanate (20 mg) in methylene chloride (5 ml) is stirred at 23°C for 18 hours. The solvent is evaporated and the residue is extracted with hexane. The hexane-insoluble residue is chromatographed on silica gel giving substantially pure O-(methylcarbamoyl)-N-Methyl-N-acetyl-thienamycin *p*-nitrobenzyl ester.

EXAMPLE 26

Preparation of O-(Methoxymethyl)-N-Methyl-N-acetyl-Thienamycin p-nitrobenzyl ester



Step A:

A solution of 58 mg of N-methyl-N-acetyl thienamycin *p*-nitrobenzyl ester in 5 ml of 1.0 ml of THF and HMPA is cooled to −78°C. To this solution is added with stirring a 2N solution of phenyllithium (0.1 ml) immediately followed by the addition of 0.2 ml of methyl chloromethyl ether. The mixture is allowed to warm to 25°C during a period of one hour. Methylene chloride (25 ml) is added and the solution is extracted with 0.1*N*, pH 7, phosphate buffer (25 ml) and water 4 × 25 ml. The methylenechloride solution is evaporated and the residue is triturated with hexane. The hexane insoluble residue is chromatographed on silica gel yielding O-methoxymethyl-N-methyl-N-acetyl-thienamycin (*p*-nitrobenzyl) ester.

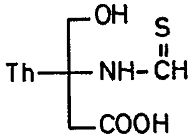
EXAMPLE 27

Preparation of O-Methyl-N-Methyl-N-acetyl-thienamycin Benzyl ester

A solution of 5 mg of N-Methyl-N-carbobenzyloxy-thienamycin benzyl ester in 0.3 ml of methylene chloride is cooled to 0°C and 0.1 ml of a 0.006M solution of fluoboric acid in 5: 1 ether-methylene chloride (v/v) is added, followed immediately by 0.5 ml of 0.1*M* diazomethane in methylene chloride. The solution is decolorized in 1 minute. The mixture is stirred with ether and pH 7 phosphate buffer and the ethereal phase is evaporated. The residue is chromatographed on 2 × 8″ 250μ silica plates in 35% by volume ethyl acetate in chloroform yielding the desired product.

EXAMPLE 28

Preparation of N-Thioformyl-Thienamycin

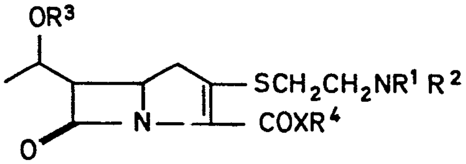


Silylated thienamycin [Th(TMS$_3$), from 100 mg thienamycin, [Example 11] is dissolved in dichloromethane (9 ml) in a stoppered flask under positive nitrogen pressure. To the magnetically stirred solution is added a solution of triethylamine (60 μl) in dichloromethane (1 ml). This is followed by the addition of ethyl thioformate (100μl). After 1 hour the reaction solution is rapidly added to a stirred solution of pH 4 0.1*N* phosphate buffer (20 ml). The mixture is stirred for 5 minutes and the pH of the mixture adjusted to 7.0 with 1*N* NaOH. The aqueous phase is separated, washed with ethyl acetate (2 × 20 ml) and cooled in an ice bath. The solution is layered with ethyl acetate (15 ml) and the pH of the stirred mixture is adjusted to 3.5 with 1*N* phosphoric acid. The organic phase is separated and the buffered aqueous solution washed with ethyl acetate (2 × 15 ml). The combined ethyl acetate washings are concentrated to half volume and layered with water (10 ml). Solid sodium bicarbonate is added until the pH of the mixture is 7.0. The aqueous phase is separated and lyophilized to give the sodium salt of *N*-thioformyl-thienamycin.

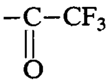
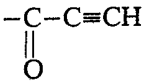
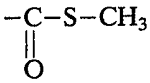
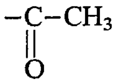
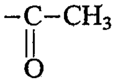
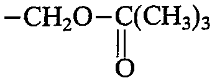
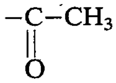
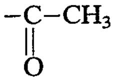
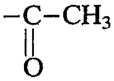
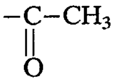
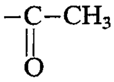
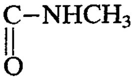
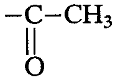
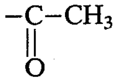
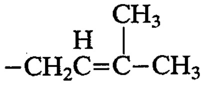
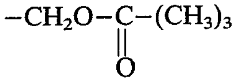
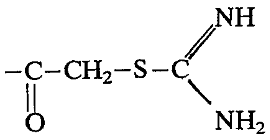
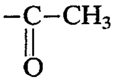
EXAMPLE 29

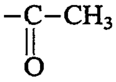
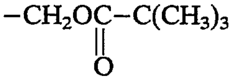
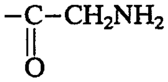
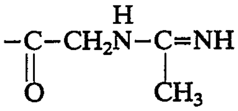
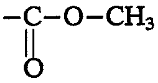
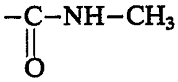
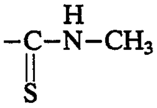
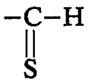
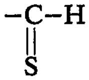
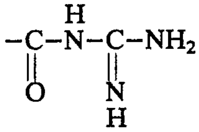
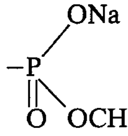
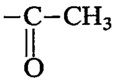
Following the procedure set forth above, the following compounds of the present invention (Table I) are obtained when the indicated N-alkylated starting material is N-acylated with the reagent calculated to provide the species represented in the Table.

