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PATENT SPECIFICATION

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1.140.663



NO DRAWINGS

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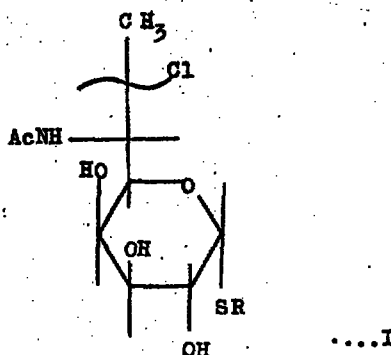
COMPLETE SPECIFICATION

Lincomycin Derivatives

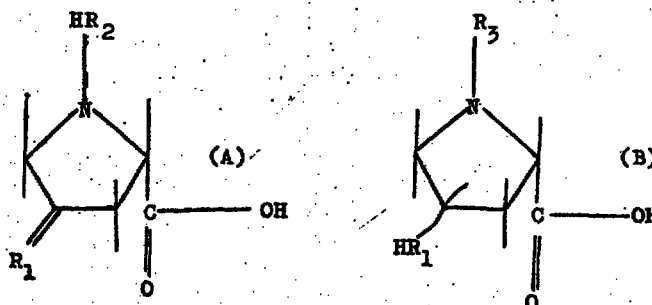
We, THE UPJOHN COMPANY, a corporation organized and existing under the laws of the State of Delaware, United States of America, of 301 Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new lincomycin derivatives, and is particularly directed to 7 - chloro 7 - deoxylincomycin and 7 - chloro - 7 - deoxyepilincomycin and analogues and isomers thereof and to processes whereby these and other lincomycin derivatives are produced.

The novel compounds according to the invention have the following structural formula:—

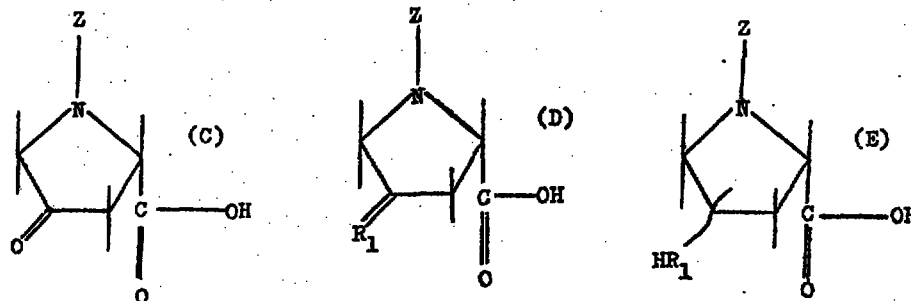


wherein R is alkyl of not more than 20 carbon atoms, advantageously not more than 8 carbon atoms, cycloalkyl or cycloalkyl-alkyl of from 3 to not more than 8 carbon atoms, or aralkyl of not more than 12 carbon atoms, advantageously not more than 8 carbon atoms; and Ac is hydrogen or the acyl radical of a 4-substituted-L-2-pyrrolidine-carboxylic acid of one of the formulae:—



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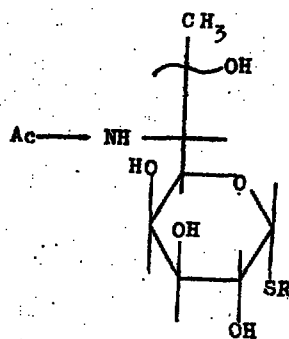


wherein R_1 and R_2 are alkylidene of not more than 20 carbon atoms (including methylene) and advantageously not more than 8 carbon atoms, cycloalkylidene or cycloalkyl-alkylidene of from 3 to not more than 8 carbon atoms, and aralkylidene of not more than 12 carbon atoms, advantageously not more than 8 carbon atoms; and R_3 is hydrogen or HR_2 and Z is a protective hydrocarboxyloxy-carbonyl or substituted hydrocarboxyloxy-carbonyl group which is removable by hydrogenolysis, trityl, diphenyl (*p*-methoxyphenyl)methyl, bis - (*p*-methoxyphenyl)phenylmethyl, benzyl, or *p*-nitrobenzyl.

The particularly preferred compounds of the invention are those in which Ac is a radical of the formula A or B.

Examples of alkyl of not more than 20 carbon atoms (R , HR_1 , and HR_2) are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, and eicosyl and the isomeric forms thereof. Examples of cycloalkyl and cycloalkyl alkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 2-methylcyclopentyl, 2,3-dimethylcyclobutyl, 2-methylcyclobutyl, and 3-cyclopentylpropyl. Examples of aralkyl are benzyl, phenethyl, 3-phenylpropyl, and 1-naphthylmethyl. Examples of alkylidene, cycloalkylidene, cycloalkyl alkylidene and aralkylidene groups (R_1 and R_2) include methylene, ethylidene, propylidene, butylidene, pentylidene, hexylidene, heptylidene, octylidene, nonylidene, decylidene, undecylidene, dodecylidene, tridecylidene, tetradecylidene, pentadecylidene, hexadecylidene, heptadecylidene, octadecylidene, nonadecylidene, eicosylidene, and the isomeric forms thereof, cyclopropylidene, cyclobutylidene, cyclopentylidene, cyclohexylidene, cycloheptylidene, cyclooctylidene, 2-cyclopropylethylidene, 3-cyclopentylpropylidene, benzylidene, 2-phenylethylidene, 3-phenylpropylidene, and 1-naphthylmethylidene.

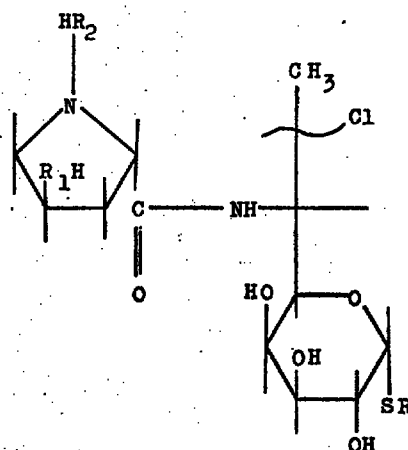
The novel compounds of the invention, Formula I, can be prepared by replacing by chlorine, the 7-hydroxy of a compound of the formula



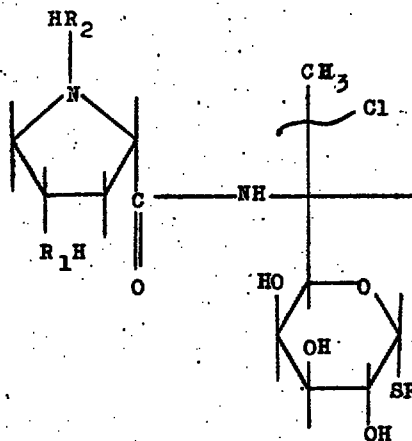
II

The replacement is effected by mixing the starting compound of Formula II with thionyl chloride and heating. For example, when a compound of Formula IIA (that is to say when Ac in Formula II is that of the acid of Formula A) is used as the starting compound, a novel compound of Formula IA (that is to say when Ac in Formula I is that of the acid of Formula A), is obtained. When this compound or the starting compound (Formula IIA) is hydrogenated with a catalyst effective to saturate an olefinic double bond, a compound of Formula IB (that is to say when Ac in Formula I is that of the acid of Formula B) is obtained as a mixture of *cis* and *trans* epimers according to the formulas

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III



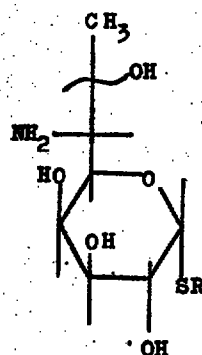
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IV

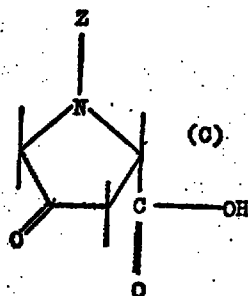
which, if desired, can be separated by counter current distribution or chromatography.

When R_3 in Formulas B, IB, and IIB (that is to say when Ac in Formula II is that of the acid of Formula B) is hydrogen, it can be replaced by suitable alkylation or like procedure. Advantageously, this replacement is effected by reacting the compound according to Formula B, IB, or IIB, wherein R_3 is hydrogen with an oxo compound (an aldehyde or a ketone) and hydrogenating the resulting adduct with a catalyst effective to saturate an olefinic double bond. Either platinum or palladium can be used as the catalyst. Suitable oxo compounds have the formula $R_4R_5C=O$ where $R_4R_5C=$ is the same as R_2 given above. Examples of suitable oxo compounds are formaldehyde, acetaldehyde, propionaldehyde, butyraldehyde, acetone, isobutyl methyl ketone, benzaldehyde, phenylacetaldehyde, hydrocinnamaldehyde, acetophenone, propionphenone, butyrophenone, 3-methyl-4-phenyl-2-butanone, 2-methyl-5-phenyl-3-pentanone, 3-cyclopentanepropionaldehyde, cyclohexaneacetaldehyde, cycloheptanecarboxaldehyde, 2,2-dimethylcyclopropylacetaldehyde, 2,2-dimethylcyclopropyl methyl ketone, cyclopentyl methyl ketone, cyclobutyl methyl ketone, cyclobutanone, cyclohexanone, 4-methylcyclohexanone, and the like.

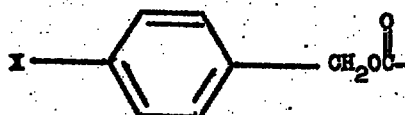
The starting compounds of Formula II are described in British Patent Specification No. 1,118,302. They are prepared by acylating a compound of the formula



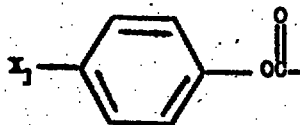
wherein R is as given above, with a 4-substituted-L-2-pyrrolidinecarboxylic acid of Formula A or B. This acylation and like acylations referred to herein can be effected by procedures already well known in the art for acylating amino sugars. The starting acid of Formula A can be prepared by reacting a 4-oxo compound of the formula



wherein Z is a protective hydrocarbonyloxycarbonyl or substituted hydrocarbonyloxycarbonyl group which is removable by hydrogenolysis, trityl; i.e., triphenylmethyl, diphenyl(*p*-methoxyphenyl)methyl, bis-(*p*-methoxyphenyl)phenylmethyl, benzyl or *p*-nitrobenzyl, with a Wittig agent, e.g., an alkylidenetriphenylphosphorane [see e.g., Wittig et al., Ber., 87, 1348 (1954); Trippett, Quarterly Reviews, XVII, No. 4, p. 406 (1963)]. Examples of optionally substituted hydrocarbonyloxycarbonyl groups (Z) are tertiary-butoxycarbonyl; benzyloxycarbonyl groups of the formula



wherein X is hydrogen, nitro, methoxy, chloro, or bromo, for example, carbobenzoxy, *p*-nitrocarbobenzoxy, *p*-bromo-, and *p*-chlorocarbobenzoxy; and phenyloxycarbonyl groups of the formula



wherein X₁ is hydrogen, allyl, or alkyl of not more than 4 carbon atoms, such as phenyloxycarbonyl, *p*-tolyyloxycarbonyl, *p*-ethylphenyloxycarbonyl, and *p*-allylphenyloxycarbonyl and the like.

In carrying out this process the 4-oxo-L-2-pyrrolidinecarboxylic acid (Formula C) is added to a freshly prepared Wittig reagent. The Wittig reagents herein used can be generally represented by the following formula:

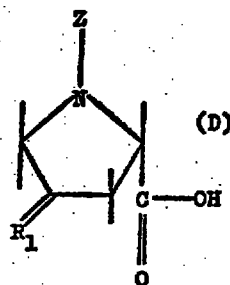
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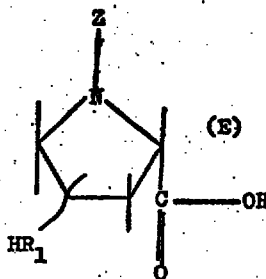
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wherein R_1 is as given above. These Wittig reagents are prepared by reacting an alkyl, cycloalkyl, cycloalkyl-alkyl or aralkyltriphenylphosphonium halide with a base such as sodamide, or sodium or potassium hydride, or the sodium or potassium metalate of dimethyl sulphoxide and the like. For example, the elimination of hydrogen halide from alkyltriphenylphosphonium halide, produces alkylidenetriphenylphosphorane. [The preparation of phosphoranes is discussed in detail by Trippett, Quart. Rev. XVII, No. 4, p. 406 (1963)]. The reaction is generally carried out in an organic solvent, such as benzene, toluene, ether, dimethylsulphoxide, tetrahydrofuran, or the like, at temperatures between 10°C. and the reflux temperature of the reaction mixture. The thus-obtained product, a 4-alkylidene-, 4-cycloalkylidene-, or 4-aralkylidene-1-protected-L-proline which has the following formula



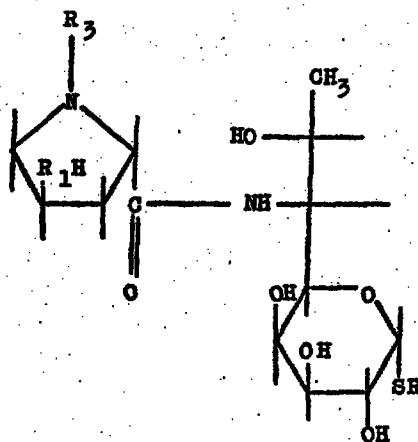
is recovered from the reaction mixture in a conventional manner, generally by extraction from aqueous solutions of the reaction mixture. The crude product can be purified by conventional means, such as recrystallization, chromatography, or formation and recrystallization of easily formed derivatives such as amine salts of the amino acid, e.g., the dicyclohexylamine salt, and the like, and liberating the amino acids from such compounds. By hydrogenating an acid of Formula D in the presence of a catalyst, e.g., platinum, which is effective to saturate a double bond, but which is ineffective to effect hydrogenolysis, a compound of the following formula



is obtained. Platinum deposited on a carrier, e.g., carbon or an anion exchange resin like Dowex-1 (Registered Trade Mark), a cross-linked polystyrene trimethylbenzylammonium resin in the hydroxide cycle is suitable. If desired, the starting compounds of Formula V can be acylated with acids of Formula C, D, or E to form compounds IIC, IID, and IIE, respectively. Compound IIC can then be converted to compound IID by treatment with a Wittig reagent and compound IID hydrogenated to compound IIE by the procedures given above. The hydrogenation, both of the acid D and the acylate IID, gives a mixture of cis and trans epimers which, if desired, can be separated by counter current distribution or chromatography. The starting acids of Formula B in which R_1 is hydrogen are obtained when an acid of Formula D or E is subjected to hydrogenolysis over a palladium catalyst, e.g., palladium on carbon. Likewise, compounds of Formula IID and IIE are converted to compounds of Formula IIB in which R_1 is hydrogen by the same process. The starting acids of Formula B in which R_1 is hydrogen as well as compounds of Formula IIB in which R_1 is hydrogen can be converted respectively to compounds of Formulas B and IIB in which R_1 is HR_2 by the procedures given above. The starting acids of Formula A are obtained by treating an

acid of Formula D with hydrogen bromide in acetic acid to remove the Z group and then replacing the N-hydrogen with an HR_2 group by the procedure given above. Compounds of Formula IID and IIE are converted to compounds of Formula IIA and IIB, respectively, by the same process.

Some of the starting compounds of Formula II are obtained biosynthetically. Lincomycin, methyl 6,8 - dideoxy - 6 - (trans - 1 - methyl - 4 - propyl - L - 2 - pyrrolidinecarboxamido) - 1 - thio - D - erythro - α - D - galacto - octopyranoside, is obtained as an elaboration product of a lincomycin-producing actinomycete according to British Patent Specification No. 976,765. It has the following structural formula:



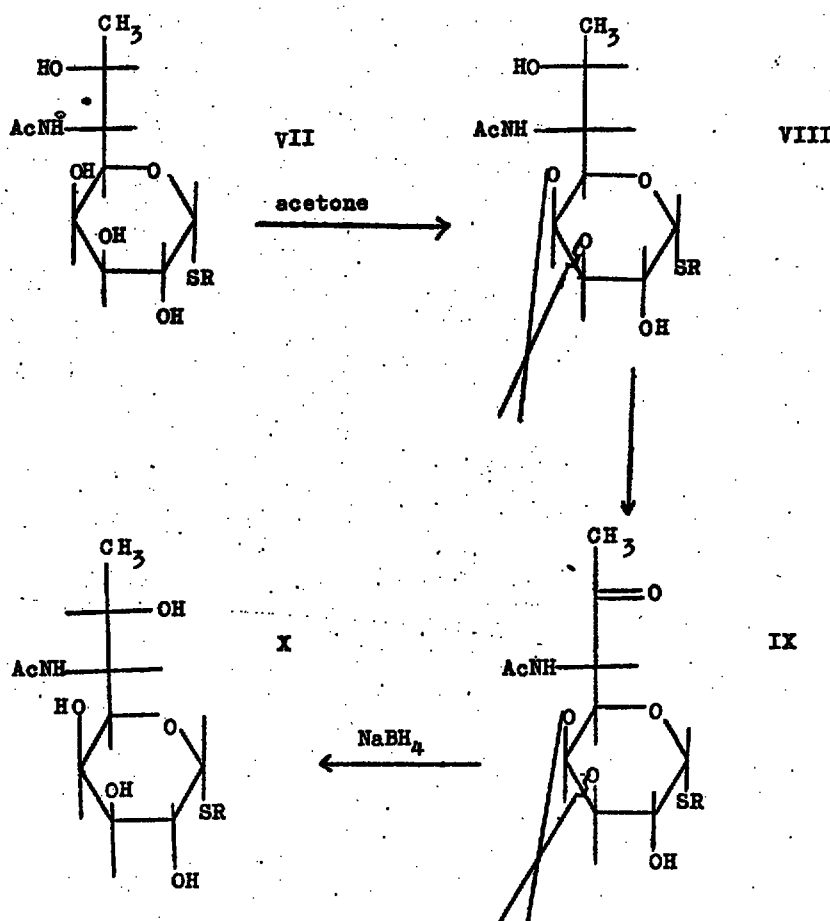
wherein R and R_3 are methyl and R_1H is propyl. Lincomycin B, methyl 6,8 - dideoxy - 6 - (trans - 1 - methyl - 4 - ethyl - L - 2 - pyrrolidine - carboxamido) - 1 - thio - D - erythro - α - D - galacto - octopyranoside (Formula VI wherein R and R_3 are methyl and $-R_1H$ is ethyl) is described in British Patent Specification No. 1,096,841. Lincomycin C, (S - ethyl - S - demethyl - lincomycin) ethyl 6,8 - dideoxy - 6 - (trans - 1 - methyl - 4 - propyl - L - 2 - pyrrolidinecarboxamido) - 1 - thio - D - erythro - α - D - galacto - octopyranoside (Formula VI wherein R is ethyl, $-R_1H$ is propyl, and R_3 is methyl) is described in British Patent Specification No. 1,087,882. Lincomycin D, methyl 6,8 - dideoxy - 6 - (trans - 4 - propyl - L - 2 - pyrrolidinecarboxamido) - 1 - thio - D - erythro - α - galacto - octopyranoside (Formula VI wherein R is methyl, $-R_1H$ is propyl, and R_3 is hydrogen) is described in British Patent Specification No. 1,102,835.

N - demethyllincomycin B, 4 methyl 6,8 - dideoxy - 6 - (trans - 4 - ethyl - L - 2 - pyrrolidinecarboxamido) - 1 - thio - D - erythro - α - D - galacto - octopyranoside (Formula VI wherein R is methyl, $-R_1H$ is ethyl and R_3 is hydrogen) is also produced in the fermentation of British Patent Specification No. 1,102,835.