TABLE I



Com-pound	R^1	R^2	R^3	R^4	X
1.)	CH_3	$-CHO$	H	Na	0
2.)	CH_3	$-\underset{\underset{O}{\Vert}}{C}-OCH_3$	H	Na	0
3.)	CH_3	$-\underset{\underset{O}{\Vert}}{C}-CH_2NH_2$	H	H	0
4.)	CH_3	$-\underset{\underset{O}{\Vert}}{C}-CH-\overset{H}{N}-\underset{\underset{CH_3}{\vert}}{C}=NH$	H	H	0
5.)	CH_3	$-\underset{\underset{O}{\Vert}}{C}-\underset{H}{N}-CH_3$	H	Na	0
6.)	CH_3	$-\underset{\underset{O}{\Vert}}{C}-CH_2Cl$	H	Na	0
7.)	CH_3	$-\underset{\underset{O}{\Vert}}{C}-CH_2CH_2NH_2$	H	H	0
8.)	CH_3	$-\underset{\underset{O}{\Vert}}{C}-CH_2CH=CH_2$	H	Na	0
9.)	CH_3	$-\underset{\underset{O}{\Vert}}{C}-CH_2-N=\underset{\underset{H}{\vert}}{C}-NH_2$	H	H	0
10.)	CH_3	$-\underset{\underset{O}{\Vert}}{C}-CH_2\overset{H}{N}-C\begin{array}{l}/\!\!/ NH\\ \backslash NH_2\end{array}$	H	H	0
11.)	CH_3	$-\underset{\underset{O}{\Vert}}{C}-CH_2\overset{+}{N}(CH_3)_3$	H	-	0
12.)	CH_3	$-\underset{\underset{O}{\Vert}}{C}-O-CH_2\emptyset$	H	Na	0

Compound	R^1	R^2	R^3	R^4	X
13.)	CH_3	 $-\underset{\underset{O}{\|}}{C}-CF_3$	H	Na	0
14.0	CH_3	 $-\underset{\underset{O}{\|}}{C}-C\equiv CH$	H	Na	0
15.)	CH_3	 $-\underset{\underset{O}{\|}}{C}-S-CH_3$	H	Na	0
16.)	CH_3	$-CHO$	$-CHO$	Na	0
17.)	CH_3	 $-\underset{\underset{O}{\|}}{C}-CH_3$  $-\underset{\underset{O}{\|}}{C}-CH_3$	 $-CH_2O-\underset{\underset{O}{\|}}{C}(CH_3)_3$		0
18.)	CH_3	 $-\underset{\underset{O}{\|}}{C}-CH_3$	 $-\underset{\underset{O}{\|}}{C}-CH_3$	K	0
19.)	CH_3	 $-\underset{\underset{O}{\|}}{C}-CH_3$	$-SO_3Na$	Na	0
20.)	CH_3	 $-\underset{\underset{O}{\|}}{C}-CH_3$	PO_3HNa	Na	0
21.)	CH_3	 $-\underset{\underset{O}{\|}}{C}-CH_3$	 $\underset{\underset{O}{\|}}{C}-NHCH_3$	K	0
22.)	CH_3	 $-\underset{\underset{O}{\|}}{C}-CH_3$	$-CH_2OCH_3$	Na	0
23.)	CH_3	 $-\underset{\underset{O}{\|}}{C}-CH_3$	H	 $-CH_2\overset{H}{C}=\overset{\overset{CH_3}{\vert}}{C}-CH_3$	O
24.)	CH_3	$-CHO$	H	 $-CH_2O-\underset{\underset{O}{\|}}{C}-(CH_3)_3$	0
25.	CH_3	 $-\underset{\underset{O}{\|}}{C}-CH_2-S-C\genfrac{}{}{0pt}{}{/\!\!/ NH}{\backslash NH_2}$	H	H	O
26.)	CH_3	$-CHO$	SO_2NH_2	Na	O
27.)	CH_3	 $-\underset{\underset{O}{\|}}{C}-CH_3$	CH_3	Na	0

Compound	R_1	R_2	R_3	R_4	X
28.)	CH_3	 $-\underset{\underset{O}{\|}}{C}-CH_3$	CH_3	 $-CH_2O\underset{\underset{O}{\|}}{C}-C(CH_3)_3$	0
29.)	C_2H_5	 $-\underset{\underset{O}{\|}}{C}-CH_2NH_2$	H	H	0
30.)	C_2H_5	 $-\underset{\underset{O}{\|}}{C}-CH_2\overset{H}{N}-\underset{\underset{CH_3}{\mid}}{C}=NH$	H	H	0
31.)	C_2H_5	 $-\underset{\underset{O}{\|}}{C}-O-CH_3$	H	Na	0
32.)	C_2H_5	 $-\underset{\underset{O}{\|}}{C}-NH-CH_3$	H	Na	0
33.)	CH_3	 $-\underset{\underset{S}{\|}}{C}-\overset{H}{N}-CH_3$	H	Na	0
34.)	CH_3	 $-\underset{\underset{S}{\|}}{C}-H$	H	Na	0
35.)	CH_3	 $-\underset{\underset{S}{\|}}{C}-H$	H	$-CH_2CH_2-S-CH_3$	0
36.)	CH_3	 $-\underset{\underset{O}{\|}}{C}-\overset{H}{N}-\underset{\underset{\underset{H}{N}}{\|}}{C}-NH_2$	H	H	0
37.)	CH_3	$-CHO$	H	$-CH_2O-NO_2$	0
38.)	CH_3	 $-\underset{\underset{O}{\|}}{P}\genfrac{}{}{0pt}{}{\diagup ONa}{\diagdown OCH_3}$	H	Na	0
39.)	$-CH_2-CH=CH_2$	 $-\underset{\underset{O}{\|}}{C}-CH_3$	H	Na	0
40.)	$-CH_2Ø$	$-CHO$	H	Na	0