Similarly, lincomycin K, ethyl 6,8 - dideoxy - 6 - (trans - 4 - propyl - L - 2 - pyrrolidinecarboxamido) - 1 - thio - D - erythro - α - D - galacto - octopyranoside (Formula VI wherein R is ethyl, $-R_1H$ is propyl, and R_3 is hydrogen) is produced when the fermentation of the British Patent Specification 976,765 is carried out in the presence of added α -ETL, ethyl 6 - amino - 6,8 - dideoxy - 1 - thio - D - erythro - α - D - galacto - octopyranoside, a compound obtained by the hydrazinolysis of lincomycin C as described in British Patent Specification No. 1,097,926 S - ethyl - SN - didemethylincomycin B, ethyl 6,8 - dideoxy - 6 - (trans - 4 - ethyl - L - 2 - pyrrolidinecarboxamido) - 1 - thio - D - erythro - α - D - galacto - octopyranoside (Formula VI wherein R is ethyl, $-R_1H$ is ethyl, and R_3 is hydrogen) is also obtained when α -ETL is added to the fermentation of the above British Patent Specification 1,097,926. The above-described N-desmethyl products are examples of compound IIB wherein R_3 is hydrogen. By the procedure described above replacement of the N-hydrogens produces compounds of Formula IIB wherein R_3 equals HR_2 , e.g. methyl 6,8 - dideoxy - 6 - (trans - 1 - ethyl - 4 - propyl - L - 2 - pyrrolidinecarboxamido) - 1 - thio - D - erythro - α - D - galacto - octopyranoside, ethyl 6,8 - dideoxy - 6 - (trans - 1 - methyl - 4 - ethyl - L - 2 - pyrrolidinecarboxamido) - 1 - thio - D - erythro - α - D - galacto - octopyranoside, and methyl 6,8 - dideoxy - 6 - (trans - 1 - ethyl - 4 - ethyl - L - 2 - pyrrolidinecarboxamido) - 1 - thio - D - erythro - α - D - galacto - octopyranoside.

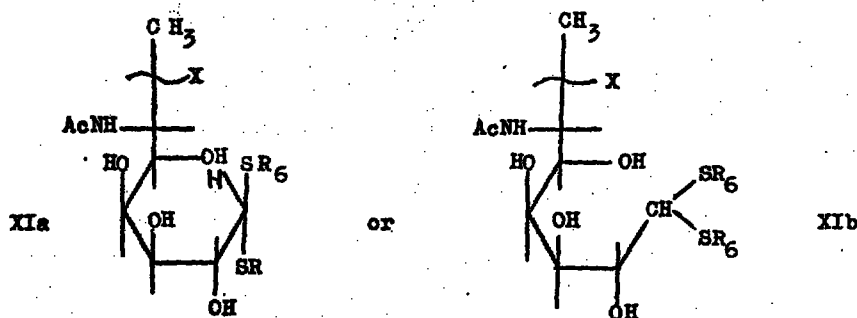
Lincomycin or any of the starting compounds of Formula II which has the D-erythro configuration can be converted to the L-threo configuration by oxidizing the

7-hydroxy group to a 7-oxo group and reducing the latter to a 7-hydroxy group. A suitable procedure for this purpose is illustrated in the following sequence:

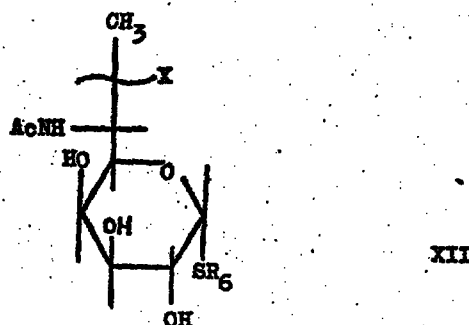


For example, lincomycin on treatment with acetone in the presence of *p*-toluenesulphonic acid is converted to 3,4 - O - isopropylidenelincomycin which on oxidation with chromic oxide gives 7 - dehydro - 3,4, - O - isopropylidenelincomycin, methyl 6,8 - dideoxy - 3,4 - O - isopropylidene - 6 - (trans - 1 - methyl - 4 - propyl - L - 2 - pyrrolidinecarboxamido) - 1 - thio - D - glycerol - α - D - galactooctanopyranoside, which on treatment with sodium borohydride is converted to 7 - epilincosamin, methyl 6,8 - dideoxy - 6 - (trans - 1 - methyl - 4 - propyl - L - 2 - pyrrolidinecarboxamido) - 1 - thio - L - threo - α - D - galactooctanopyranoside. Any of the starting compounds of Formula II having a D-erythro configuration can be converted to the corresponding L-threo configuration by this procedure.

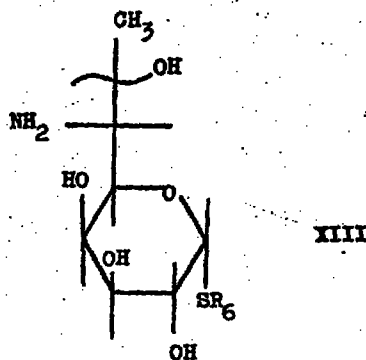
As the biosynthetic-produced lincomycins, as well as the amino sugars derived therefrom, are either methyl or ethyl thioglycosides, it is sometimes desirable to convert them to higher or lower glycosides. It is also sometimes desirable to convert any of the compounds of Formulas I, II, or V to higher or lower glycosides. This can effectively be accomplished by reacting the compound to be converted with a mercaptan of the formula R_sSH wherein R_s is an alkyl group of not more than 20 carbon atoms, but one different from R and cyclizing the resulting dimercaptal. For example, compounds of Formula I and II on reaction with a mercaptan of Formula R_sSH produce dithioacetals of the formula



wherein X is hydroxy or chlorine, which on treatment with acid or on heating, either in the presence of acid or not, are recycled to a compound of the following formula:

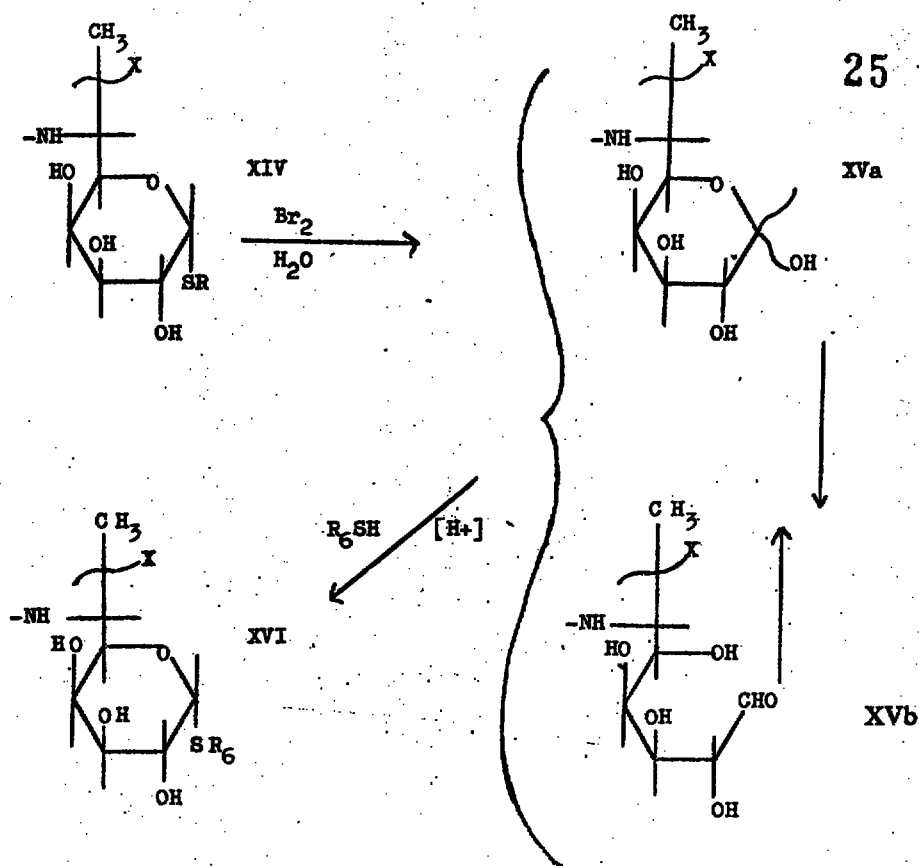


- 5 The process can be applied directly to any of the starting products of Formula II, i.e., IIA, IIB, IIC, IID, and IIE. The resulting products can be subjected to hydrazinolysis to form compounds of the following formula:



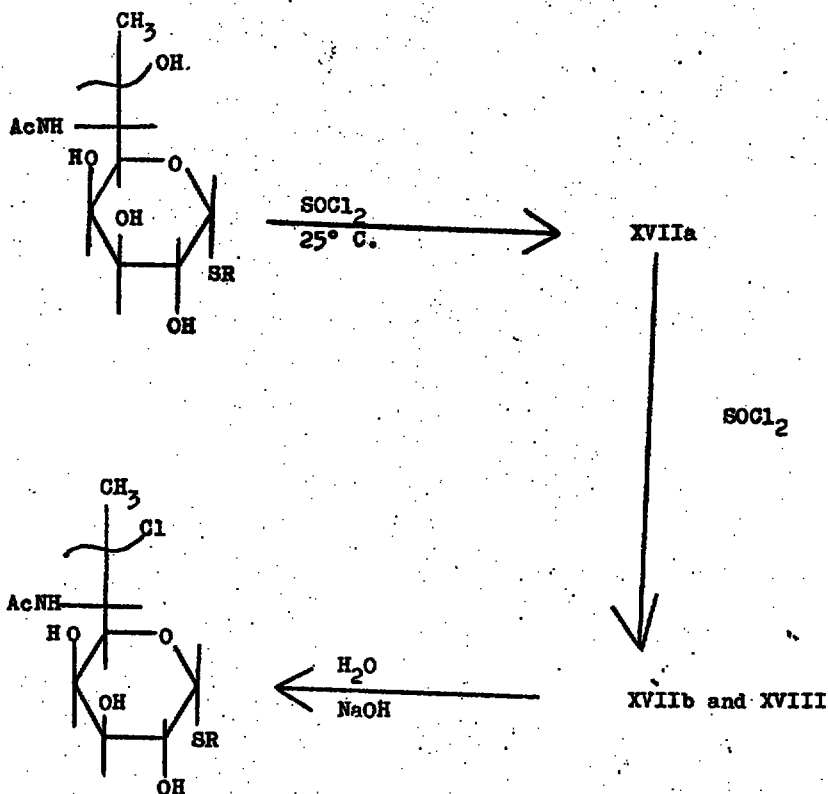
- 10 which can be N-acylated as described above with acids of Formula A, B, C, D, and E to provide compounds according to Formula XII wherein X is hydroxy. The process can also be applied to the starting compounds of Formula V. For example, α -MTL on treatment with ethyl mercaptan followed by cyclization as described above is converted to α -ETL. α -MTL is the S-methyl analogue of α -ETL. It is described in British Patent Specification No. 1008647.

- 15 An alternative process for making compounds of Formula XII or Formula XIII is to brominate the starting material (Formulas I, II, or V) and then react the product with a mercaptan according to the following sequence:

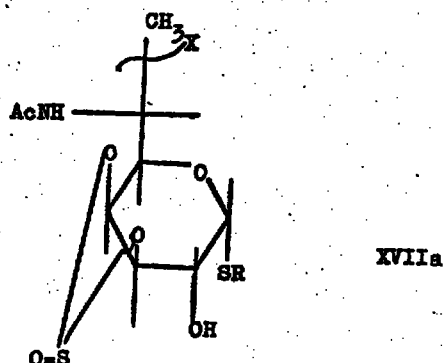


The starting compound, XIV, is dissolved in water as a soluble salt, e.g., the hydrochloride, and bromine added with cooling advantageously to between about -10 and 20°C . It is sufficient if the aqueous solution is cooled to about 0°C . and the bromine added dropwise. The stoichiometric amount of bromine is 1 mole for each mole of starting compound, though more or less can be used. Advantageously a slight excess, say from 5 to 20% excess, of bromine is used. The bromine initially replaces the RS— group and the resulting intermediate hydrolyzes to the sugar in which the pyranose form XVa is in equilibrium with the aldose form XVb. In the presence of acid, e.g., hydrochloric acid or other strong non-oxidizing acid such as *p*-toluenesulphonic acid and sulphonic acid type anion exchange resins, the mercaptan R_6SH reacts with the sugar XV to form the thioglycoside XVI. Concomitantly some diacetal may be formed which after separation can be cyclized as described above to form more of the desired thioglycoside XVI.

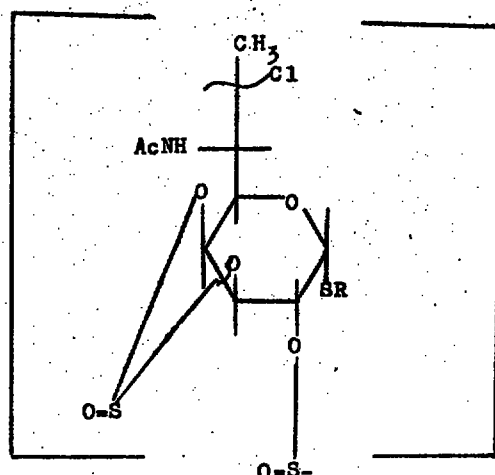
The mechanism by which thionyl chloride effects the substitution of the 7-hydroxy by chlorine is not fully understood. The mechanism is such that a change in configuration results. Thus a 7-hydroxy compound of the *D-erythro* configuration yields a 7-chloro compound of the *L-threo* configuration. For example, 7-chloro-7-deoxylincomycin which is derived from lincomycin and has the *D-erythro* configuration, have the *L-threo* configuration. It has been tentatively established, however, that the process goes through a series of intermediates in accordance with the following sequence:



wherein Ac and R are as given above. Intermediate **XVIIa** is the 3,4-cyclic sulphite of the starting material **II** and has the following formula:



wherein **X** is hydroxy. Intermediate **XVIIb** is the corresponding 3,4-cyclic sulphite of the 7-chloro compound (Formula I) and is represented by Formula **XVIIa** wherein **X** is chlorine. Intermediate **XVIII** may be a bis-sulphite of the 3,4-cyclic sulphite of the 7-chloro compound which can be represented by the following formula:



27

XVIII

If desired, each of the three intermediates, XVIIa, XVIIb and XVIII can be isolated during the course of the reaction. All that is necessary, however, to effect the substitution of the 7-hydroxy by chlorine is to mix the starting compound of Formula II or V, advantageously in the form of an acid-addition salt, e.g., the hydrochloride, with thionyl chloride, advantageously in the presence of an inert solvent, with mild heating, advantageously at reflux temperature; until the desired substitution of the 7-hydroxy group by chlorine is effected. Advantageously, the reaction is carried out in an inert atmosphere, e.g., under nitrogen. Carbon tetrachloride can be used effectively as the solvent vehicle but other inert solvents such as chloroform, methylene chloride, ethylene chloride, ether, benzene, and the like can be used. A satisfactory procedure is to stir the reaction mixture at room temperature for a considerable period, say from about 1 to 18 hours or as long as necessary to obtain a reasonably clear solution and then to raise the temperature to between about 50 and 100°C., for example, to the reflux temperature (77°C. for carbon tetrachloride). After the reaction is complete, usually after heating at reflux for about 1 to 5 hours, the reaction mixture is allowed to cool, advantageously under nitrogen. Any material that separates on the cooling is collected and dried. The solvent is removed by vacuum distillation at a pot temperature advantageously less than about 35°C. and the material which precipitates is collected and dried and treated with ethanol to convert any residual sulphite intermediates to the desired product. The collected material can then be further purified by solvent extraction and/or recrystallization and can be recovered either as the free base or an acid addition salt.

The proportions of the reagents can be varied widely. Stoichiometrically, however, at least 3 moles of thionyl chloride is required for each mole of starting compound. Any larger amount can be used but ordinarily it is not necessary or desirable to use more than about a 10 fold excess. Advantageously, an excess of about 2 to 3 fold is used. The amount of solvent is not critical and can be varied widely in accordance with the practices in the art. Ordinarily from about 15 to about 30 volumes of solvent for each part of solid starting compound will suffice. The proportion of solvent to thionyl chloride, however, is important because of the solubility of the product in thionyl chloride. If the ratio of solvent to thionyl chloride (v/v) is high, the desired product precipitates on cooling of the reaction mixture and the work up of the product is simplified. For example, with carbon tetrachloride a mixture of products precipitates directly on cooling the reaction mixture if the v/v proportion of carbon tetrachloride to thionyl chloride is kept above about 10 to 1.

The compounds of Formulas IA, IB, IIA, IIB, and V exist either in the protonated or non-protonated forms according to the pH of the environment. The protonated form is presented as an acid-addition salt and the non-protonated form as the free base. The free bases can be converted to stable acid-addition salts by neutralizing the free base with the appropriate acid to below about pH 7.0, and advantageously to about pH 2 to pH 6. Suitable acids for this purpose include hydrochloric, sulphuric, phosphoric, thiocyanic, fluosilicic, hexafluoroarsenic, hexafluorophosphoric, acetic, succinic, citric, lactic, maleic, fumaric, pantoic, cholic, palmitic, mucic, camphoric, glutaric, glycolic, phthalic, tartaric, lauric, stearic, salicylic, 3-phenylsalicylic, 5-phenylsalicylic, 3-

methylglutaric, orthosulphobenzoic, cyclopentanepropionic, 1,2-cyclohexanedicarboxylic, 4-cyclohexanecarboxylic, octadecenylsuccinic, octenylsuccinic, methanesulphonic, benzenesulphonic, helianthic, Reinecke's, dimethyldithiocarbamic, cyclohexylsulphamic, hexadecylsulphamic, octadecylsulphamic, sorbic, monochloroacetic, undecylenic, 4'-hydroxyazobenzene-4-sulphonic, octodecylsulphuric, picric, benzoic, cinnamic, and like acids.

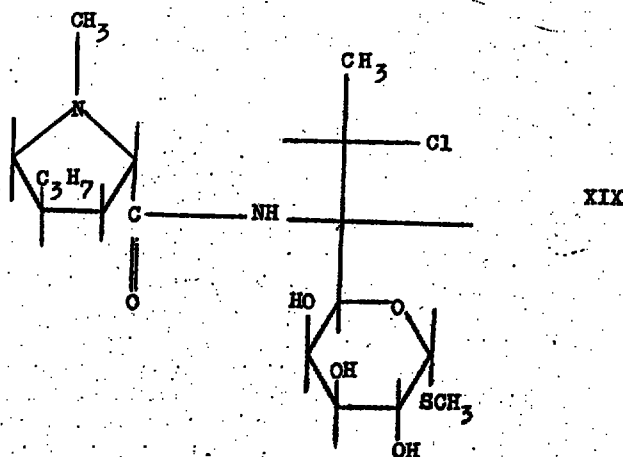
The acid-addition salts can be used for the same purposes as the free base or they can be employed to upgrade the same. For example, the free base can be converted to a water-insoluble salt, such as the picrate, which can be subjected to purification procedures, for example, solvent extractions and washings, chromatography, fractional liquid-liquid extractions, and crystallization and then used to regenerate the free base form by treatment with alkali or to make a different salt by metathesis. Or the free base can be converted to a water-soluble salt, such as the hydrochloride or sulphate, and the aqueous solution of the salt extracted with various water-immiscible solvents before regenerating the free base form by treatment of the thus-extracted acid solution or converted to another salt by metathesis. The free bases of Formulas IA, IB, IIA, IIB, and V can be used as buffers or as antacids. The compounds of Formulas I, II, and V react with isocyanates to form urethanes and can be used to modify polyurethane resins. The long chain compounds, i.e., where HR_2 is alkyl of from 8 carbon atoms up, have surface active properties and can be used as wetting and emulsifying agents. The thiocyanic acid addition salt when condensed with formaldehyde forms resinous materials useful as pickling inhibitors according to U.S. Patents 2,425,320 and 2,606,155. The free bases also make good vehicles for toxic acids. For example, the fluosilicic acid addition salts are useful as mothproofing agents according to U.S. Patents 1,915,334 and 2,075,359 and the hexafluoroarsenic acid and hexafluorophosphoric acid addition salts are useful as parasiticides according to U.S. Patents 3,122,536 and 3,122,552.

The close analogues of 7-chloro-7-deoxy lincomycin, i.e., where $-R_1H$ is *cis* or *trans* alkyl of not more than 8 carbon atoms; R_2 is methyl or ethyl; R is alkyl of not more than 8 carbon atoms, have anti-bacterial properties, and some are comparable or superior to lincomycin and can be used for the same purposes as lincomycin. The corresponding compounds where R_2 is hydrogen have like antibacterial properties, and moreover have improved Gram-negative activity. The other analogues and isomers have similar antibacterial properties but to a lesser degree and can be used for the same purposes as lincomycin where larger amounts are not objectionable.

The following examples are illustrative of the process and products of the present invention but are not to be construed as limiting. The parts and percentages are by weight and the solvent ratios are by volume unless otherwise specified.

EXAMPLE 1

7 - Chloro - 7 - deoxylincomycin [methyl 7 - chloro - 6,7,8 - trideoxy - 6 - (trans - 1 - methyl - 4 - propyl - L - 2 - pyrrolidinecarboxamido) - 1 - thio - L - threo - α - D - galactooctopyranoside.