Compound 11 is an internal salt.

EXAMPLE 30

Preparation of pharmaceutical compositions

A unit dosage form is prepared by mixing N-methyl-N-acetyl-thienamycin with 20 mg of lactose and 5 mg of 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:

Tablet	*Per Tablet*
N-methyl-N-acetyl-thienamycin	125 mg.
Corn starch, U.S.P.	6 mg.
Dicalcium Phosphate	192 mg.
Lactose, U.S.P.	190 mg.
Magnesium Stearate	Balance/800 mg.

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

Parenteral solution

Ampoule:	*Per Tablet*
N-Methyl-N-Acetyl -Thienamycin	500 mg.
Diluent: Sterile Water for Injection	2 cc.

Opthalmic solution

N-methyl-N-Acetyl- -Thienamycin		100 mg.
Hydroxypropylmethyl Cellulose		5 mg.
Sterile Water	to	1 ml.

Otic solution

N-methyl-N-Acetyl- Thienamycin		100 mg.
Benzalkonium Chloride		0.1 mg.
Sterile Water	to	1 ml.

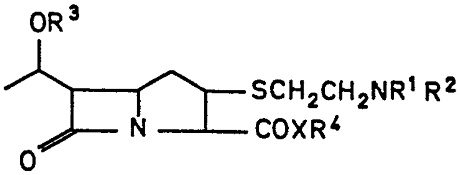
Topical ointment

N-methyl-N-Acetyl 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, gentamicin, neomycin, colistin and kanamycin, or with other therapeutic agents such as probenecid.

WHAT WE CLAIM IS:-

1. A compound having the structural formula:

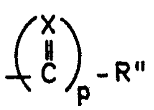


in which R^1 is substituted or unsubstituted C_{1-10} alkyl, C_{2-10} alkenyl or C_{2-10} alkynyl; ring-substituted or unsubstituted cycloalkyl, cycloalkenyl, cycloalkenylalkyl or cycloalkylalkyl having 3-6 ring carbon atoms and 1-6 carbon atoms in the alkyl chain if any; C_{6-10} aryl; aralkyl having 6-10 ring carbon atoms and 1-6 carbon atoms in the alkyl chain; monocyclic or bicyclic heteroaryl or heteroaralkyl comprising 4-10 ring atoms, one or more of which is oxygen, nitrogen and/or sulfur, and 1-6 carbon atoms in the alkyl chain; and in which the ring or chain substituent (or substituents) in the aforementioned radicals is chloro, bromo, iodo, fluoro, azido, cyano, amino, alkylamino, dialkylamino, or a trialkylamino salt in which the or each alkyl has 1-6 carbon atoms, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkylthioalkyl, carboxyl, oxo, (C_{1-6} alkoxy) carbonyl, C_{2-10} acyloxy, carbamoyl, alkylcarbamoyl or dialkylcarbamoyl in which the alkyl groups have 1-4 carbon atoms, cyanothio (−SCN), or nitro; R^2 is acyl; R^3 is hydrogen, acyl or a univalent hydrocarbon or substituted hydrocarbon radical; X is oxygen, sulfur, imino, or C_{1-6} alkylimino; and R_4 is a hydrogen atom, a pharmaceutically acceptable cation, a conventional carboxyl-protecting group (when X is O), an acyl radical, or a C_{1-10} alkyl, substituted carbonylmethyl, substituted or unsubstituted aminoalkyl, (C_{1-10} straight, branched or cyclic alkoxy)-(C_{1-6} alkyl), (C_{1-6} alkanoyloxy)-(C_{1-6} alkyl), halogenated C_{1-6} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-14} alkoxycarbonyloxyalkyl, C_{4-21} dialkylaminoacetoxyalkyl, C_{2-13} alkanamidoalkyl, C_{1-10} alkanoyl, aralkyl in which the alkyl residue is C_{1-3} alkyl, aromatic or cycloaliphatic heterocyclylalkyl in which the alkyl residue is C_{1-3} alkyl and there are from 6 to 10 ring atoms, including from 1 to 4 hetero atoms that are O, S and/or N, arylthioalkyl, aryloxyalkyl, substituted aryloxyalkyl having up to 3 substituents, aryl, substituted aryl having up to 3 substituents, phenyl-(C_{2-6} alkenyl), benzyloxy-(C_{1-3} alkyl), (C_{1-10} straight, branched or cyclic alkylthio)-(C_{1-6} alkyl), or (C_{2-10} acylthio)-(C_{1-6} alkyl) radical.