A. *The free base.*

A suspension of 221.0 g. (0.5 mole) of lincomycin hydrochloride in 5 l. of carbon tetrachloride was stirred well at 25° under nitrogen. 900 ml. of thionyl chloride was added all at once and stirring continued for 2 hr. During this period the solid dissolved and a clear solution was obtained. The reaction mixture was heated at reflux for 2 hr., the heat source then removed and nitrogen bubbled into the amber solution until the pot temperature dropped to 25°. About 4 l. of liquid was removed *via* vacuum distillation at a pot temperature of less than 35°. The yellow solid which precipitated during this distillation was collected and dried. This solid was dissolved in about 300 ml. of methanol, cooled at 25°, made basic (pH 11) with dilute aqueous sodium hydroxide solution (2N), diluted to about 1200 ml. with water and extracted well with ether. The ether extracts were combined, washed with a small amount of water, dried over anhydrous magnesium sulphate and filtered. On evaporation of an aliquot of the combined ether extract 7-chloro-7-deoxylincomycin free base is obtained as a yellow amorphous solid.

B. *The hydrochloride*

Addition of hydrogen chloride gas to the filtrate of part A resulted in the precipitation of 7-chloro-7-deoxylincomycin hydrochloride which was separated and recrystallized from ethanol and ethyl acetate. A 32% yield of white, crystalline 7-chloro-7-deoxylincomycin hydrochloride solvated with approximately one molecular proportion of water was obtained.

Anal. Calcd. for $C_{18}H_{23}ClN_2O_5 \cdot S \cdot HCl \cdot H_2O$

C, 45.18; H, 7.37; Cl, 14.82; N, 5.86; S, 6.70; H_2O , 3.77.

Found: C, 44.70; H, 7.65; Cl, 14.27; N, 5.78; S, 6.45; H_2O , 3.85.

$[\alpha]_D^{25} + 130^\circ$ (C—0.9858 g./100 ml.).

Activity: About 4 to 8 times lincomycin.

Antibacterial spectrum: Same as lincomycin.

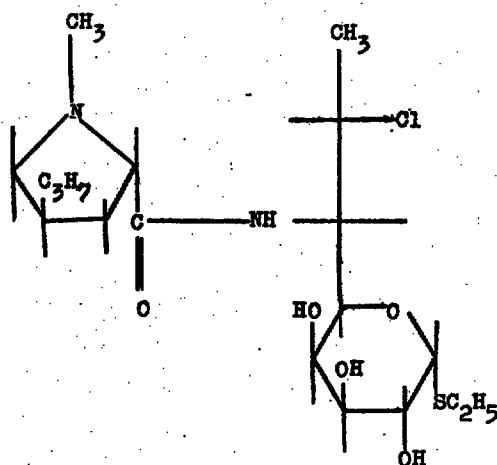
EXAMPLE 2

7-chloro-7-deoxylincomycin free base.

The process of Example 1, part A, was repeated except that methylene chloride was used in place of ether as the extracting solvent and the combined extracts were filtered and evaporated to dryness. There was obtained a 64% yield of 7-chloro-7-deoxylincomycin free base as a yellow amorphous solid. 15 grams of this amorphous solid was adsorbed on 30 grams of silica gel in methylene chloride, dried and sifted onto a 3 inch diameter column of 1500 grams of silica gel. The column was then eluted with a mixture of methanol and chloroform in the proportions of 1 to 19, respectively, in 200 ml. portions after a 2 liter forerun. Fractions 26, 27, and 28 were pooled and evaporated to dryness yielding 1.04 grams of essentially pure 7-chloro-7-deoxylincomycin free base as an amorphous solid having an antibacterial spectrum of the same scope and magnitude as the 7-chloro-7-deoxylincomycin hydrochloride of Example 1.

EXAMPLE 3

7 - chloro - 7 - deoxylincomycin C [ethyl 7 - chloro - 6,7,8 - trideoxy-
6 - (trans - 1 - methyl - 4 - propyl - L - 2 - pyrrolidinecarboxamido) -
1 - thio - L - threo - α - D - galacto - octopyranoside]



A. Chlorine substitution

A suspension of 1 gram of lincomycin C hydrochloride in 25 ml. of carbon tetrachloride and 4.5 ml. of thionyl chloride was stirred under nitrogen for 2 hours at 25°C. A clear solution was obtained in about 15 minutes. The reaction mixture was then heated at reflux for 2 hours and evaporated to dryness under vacuum to give a yellow solid which was dried under vacuum at 40°C. for 18 hours. The product was then dissolved in about 15 ml. of warm ethanol, made basic with sodium hydroxide as in Example 1 and diluted to 300 ml. with water. The water solution was extracted 5 times with 100 ml. portions of ether. The ether extracts were pooled, dried over magnesium sulphate, filtered, saturated with hydrogen chloride gas, and evaporated to a brown residue which on being recrystallized two times from a mixture of ethanol and ethyl acetate (dissolved in a minimum amount of ethanol and ethyl acetate added to turbidity) yielded 200 mg. of 7-chloro-7-deoxylincomycin C hydrochloride as white crystals which had the same activity and spectrum as the 7-chloro-7-deoxylincomycin hydrochloride of Example 1.

Lincomycin C can be obtained by the fermentation process of British Patent Specification No. 1,087,882 or by reacting lincomycin with ethanethiol (ethyl mercaptan) as described in British Patent Specification No. 1,127,139 and heating the reaction mixture in the presence of *p*-toluenesulphonic acid or heating to fusion.

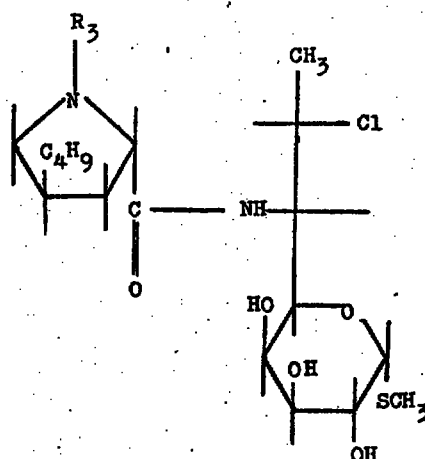
Other alkyl, cycloalkyl, cycloalkyl-alkyl and aralkyl 7-chloro-6,7,8-trideoxy-6-(trans - 1 - methyl - 4 - propyl - L - 2 - pyrrolidinecarboxamido) - 1 - thio - L - threo - α - D - galacto - octopyranosides:

By substituting the lincomycin C by the appropriate alkyl, cycloalkyl, cycloalkyl-alkyl and aralkyl 6,8 - dideoxy - 6 - (trans - 1 - methyl - 4 - propyl - L - 2 - pyrrolidine carboxamide, 1 - thio - D - erythro - α - D - galacto - octopyranoside, for example where alkyl is propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl or eicosyl and the isomeric forms thereof; where cycloalkyl or cycloalkyl-alkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 2-methylcyclopentyl, 2,3-dimethylcyclobutyl, 2-methylcyclobutyl or 3-cyclopentylpropyl and where aralkyl is benzyl, phenethyl, 3-phenylpropyl, or 1-naphthylmethyl there are obtained the corresponding alkyl, cycloalkyl, cycloalkyl-alkyl and aralkyl 7 - chloro - 6,7,8 - trideoxy - 6 - (trans - 1 - methyl - 4 - propyl - L - 2 - pyrrolidinecarboxamido) - 1 - thio - L - threo - α - D - galacto - octanopyranosides. The compounds thus obtained (both the 6,8 - dideoxy and the 7 - chloro - 6,7,8 - trideoxy compounds) wherein alkyl is propyl, butyl, pentyl, and hexyl (obtained respectively when propyl, butyl, pentyl, and hexyl mercaptans are used) are especially effective antibacterials, having the same spectrum as lincomycin and equal or greater activity.

EXAMPLE 4

Methyl 7 - chloro - 6,7,8 - trideoxy - 6 - (*trans* - 1 - alkyl - 4 - butyl - L - 2 - pyrrolidinecarboxamido) - 1 - thio - L - *threo* - α - D - *galacto* - octopyranosides.

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XXII

R_3 = methyl or ethyl.

A suspension of 116 mg. of methyl 6,8 - dideoxy - 6 - (*trans* - 1 - ethyl - 4 - butyl - L - 2 - pyrrolidinecarboxamido) - 1 - thio - D - *erythro* - α - D - *galacto* - octopyranoside free base in 3 ml. carbon tetrachloride and 0.7 ml. of thionyl chloride was stirred at 25°C. until a clear solution was obtained (about 15 minutes) and allowed to stand at 25°C. for 2 hours. The reaction mixture was then heated at reflux for 2 hours and then evaporated to dryness under vacuum to a yellow solid which was worked up as described in Example 3. The product, however, did not crystallize so the crystallizing solvents were evaporated to yield 17 mg. of methyl 7 - chloro - 6,7,8 - trideoxy - 6 - (*trans* - 1 - ethyl - 4 - butyl - L - 2 - pyrrolidinecarboxamido) - 1 - thio - L - *threo* - α - D - *galacto* - octopyranoside hydrochloride as a tan amorphous solid which assayed 8 times the activity of lincomycin against Gram-positive bacteria and 16 to 64 times that of lincomycin against Gram-negative bacteria.

On substituting the *cis* epimer, there is obtained methyl - 7 - chloro - 6,7,8 - trideoxy - 6 - (*cis* - 1 - ethyl - 4 - butyl - L - 2 - pyrrolidinecarboxamido) - 1 - thio - L - *threo* - α - D - *galacto* - octopyranoside hydrochloride having the same antibacterial spectrum.

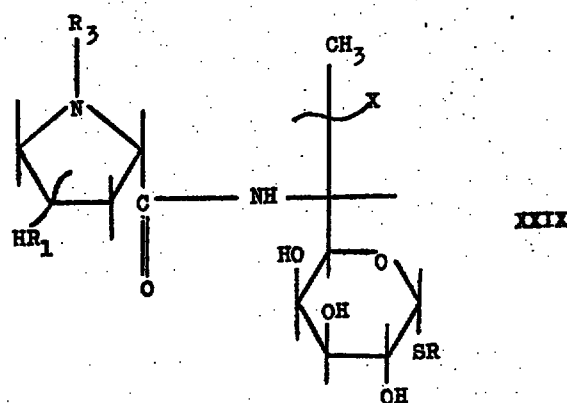
On substituting the 1 - methyl analogs, methyl 7 - chloro - 6,7,8 - trideoxy - 6 - (*cis* and *trans* - 1 - methyl - 4 - butyl - L - 2 - pyrrolidinecarboxamido) - 1 - thio - L - *threo* - α - D - *galacto* - octopyranosides hydrochlorides are obtained.

The *cis* and *trans* epimers used as starting materials in the above example are described in British Patent Specification 1,118,306.

If desired the above procedure can be applied to the S analogues of α -MTL obtained by the hydrazinolysis of lincomycin C or the S-analogues thereof described above using the hydrochloride or other salt of a strong acid and acylating the resulting alkyl, cycloalkyl, cycloalkyl-alkyl or aralkyl 6 - amino - 7 - chloro - 6,9,8 - trideoxy - 1 - thio - D - *erythro* - α - D - *galacto* - octopyranoside with an acid of Formula A, B, C, D or E by the procedure of British Patent Specification No. 1,118,306. If desired the above procedure can be applied to any of the intermediate starting compounds such as those of Formulae IIA, IIB, IIC, IID, and IIE where R_3 is hydrogen to produce the same compounds. The resulting 7-chloro compounds can be processed by the procedures given in British Patent Specification No. 1,118,306 to convert the acyl moiety to the desired form.

Separation of the *cis* and *trans* isomers is not a necessary step as the 7-chloro derivatives of the mixed epimers are useful per se. It is desirable, however, to keep the content of *trans* isomer high as this is the most active form. By carrying out the process with this in mind mixed epimeric products containing a ratio of *trans* and *cis* epimers of 3:1 to 1:5 can readily be obtained.

A preferred group of compounds are represented by the formula



wherein X is chlorine, R, HR₁, and R₂ are alkyl of not more than six carbon atoms, advantageously of not more than twelve carbon atoms in the aggregate; and the configuration is *L-threo*, are obtained on treatment with thionyl chloride by the procedure of Part A if compounds according to Formula XXIX where X is hydroxy, R, HR₁, and R₂ are alkyl as given above; and the configuration is *L-erythro*. The 6,8-dideoxy compounds of Formula XXIX as characterized above are active antibacterials comparable with lincomycin. The 7-chloro-6,7,8-trideoxy compounds of Formula XXIX as characterized above have the same spectrum of antibacterial activity but are substantially more active. Representative compounds of Formula XXIX wherein X is chlorine but which have the *L-threo* configuration are given in the following table:

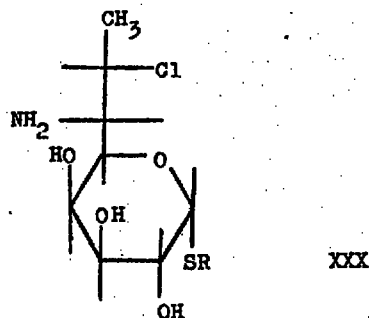
TABLE I

Compounds of Formula XXIX where X is Chlorine

		R	HR ₁	R ₂
4A		methyl	trans-ethyl	methyl
4B		methyl	cis-ethyl	methyl
4C	(7-chloro-7-deoxylincomycin)	methyl	trans-propyl	methyl
4D	(7-chloro-7-deoxyallolincomycin)	methyl	cis-propyl	methyl
4E	(7-chloro-7-deoxylincomycin E)	methyl	trans-propyl	ethyl
4F	(7-chloro-7-deoxyallolincomycin E)	methyl	cis-propyl	ethyl
4G		ethyl	trans-propyl	methyl
4H		ethyl	cis-propyl	methyl
4I		methyl	trans-butyl	methyl
4J		methyl	cis-butyl	methyl
4K		methyl	trans-propyl	ethyl
4L		methyl	cis-propyl	ethyl
4M		ethyl	trans-propyl	ethyl
4N		ethyl	cis-propyl	ethyl
4O		methyl	trans-butyl	ethyl
4P		methyl	cis-butyl	ethyl
4Q		methyl	trans-pentyl	methyl
4R		methyl	cis-pentyl	methyl
4S		ethyl	trans-butyl	ethyl
4T		ethyl	cis-butyl	ethyl
4U		methyl	trans-pentyl	ethyl
4V		methyl	cis-pentyl	ethyl
4W		ethyl	trans-pentyl	methyl
4X		ethyl	cis-pentyl	methyl
4Y		methyl	trans-hexyl	methyl
4Z		methyl	cis-hexyl	methyl
4AA		butyl	trans-propyl	methyl
4AB		butyl	cis-oropyl	methyl
4AC		ethyl	trans-pentyl	ethyl
4AD		ethyl	cis-pentyl	ethyl
4AE		butyl	trans-butyl	ethyl
4AF		butyl	cis-butyl	ethyl
4AG		butyl	trans-pentyl	methyl
4AH		butyl	cis-pentyl	methyl
4AI		cyclohexyl	trans-propyl	methyl
4AJ		cyclohexyl	cis-propyl	methyl
4AK		butyl	trans-pentyl	ethyl
4AL		butyl	cis-pentyl	ethyl
4AM		pentyl	trans-pentyl	ethyl
4AN		pentyl	cis-pentyl	ethyl

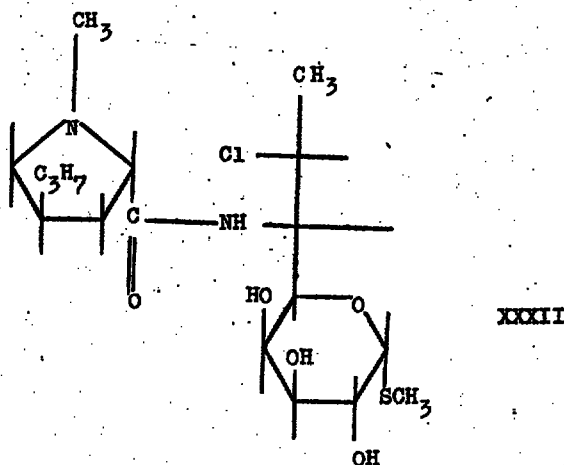
Intermediates for the preparation of the above compounds correspond to the above table where (1) X is hydroxy; (2) R₂ is hydrogen; (3) X is hydroxy and R₂ is hydrogen; (4) X is hydroxy and R₂ is carbobenzoxy; (5) X is chlorine and R₂ is carbobenzoxy; (6) X is hydroxy, R₂ is carbobenzoxy, and HR₁ and H in the 4-position are replaced by the ylidene group, R₁; (7) X is chlorine, R₂ is carbobenzoxy, and HR₁ and H in the 4-position are replaced by the ylidene group, R₁; (8) X is hydroxy, R₂ is hydrogen, and HR₁ and H in the 4-position are replaced by the ylidene group, R₁; (9) X is chlorine, R₂ is hydrogen, and HR₁ and H in the 4-position are replaced by the ylidene group, R₁; (10) X is hydroxy, and HR₁ and H in the 4-position are replaced by the ylidene group, R₁; and (11) X is chlorine and HR₁ and H in the 4-position are replaced by the ylidene group, R₁; it being understood that when X is hydroxy its configuration is *D-erythro* and that when X is chlorine, the configuration is *L-threo*.

When the lincomycin of Example 4 is replaced by an alkyl, cycloalkyl, cycloalkyl-alkyl or aralkyl 6-amino-6,8-dideoxy-1-thio-*D-erythro-α-D-galacto*-octopyranoside free base there are obtained compounds of the formula:



wherein R is for example ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, and eicosyl, or any of the isomeric forms thereof, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 2-methylcyclopentyl, 2,3-dimethylcyclobutyl, 2-methylcyclobutyl, and 3-cyclopentylpropyl; benzyl, phenethyl, 3-phenylpropyl, and 1-naphthylmethyl which can be acylated by the procedures of Example 4 to form the corresponding 7 - chloro - 7 - deoxylincomycin analogues, for example, the compounds of Formula XXIX as given and illustrated above, as well as the intermediates therefor.

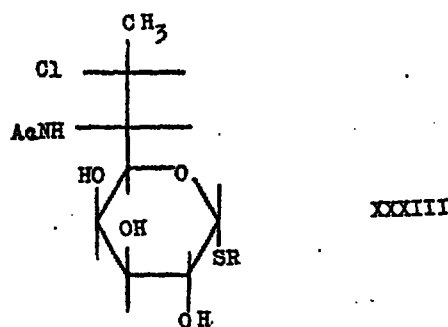
EXAMPLE 5
7-Epichloro-7-deoxylincomycin.HCl



7-Epilincomycin hydrochloride (0.85 g.) was suspended in 17 ml. of carbon tetrachloride. Thionyl chloride (4.5 ml.) was added and the reaction mixture stirred at 25° for 15 minutes. The solid dissolved to give a clear, colorless solution. The reaction was then heated at reflux for 2 hours, cooled to 25°, evaporated under vacuum to a solid yellow residue. This crude product was dissolved in 10 ml. of ethanol, made basic with 0.1N sodium hydroxide, diluted to 500 ml. with water and extracted four times with 50-ml. portions of chloroform. The combined chloroform extracts were back-washed two times with 20-ml. portions of saturated sodium chloride solution, filtered and evaporated under vacuum. The solid residue was slurried with 500 ml. of ether, filtered and hydrogen chloride gas passed into the filtrate. The solid precipitate was collected, dissolved in 3 ml. of ethanol, and re-precipitated by the addition of ether.

The solid was collected and dried. A 30% yield (270 mg.) of 7 - epichloro-7-deoxylincomycin assaying about 2 to 3 times the activity of lincomycin was obtained. TLC on silica gel (MeOH: CHCl₃ system, 1: 6, v/v) showed one spot having an R_f of 0.44 as compared with an R_f of 0.52 for 7-chloro-7-deoxylincomycin.

By substituting epilncomycin in this example by epilncomycin analogs of Formula II wherein Z, R, R₁, R₂, R₃ of the Ac group are as given and illustrated above, and the configuration is L-threo the corresponding 7-chloro-7-deoxyepilincomycin analogs of the formula



wherein Z, R, R₁, R₂, and R₃ of the Ac group are as given and illustrated above, are obtained. The preparation of epilincomycin and analogues thereof is described in British Patent Specification No. 1,118,306. All the compounds that have been described above, therefore, have their counterpart in the opposite configuration, that is, the configuration derived from the 7-*epi* form. As inversion is effected by the substitution of the 7-hydroxy group by chlorine, the *epi*-compounds which have the *L-threo* configuration, are inverted to the *D-erythro* configuration. Thus both the *D-erythro* and the *L-threo* forms are obtained depending on whether the normal lincomycins (*D-erythro*) or the *epi*-lincomycins (*L-threo*) are used.