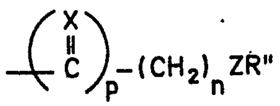
2. A compound according to claim 1, in which R^1 is C_{1-6} alkyl.

3. A compound according to claim 1, in which, in the formula, R^1, R^2 and X are as defined in claim 1, R^3 is hydrogen, acyl, alkyl, aryl, aralkyl, alkenyl or alkynyl; and R^4 is hydrogen; C_{1-10} alkyl, phenacyl or nuclear-substituted phenacyl in which the substituent is chloro, bromo, fluoro or C_{1-6} alkyl; (C_{1-6} alkoxy)-(C_{1-6} alkyl) in which the alkoxyl residue is open chain or cyclic; (C_{1-6} alkanoyloxy)-(C_{1-6} alkyl); C_{1-6} halogenated alkyl in which the halogen is chlorine, bromine or fluorine; C_{2-10} C_{3-14} alkoxycarbonyloxyalkyl; C_{4-21} dialkylaminoacetoxyalkenylalkyl; C_{2-13} alkanamidoalkyl; aralkyl in which the alkyl residue contains 1 to 3 carbon atoms and the aryl residue contains 6 to 10 carbon atoms; monocyclic or bicyclic aromatic or cycloaliphatic heterocyclyl (C_{1-3} alkyl) containing 6 to 10 ring atoms and 1-4 hetero atom(s) selected from oxygen, sulfur and/or nitrogen; nuclear-substituted aralkyl or heteroaralkyl in which there are 1-3 substituents selected from chlorine, fluorine, bromine, iodine, C_{1-4} alkyl, C_{1-15} alkanoyloxy and/or C_{1-4} alkoxy; aryl or nuclear-substituted aryl having up to 3-substituents, containing from 6 to 10 ring carbon atoms and in which the nuclear substituent is hydroxy, C_{1-6} alkyl, chlorine, fluorine or bromine; or alkylthioalkyl or arylthioalkyl as defined in claim 1.

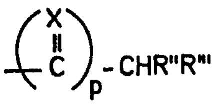
4. A compound according to claim 3, in which R^3 is a hydrogen atom or a group of a formula set forth below and R^2 is a group of a formula set forth below in which *p* = 1:



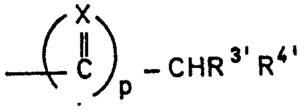
$-\left(\overset{X}{\overset{\|}{C}}\right)_p-R''$



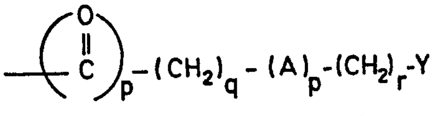
$-\left(\overset{X}{\overset{\|}{C}}\right)_p-(CH_2)_nZR''$



$-\left(\overset{X}{\overset{\|}{C}}\right)_p-CHR''R'''$



$-\left(\overset{X}{\overset{\|}{C}}\right)_p-CHR^{3'}R^{4'}$

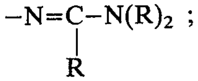


$-\left(\overset{O}{\overset{\|}{C}}\right)_p-(CH_2)_q-(A)_p-(CH_2)_r-Y$

in which n is 0, 1, 2, 3 or 4; p is 0 or 1; q is 0, 1, 2, 3, 4 or 5; r is 0, 1, 2, 3, 4 or 5; Z is O, S, −CO− or −NH−; A is O, S, −NH− or $-N(C_{1-6}$ alkyl)−; X is O or S; R″ is hydrogen. amino; C_{1-6} alkylamino; di(C_{1-6} alkyl) amino; substituted or unsubstituted C_{1-6} straight or branched alkyl; mercapto; a substituted or unsubstituted aryloxy, alkenyl, alkynyl, aryl, aralkyl or cycloalkyl group or a substituted or unsubstituted heteroaryl or heteroaralkyl group (monocyclic or bicyclic) where the alkyl residue comprises 1 to 3 carbon atoms, the heterocyclic ring comprises 4 to 10 atoms and the hetero atom or atoms are O, N and/or S; R‴ is amino, hydroxy, azido, carbamoyl, guanidino, amidino, acyloxy, Cl, F, Br, I, sulfamino, tetrazolyl, sulfo, carboxy, carbalkoxy or phosphono; $R^{3'}$ is hydrogen, chloro, fluoro, bromo, iodo, amino, guanidino, phosphono, hydroxy, tetrazolyl, carboxy, sulfo or sulfamino and $R^{4'}$ is phenyl, substituted phenyl, a monocyclic or bicyclic substituted or unsbustituted heterocyclyl containing one or more oxygen, sulfur or nitrogen atoms in the ring, phenylthio, phenyloxy, C_{1-6} alkyl, a heterocyclic-thio or substituted heterocyclic-thio group, or cyano, in which any substituents on the $R^{3'}$ and $R^{4'}$ residues are halo, carboxymethyl, guanidino, guanidinomethyl, carbamoylmethyl, aminomethyl, nitro, methoxy or methyl; Y is (1) substituted or unsubstituted amino or ammonium group of formula:

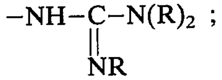
$-N(R)_2$ or an $-\overset{+}{N}(R)_3$ salt;

an amidino or substituted amidino radical of formula:



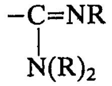
$-N{=}\underset{\displaystyle R}{\underset{|}{C}}-N(R)_2$;

a guanidino or substituted guanidino radical of formula:



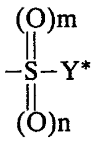
$-NH-\underset{\displaystyle NR}{\underset{\|}{C}}-N(R)_2$;

or a guanyl or substituted guanyl radical of formula:



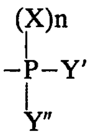
$-\underset{\displaystyle N(R)_2}{\underset{|}{C}}{=}NR$

where each R, independently of the others, is hydrogen; $N(R')_2$ (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, (C_{3-6} cycloalkyl)-(C_{1-3} alkyl), or (but only when R is attached to carbon), (C_{1-6} alkoxy)-methyl; or two R groups are joined to form, together with the atom(s) to which they are attached, a ring having 3-6 atoms; or (2) a nitrogen-containing monocyclic or bicyclic aromatic or non-aromatic heterocycle having 4 to 10 nuclear atoms in which the hetero atom(s), in addition to nitrogen, if any, is/are oxygen and/or sulfur; or one or both of R^2 and R^3 is



$-\underset{\underset{(O)n}{\|}}{\overset{\overset{(O)m}{\|}}{S}}-Y^*$

1



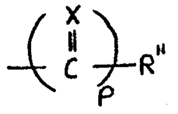
$-\underset{\underset{Y''}{|}}{\overset{\overset{(X)n}{|}}{P}}-Y'$

2

where, with respect to (1, each of *m* and *n* is 0 or 1 and $Y^* = O^{\ominus}M^{\oplus}$, $-N(R'')_2$ or R''; where $M^{\oplus}$ is hydrogen, an alkali metal cation or an organic base; and R'' is as defined above, and with respect to (2), $X = O$ or S, $n = 0$ or 1, and each of Y' and Y'' is $O^{\ominus}M^{\oplus}$, $-N(R'')_2$, R'' or ZR'' where all symbols are as defined above, or Y' and Y'', including R'' residues, are joined together to form a cyclic ester, ester- amide or amide function.

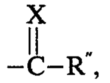
5. A compound according to claim 4 in which X of the radical $COXR^4$ is oxygen and R^4 is hydrogen, methyl, *t*-butyl, phenacyl, *p*-bromphenacyl; pivaloyloxymethyl, 2,2,2-trichloroethyl, allyl, 3-methyl-2-butenyl, 2-methyl-2-propenyl, benzyl, benzylhydryl, *p*-*t*-butylbenzyl, phthalidyl, phenyl, 5-indanyl, acetylthiomethyl, acetoxymethyl, propionyloxymethyl, methallyl, 3-butenyl, 4-pentenyl, 2-butenyl, acetoxyacetylmethyl, pivaloyloxymethyl, 2-diethylaminoethyl, 2-methylaminoethyl, methoxymethyl, *p*-acetoxybenzyl, *p*-pivaloyloxybenzyl, *p*-isopropoxybenzyl, 5-indanylmethyl, benzyloxymethyl, methylthioethyl, dimethylaminoacetoxymethyl, crotonolacton-3-yl, acetamidomethyl, pivaloylthiomethyl or methylthiomethyl.

6. A compound according to claim 5 in which the radical R^3 is hydrogen or



$-\left(\overset{\overset{X}{\|}}{C}\right)_p-R''$

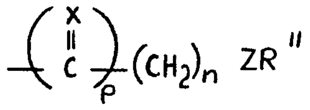
and R^2 is



$-\overset{\overset{X}{\|}}{C}-R''$,

where *p* is 0 or 1, X is O or S, R'' is benzyl, *p*-hydroxybenzyl, 4-amino-4-carboxybutyl, methyl, cyanomethyl, 2-pentenyl, n-amyl, n-heptyl, ethyl, 3- and 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-guanidinomethyl-benzyl, 4-guanidinobenzyl, 4-guanidinophenyl, 2,6-dimethoxy-4-guanidinophenyl, *o*-sulfobenzyl, *p*-carboxymethylbenzyl, *p*-carbamoylmethylbenzyl, *m*-fluorobenzyl, *m*-bromobenzyl, *p*-chlorobenzyl, *p*-methoxybenzyl, l-naphthylmethyl, 3-isothiazolylmethyl, 4-isothiazolylmethyl, 5-isothiazolylmethyl, guanylthiomethyl, 4-pyridylmethyl, 5-isoxazolylmethyl, 4-methoxy-5-isoxazolylmethyl, 4-methyl-5-isoxazolylmethyl, 1-imidazolylmethyl, 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 2-(4-carbamoylthienyl)-methyl, 2- or 3-(5-methylthienyl) methyl, 2- or 3-(5-methoxythienyl) methyl, 2- or 3-(4-chlorothienyl)-methyl, 2- or 3-(5-sulfothienyl) methyl, 2- or 3-(5-carboxythienyl) methyl, 3-(1,2,5-thiadiazolyl) 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.