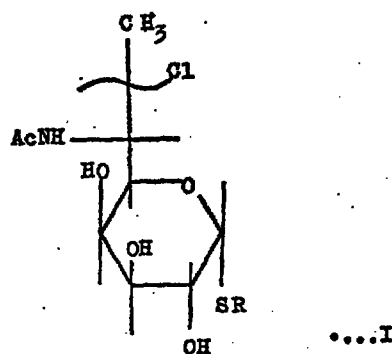
EXAMPLE 6

7-Chloro-7-deoxylincomycin Hydrochloride

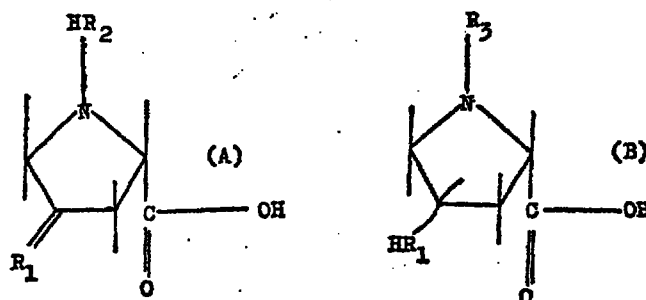
Lincomycin hydrochloride (10 g.—0.0226 mole), 200 ml. carbon tetrachloride, and 10 ml. SOCl₂ were stirred and heated at reflux for 4 hours. The reaction mixture was cooled to 25°C. and filtered. The yellow solid was dried under vacuum and then dissolved in about 10 ml. of boiling ethanol. Ethyl acetate was added to turbidity and the solution allowed to cool. The crystals of 7-chloro-7-deoxylincomycin hydrochloride thus formed were recovered in a yield of about 43%.

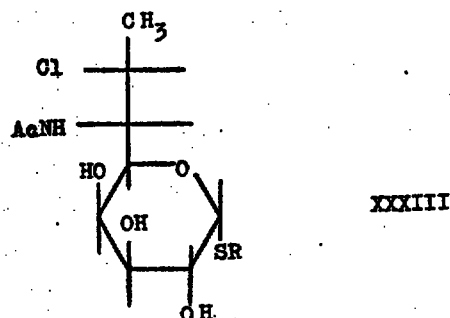
WHAT WE CLAIM IS:—

1. A compound of the formula:—



wherein R is alkyl of not more than 20 carbon atoms, cycloalkyl or cycloalkyl-alkyl of from 3 to not more than 8 carbon atoms or aralkyl of not more than 12 carbon atoms and Ac is hydrogen or the acyl radical of a 4-substituted-L-2-pyrrolidinecarboxylic acid of the formula:





wherein Z, R, R₁, R₂, and R₃ of the Ac group are as given and illustrated above, are obtained. The preparation of epilincosmycin and analogues thereof is described in British Patent Specification No. 1,118,306. All the compounds that have been described above, therefore, have their counterpart in the opposite configuration, that is, the configuration derived from the 7-*epi* form. As inversion is effected by the substitution of the 7-hydroxy group by chlorine, the *epi*-compounds which have the *L-threo* configuration, are inverted to the *D-erythro* configuration. Thus both the *D-erythro* and the *L-threo* forms are obtained depending on whether the normal lincomycins (*D-erythro*) or the *epi*-lincomycins (*L-threo*) are used.

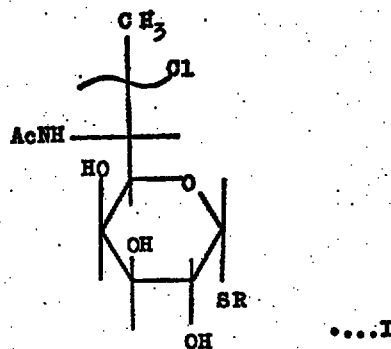
EXAMPLE 6

7-Chloro-7-deoxylincomycin Hydrochloride

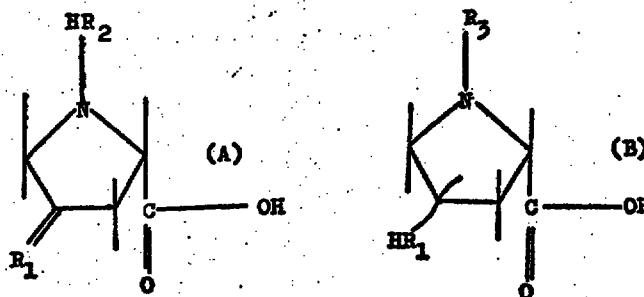
Lincomycin hydrochloride (10 g.—0.0226 mole), 200 ml. carbon tetrachloride, and 10 ml. SOCl₂ were stirred and heated at reflux for 4 hours. The reaction mixture was cooled to 25°C. and filtered. The yellow solid was dried under vacuum and then dissolved in about 10 ml. of boiling ethanol. Ethyl acetate was added to turbidity and the solution allowed to cool. The crystals of 7-chloro-7-deoxylincomycin hydrochloride thus formed were recovered in a yield of about 43%.

WHAT WE CLAIM IS:—

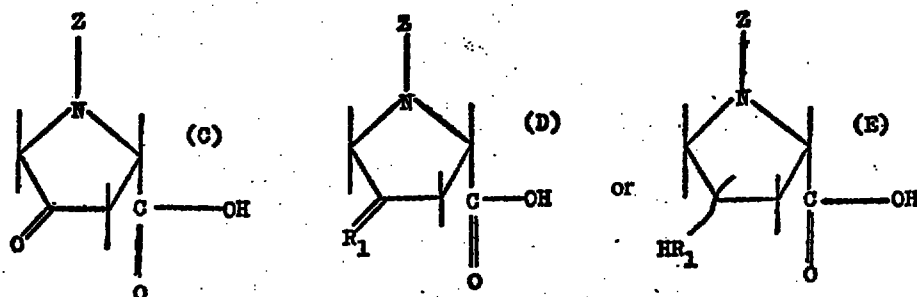
1. A compound of the formula:—



wherein R is alkyl of not more than 20 carbon atoms, cycloalkyl or cycloalkyl-alkyl of from 3 to not more than 8 carbon atoms or aralkyl of not more than 12 carbon atoms and Ac is hydrogen or the acyl radical of a 4-substituted-L-2-pyrrolidinecarboxylic acid of the formula:

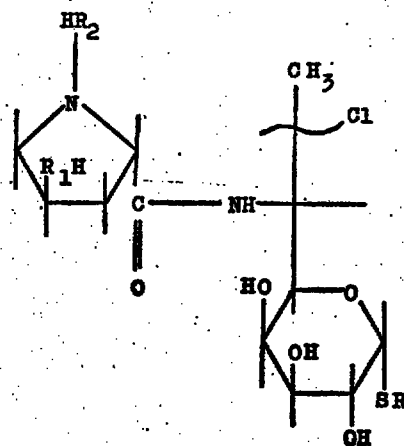


* C L M S *



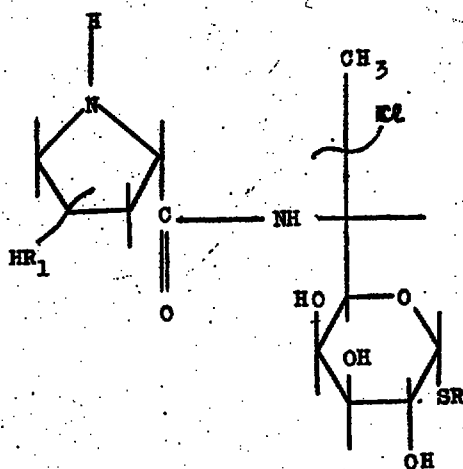
wherein R_1 and R_2 are alkylidene of not more than 20 carbon atoms, cycloalkylidene or cycloalkyl-alkylidene of from 3 to not more than 8 carbon atoms, or aralkylidene of not more than 12 carbon atoms; and R_3 is hydrogen or HR_2 , and Z is a protective hydro-carbonyloxy-carbonyl or substituted hydrocarbonyloxy-carbonyl group which is removable by hydrogenolysis, trityl, diphenyl(*p*-methoxyphenyl)methyl, bis-(*p*-methoxyphenyl)phenylmethyl, benzyl, or *p*-nitrophenyl.

2. A compound of the formula:—



wherein R , HR_1 , and HR_2 are lower alkyl of not more than 8 carbon atoms.

3. A compound of the formula:—



wherein R and HR_1 are lower alkyl of not more than 8 carbon atoms.