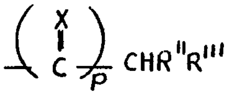
7. A compound according to Claim 5 in which R^3 and/or R^2 is



$$-\left(\overset{\overset{X}{\|}}{C}\right)_{p}(CH_2)_n\;ZR''$$

in R^3 and is 1 in R^2 where R is O or Y, X is O or S, and P $-(CH_2)_nZR''$ allylthiomethyl, phenylthiomethyl, butylmercaptomethyl, α-chlorocrotylmercaptomethyl, phenoxymethyl, phenoxyethyl, phenoxybutyl, phenoxybenzyl, diphenoxymethyl, dimethylmethoxymethyl, dimethylbutoxymethyl, dimethylphenoxymethyl, 4-guanidinophenoxymethyl, 4-pyridylthiomethyl, *p*(carboxymethyl)phenoxymethyl, *p*-(carboxymethyl)-phenylthiomethyl, 2-thiazolylthiomethyl, *p*-(sulfo)phenoxymethyl, *p*-(carboxymethyl)phenylthiomethyl, 2-pyrimidinylthiomethyl, phenethylthiomethyl, 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 salt, cyanomethylthiomethyl, trifluoromethylthiomethyl, 4-pyridylethyl, 4-pyridylpropyl, 4-pyridylbutyl, 3-imidazolylethyl, 3-imidazolylpropyl, 3-imidazolylbutyl, 1-pyrroloethyl, 1-pyrrolopropyl and 1-pyrrolobutyl.

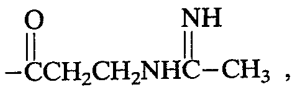
8. A compound according to Claim 5 in which R^3 and/or R^2 is



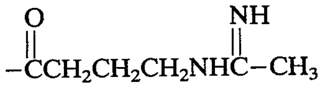
$$-\left(\overset{\overset{X}{|}}{C}\right)_{p}CHR''R'''$$

in which R is as defined in Claim 7, X is O or S and $-CHR''R'''$ is α-aminobenzyl, α-amino-(2-thienyl)methyl, α-(methylamino)benzyl, α-amino-methylmercaptopropyl, 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-1,2,3-thiadiazolyl)-hydroxymethyl, 4-(5-chlorothienyl)-aminomethyl, 2-(5-chlorothienyl)-hydroxymethyl, 2-(5-chlorothienyl)-carboxymethyl, 3-(isothiazolyl)-aminomethyl, 3-(isothiazolyl)-hydroxymethyl, 3-(isothiazolyl)-carboxymethyl, 2-(thiazolyl)aminomethyl, 2-(thiazolyl)-hydroxymethyl, 2-(thiazolyl)carboxymethyl, 2-benzothienylcarboxymethyl, 2-benzothienylhydroxymethyl, 2-benzothienylcarboxymethyl, α-sulfobenzyl, α-phosphonobenzyl, α-diethylphosphono, or α-monoethylphosphono.

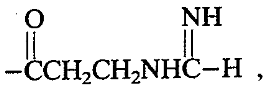
9. A compound according to Claim 5 in which each of R^3 and R^2 is hydrogen (except that R^2 is not hydrogen) or



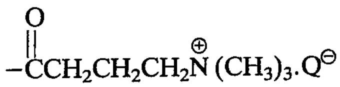
$-\overset{\overset{O}{\|}}{C}CH_2CH_2NH\overset{\overset{NH}{\|}}{C}-CH_3$,



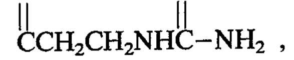
$-\overset{\overset{O}{\|}}{C}CH_2CH_2CH_2NH\overset{\overset{NH}{\|}}{C}-CH_3$



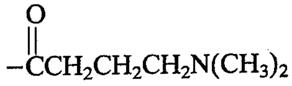
$-\overset{\overset{O}{\|}}{C}CH_2CH_2NH\overset{\overset{NH}{\|}}{C}-H$,



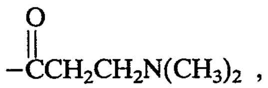
$-\overset{\overset{O}{\|}}{C}CH_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3.Q^{\ominus}$

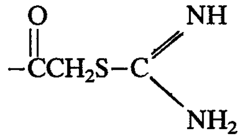


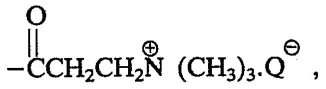
$\overset{\overset{-O}{\|}}{C}CH_2CH_2NH\overset{\overset{NH}{\|}}{C}-NH_2$,

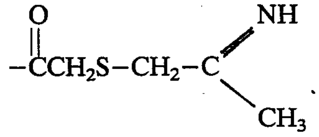


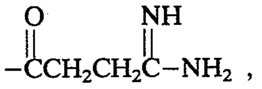
$-\overset{\overset{O}{\|}}{C}CH_2CH_2CH_2N(CH_3)_2$

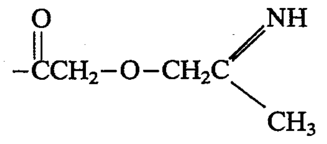

$-\overset{\overset{O}{\|}}{C}CH_2CH_2N(CH_3)_2$,




$-\overset{\overset{O}{\|}}{C}CH_2CH_2\overset{\oplus}{N}(CH_3)_3.Q^{\ominus}$,

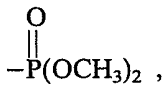


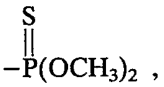

$-\overset{\overset{O}{\|}}{C}CH_2CH_2\overset{\overset{NH}{\|}}{C}-NH_2$,

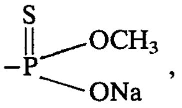


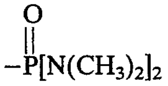
where $Q^{\ominus}$ is an anion

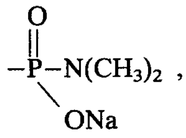
10. A compound according to claim 5 in which each of R^3 and R^2 is hydrogen (except that R^2 is not hydrogen), formyl, acetyl, propionyl, butyryl, chloroacetyl, methoxyacetyl, aminoacetyl, methoxycarbonyl, ethoxycarbonyl, methylcarbamoyl, ethylcarbamoyl, phenylthiocarbonyl, 3-aminopropionyl, 4-aminobutyryl, N-methylaminoacetyl, N,N-dimethylaminoacetyl, an N,N,N-trimethylammonium acetyl salt, 3-(N,N-dimethyl)aminopropionyl, a 3-(N,N,N-trimethyl)ammonium-propionyl salt, N,N,N-triethyl ammonium acetyl 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, a 3-methyl-1-imidazoliumacetyl salt, 3-sydnonylacetyl, *o*-aminomethylbenzoyl, *o*-aminobenzoyl,

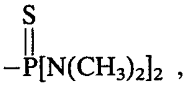

$-\overset{\overset{O}{\|}}{P}(OCH_3)_2$,

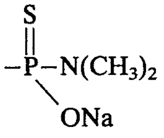

$-\overset{\overset{S}{\|}}{P}(OCH_3)_2$,

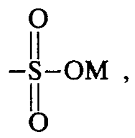


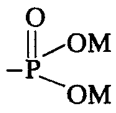

$-\overset{\overset{O}{\|}}{P}[N(CH_3)_2]_2$




$-\overset{\overset{S}{\|}}{P}[N(CH_3)_2]_2$,




$-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-OM$,



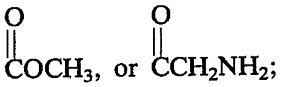
where M is hydrogen or an alkali or alkaline-earth metal cation.

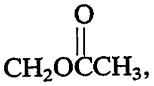
11. A compound according to Claim 5 in which each of R^3 and R^2 is sulfo, phosphono, carbamoyl, methylsulfonyl, sulfamoyl, dimethyl-sulfamoyl, N-methylcarbamoyl, bromoacetyl, hydroxyacetyl, aminoacetyl, dimethylaminoacetyl, a trimethylammoniumacetyl salt, amidinoacetyl, guanidinoacetyl, methoxyacetyl, guanylacetyl, guanylthioacetyl, phos-

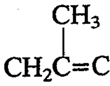
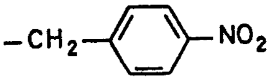
phamoyl, phosphonothioyl or, thiocarbamoyl, or R^3 is hydrogen, methoxymethyl, hydroxyethyl, methoxyethyl, dimethylaminomethyl, dimethylaminoethyl, methylthiomethyl, amidinomethyl, and guanidinoethyl and R^2 is as defined above.

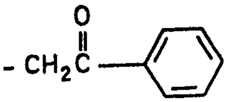
12. A compound according to Claim 3 in which

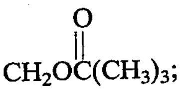
X is oxygen;

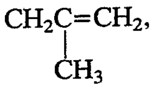
R^3 is hydrogen, CH_3, SO_3H, CH_2OCH_3,  $\overset{O}{\overset{\|}{C}}OCH_3$, or $\overset{O}{\overset{\|}{C}}CH_2NH_2$;

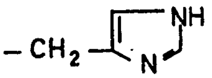
R^4 is hydrogen,  $CH_2O\overset{O}{\overset{\|}{C}}CH_3$, $CH_2OCH_2C(CH_3)_3$, $CH_2CH{=}CH_2$,

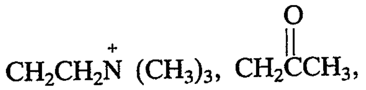
 $CH_2\underset{}{\overset{CH_3}{\overset{|}{C}}}{=}CH_2$, $CH_2CH_2N(C_2H_5)_2$,  ,

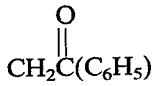
$CH_2CH_2CH_3$, $CH_2CH_2N(CH_3)_2$,  ,

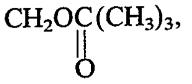
 CH_2SCH_3, or $CH_2O\overset{O}{\overset{\|}{C}}(CH_3)_3$; and

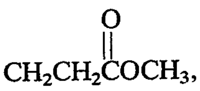
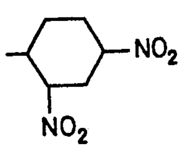
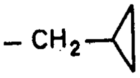
R^1 is CH_3, CH_2CH_3, $CH_2CH{=}CH_2$, $CH_2CH_2CH_3$, $CH_2(C_6H_5)$, $CH(C_6H_5)$, $C(C_6H_5)_3$,  $CH_2\underset{CH_3}{\underset{|}{C}}{=}CH_2$, CH_2OCH_3, $CH_2CH{=}CH{-}CH_3$

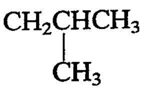
$CH_2CH_2CH{=}CH_2$,  , a salt of

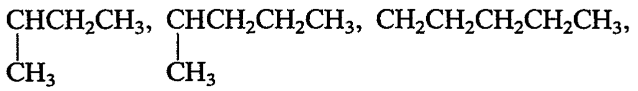
 $CH_2CH_2\overset{+}{N}(CH_3)_3$, $CH_2\overset{O}{\overset{\|}{C}}CH_3$, $CH_2CH_2(OCH_3)_2$,