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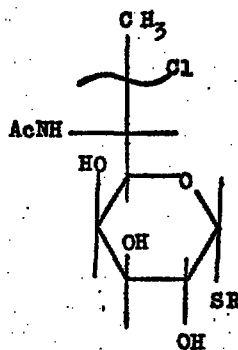
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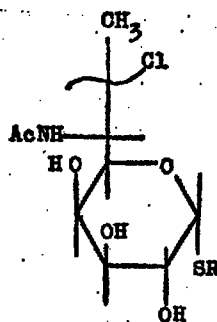
4. A compound according to claim 2 wherein R is methyl, HR₁ is propyl, and HR₂ is methyl.
5. A compound according to claim 2 wherein R is methyl, HR₁ is propyl, and HR₂ is hydrogen.
- 5 6. A compound according to claim 2 wherein R is methyl, HR₁ is propyl, and HR₂ is ethyl.
7. A compound according to claim 2 wherein R is ethyl, HR₁ is propyl, and HR₂ is methyl.
8. A compound according to claim 2 wherein R is ethyl, HR₁ is propyl, and HR₂ is hydrogen.
- 10 9. A compound according to claim 2 wherein R is ethyl, HR₁ is propyl, and HR₂ is ethyl.
- 10 10. A compound according to claim 2 wherein R is propyl, HR₁ is propyl, and HR₂ is methyl.
- 15 11. A compound according to claim 2 wherein R is propyl, HR₁ is propyl, and HR₂ is hydrogen.
- 15 12. A compound according to claim 2 wherein R is propyl, HR₁ is propyl, and HR₂ is ethyl.
- 20 13. A compound according to claim 2 wherein R is butyl, HR₁ is propyl, and HR₂ is methyl.
- 20 14. A compound according to claim 2 wherein R is butyl, HR₁ is propyl, and HR₂ is hydrogen.
15. A compound according to claim 2 wherein R is butyl, HR₁ is propyl, and HR₂ is ethyl.
- 25 16. A compound according to claim 2 wherein R is methyl, HR₁ is pentyl, and HR₂ is methyl.
- 25 17. A compound according to claim 2 wherein R is methyl, HR₁ is pentyl, and HR₂ is hydrogen.
- 30 18. A compound according to claim 2 wherein R is methyl, HR₁ is pentyl, and HR₂ is ethyl.
- 30 19. A compound according to claim 2 wherein R is methyl, HR₁ is butyl, and HR₂ is methyl.
20. A compound according to claim 2 wherein R is methyl, HR₁ is butyl, and HR₂ is hydrogen.
- 35 21. A compound according to claim 2 wherein R is methyl, HR₁ is butyl, and HR₂ is ethyl.
- 35 22. A compound according to claim 2 wherein R is ethyl, HR₁ is butyl, and HR₂ is methyl.
- 40 23. A compound according to claim 2 wherein R is ethyl, HR₁ is butyl, and HR₂ is hydrogen.
- 40 24. A compound according to claim 2 wherein R is ethyl, HR₁ is butyl, and HR₂ is ethyl.
25. A compound according to claim 2 wherein R is propyl, HR₁ is butyl, and HR₂ is methyl.
- 45 26. A compound according to claim 2 wherein R is propyl, HR₁ is butyl, and HR₂ is hydrogen.
27. A compound according to claim 2 wherein R is propyl, HR₁ is butyl, and HR₂ is ethyl.
- 50 28. A compound according to claim 2 wherein R is butyl, HR₁ is butyl, and HR₂ is methyl.
- 50 29. A compound according to claim 2 wherein R is butyl, HR₁ is butyl, and HR₂ is hydrogen.
30. A compound according to claim 2 wherein R is butyl, HR₁ is butyl, and HR₂ is ethyl.
- 55 31. A compound according to claim 2 wherein R is cyclohexyl, HR₁ is butyl, and HR₂ is methyl.
- 55 32. A compound according to claim 2 wherein R is cyclohexyl, HR₁ is butyl, and HR₂ is hydrogen.
33. A compound according to claim 2 wherein R is cyclohexyl, HR₁ is butyl, and HR₂ is ethyl.
- 60 34. 7-chloro-7-deoxylincomycin.
35. Methyl 7 - chloro - 6,7,8 - trideoxy - 6 - (trans - 1 - ethyl - 4 - propyl - L - 2 - pyrrolidinecarboxamido) - 1 - thio - L - threo - α - D - galacto - octopyranoside.
36. Methyl 7 - chloro - 6,7,8 - trideoxy - 6 - (trans - 1 - ethyl - 4 - butyl - L -



- 2 - pyrrolidinecarboxamido) - 1 - thio - L - threo - α - D - galacto - octopyranoside.
 37. Methyl 7 - chloro - 6,7,8 - trideoxy - 6 - (trans - 1 - methyl - 4 - butyl - L -
 2 - pyrrolidinecarboxamido) - 1 - thio - L - threo - α - D - galacto - octopyranoside.
 38. Methyl 7 - chloro - 6,7,8 - trideoxy - 6 - (trans - 1 - methyl - 4 - pentyl - L -
 2 - pyrrolidinecarboxamido) - 1 - thio - L - threo - α - D - galacto - octopyranoside.
 39. Methyl 7 - chloro - 6,7,8 - trideoxy - 6 - (trans - 1 - ethyl - 4 - pentyl - L -
 2 - pyrrolidinecarboxamido) - 1 - thio - L - threo - α - D - galacto - octopyranoside.
 40. The process of making compounds of the formula

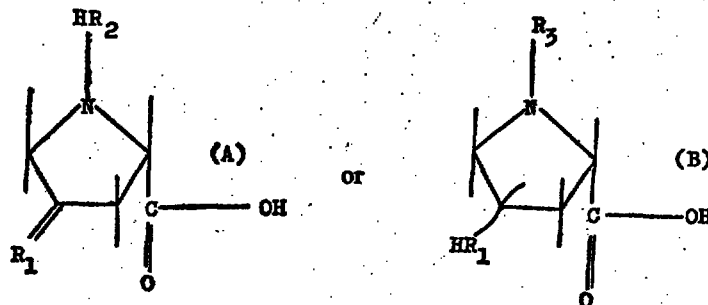


- 10 wherein R and Ac are as defined in claim 1, which comprises reacting a compound of the formula:—



with thionyl chloride at an elevated temperature.

- 15 41. A process according to claim 40 wherein R is alkyl and Ac is the acyl radical of Formula B as defined in claim 1.
 42. A process according to claim 40 wherein R is alkyl and Ac is hydrogen.
 43. A process as claimed in claim 40 wherein R is alkyl of not more than 20 carbon atoms and Ac is the acyl radical of a 4-substituted-L-2-pyrrolidinecarboxylic acid of the formula:—

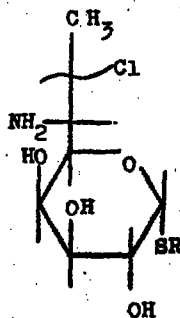


wherein R_1 and R_2 are alkylidene of not more than 20 carbon atoms, cycloalkylidene or cycloalkyl-alkylidene of from 3 to not more than 8 carbon atoms or aralkylidene of not more than 12 carbon atoms; and R_3 is hydrogen or HR_2 .

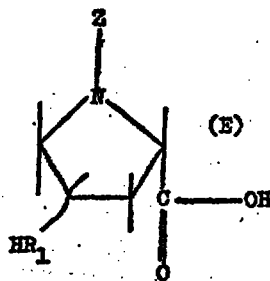
44. A process for the preparation of a 7-chloro-7-deoxylincomycin D and analo-



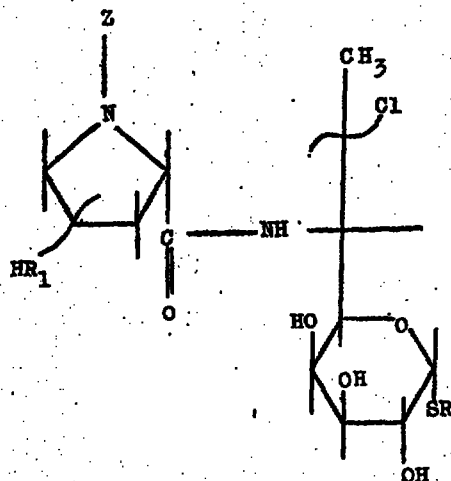
gues and isomers thereof which comprises acylating a compound of the general formula:—



with a compound of the formula:—



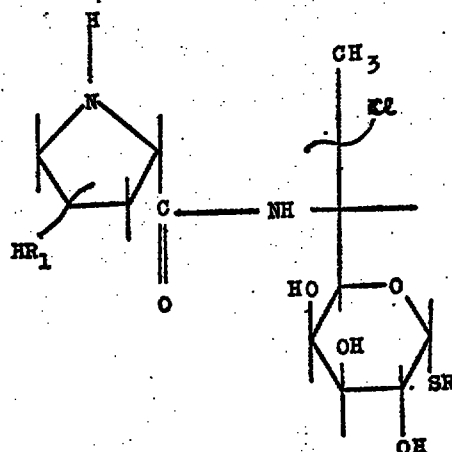
to form a compound of the formula:—



wherein R and R₁ are alkyl of not more than 20 carbon atoms, cycloalkyl or cycloalkyl-alkyl of from 3 to not more than 8 carbon atoms, or aralkyl of not more than 12 carbon atoms, Z is a protective hydrocarbonyloxy-carbonyl or substituted hydrocarbonyloxy-carbonyl group and then removing the Z group to form a compound of the general formula:—

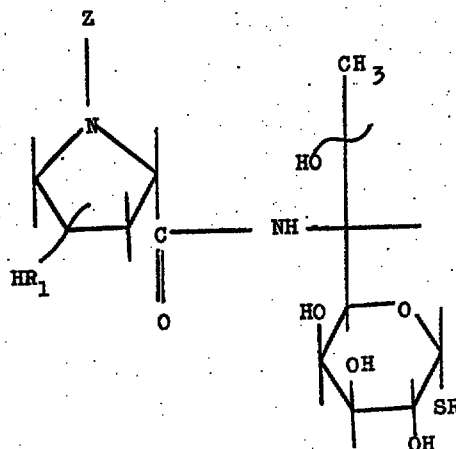


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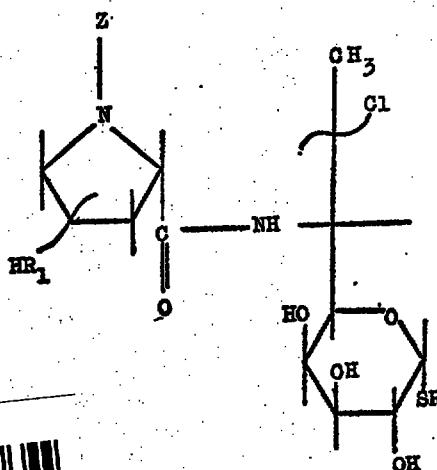


wherein R and R₁ are as defined above.

45. A process for making 7-chloro-7-deoxylincomycin D and analogues and isomers thereof which comprises reacting a compound of the general formula:—



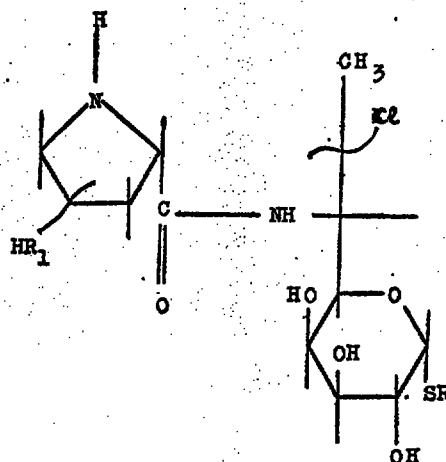
wherein R and R₁ are alkyl of not more than 20 carbon atoms, cycloalkyl or cycloalkyl-alkyl of from 3 to not more than 8 carbon atoms or aralkyl of not more than 12 carbon atoms and Z is a protective hydrocarbonyloxy-carbonyl or substituted hydrocarbonyloxy-carbonyl group with thionyl chloride at an elevated temperature to form a compound having the general formula:—



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wherein R, R₁ and Z are as defined above and removing the Z group to form a compound of the formula:—



wherein R and R₁ are as defined above.

46. A process for the preparation of a compound as claimed in any of claims 1 to 39 substantially as herein described with reference to the Examples.

47. A compound as claimed in any of claims 1 to 39 when prepared by a process as claimed in any of claims 40 to 46.

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