$CH_2{-}C{\equiv}CH$,  $CH_2\overset{O}{\overset{\|}{C}}(C_6H_5)$,

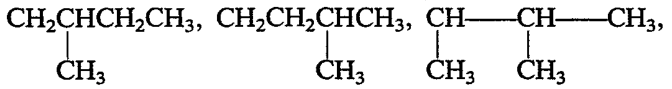
CH_2SCH_3,  $CH_2O\underset{O}{\underset{\|}{C}}(CH_3)_3$, $CH_2CH_2C{\equiv}N$,

 $CH_2CH_2\overset{O}{\overset{\|}{C}}OCH_3$,  

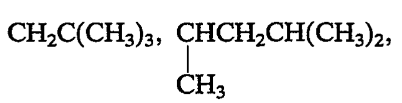
$CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$,  $CH_2\underset{CH_3}{\underset{|}{C}}HCH_3$



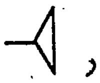
$CH(CH_3)CH_2CH_3$, $CH(CH_3)CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_2CH_3$,

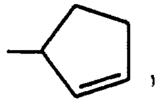


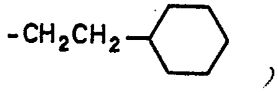
$CH_2CH(CH_3)CH_2CH_3$, $CH_2CH_2CH(CH_3)CH_3$, $CH(CH_3)-CH(CH_3)-CH_3$,

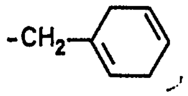


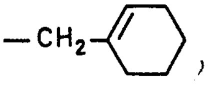
$CH_2C(CH_3)_3$, $CH(CH_3)CH_2CH(CH_3)_2$,

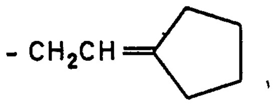


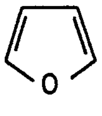


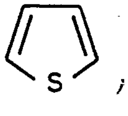


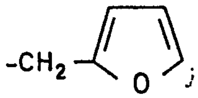


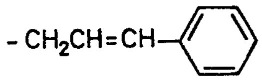




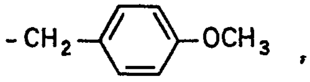








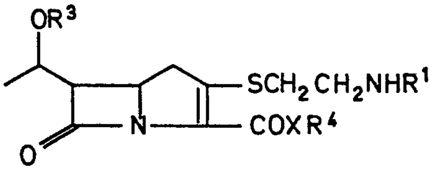
or



13. A compound according to Claim 12 in which R^3 is hydrogen, X is oxygen, and R^4 is hydrogen and the pharmaceutically acceptable salts thereof.

14. A compound according to Claim 3 wherein R^1 is methyl or ethyl.

15. A process for preparing a compound according to Claim 3 comprising treating a compound of the formula:



with an acylating agent calculated to provide the substituent R^2.

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

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

18. A pharmaceutical composition comprising a compound according to Claim 3 and a pharmaceutical carrier therefor.

19. A pharmaceutical composition comprising, in unitary dosage form, a therapeutically effective amount of a compound according to Claim 3 and a pharmaceutical carrier therefor.

20. A composition as claimed in Claim 16 or 17, in which the compound is a compound as claimed in any one of claims 2 and 4 to 14.

21. A composition as claimed in any one of Claims 16 to 20 that also contains an antibiotic and/or therapeutic agent that is not a compound as claimed in Claim 1.

22. A composition as claimed in any one of claims 16 to 21 in orally administrable form.

23. A composition as claimed in any one of Claims 16 to 21 in injectable form.

24. A composition as claimed in any one of Claims 16 to 21 in topical form.

25. A composition as claimed in any one of Claims 16 to 21 in the form of a suppository.

26. A composition as claimed in claim 22 in the form of a tablet or capsule.

27. A composition as claimed in claim 23 in the form of an ampoule.

28. A composition as claimed in claim 24 in the form of an ointment or an ophthalmic or otic liquid.

29. A composition as claimed in claim 22 in the form of an aqueous or oily suspension, solution, emulsion, syrup, elixir, dry powder for reconstitution with liquid, or a pill.

30. A composition as claimed in Claim 23 in the form of an aqueous or oily suspension, solution, emulsion, or a dry powder for reconstitution with sterile liquid.

31. A composition as claimed in Claim 28 in the form of a cream, lotion, paint, powder, semisolid, ophthalmic or otic capsule or drops.

32. A composition as claimed in any one of Claims 16 to 21 in the form of a powder or liquid spray or inhalant, a throat paint or a lozenge.

33. A composition as claimed in any one of Claims 16 to 21 in the form of an intramammary preparation for veterinary use.

34. A disinfectant containing as antibacterial ingredient a compound as claimed in any one of Claims 1 to 14.

35. An animal feed or human food containing as antibacterial ingredient a compound as claimed in any one of Claims 1 to 14.

36. Water-based paint or paper-mill white water containing as antibacterial ingredient a compound as claimed in any one of Claims 1 to 14.

37. A method of preparing a compound as claimed in claim 1, substantially as hereinbefore described in any appropriate Example.

For the Applicants,
D. YOUNG & CO.,
Chartered Patent Agents,
9 & 10 Staple Inn,
London WC1V 7RD

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