

L140.833



PATENT SPECIFICATION

NO DRAWINGS

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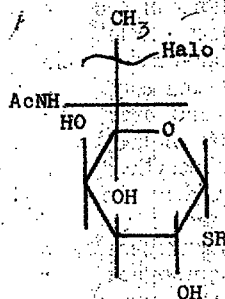
COMPLETE SPECIFICATION

Lincomycin Derivatives

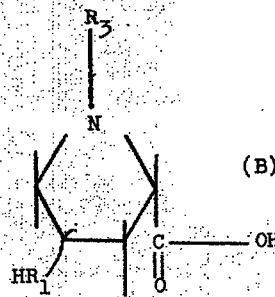
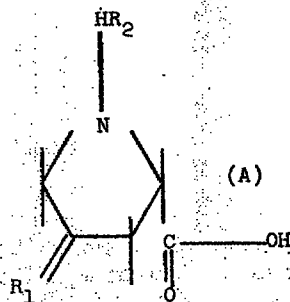
We, THE UPJOHN COMPANY, a corporation organized and existing under the laws of the State of Delaware, United States of America, of 301 Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the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

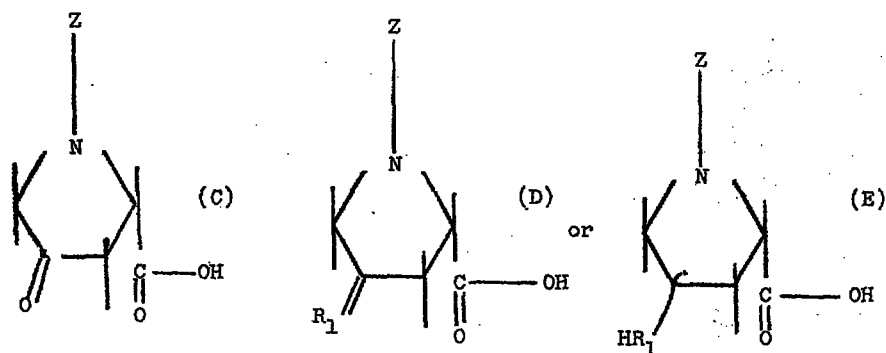
This invention relates to novel processes for the preparation of 7-halo-7-deoxylincomycin and 7-halo-7-deoxyepilcomycin and analogues and isomers thereof and to novel 7-bromo compounds produced thereby.

The compounds prepared according to the present invention can be represented by 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; halo is chlorine or bromine and Ac is hydrogen or the acyl radical of a 4-substituted-L-2-pyrrolidinecarboxylic acid of one of the formulae:





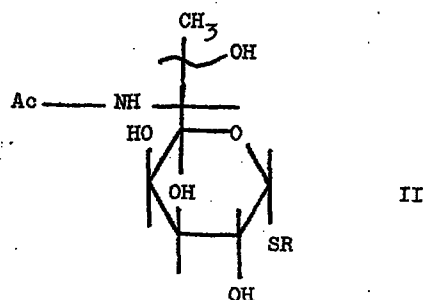
wherein R_1 and R_2 are alkylidene of not more than 20 carbon atoms (including methylene) and advantageously not more than 8 carbon atoms, cycloalkylidene or cycloalkyl-alkylidene of from 3 to not more than 8 carbon atoms, or aralkylidene of not more than 12 carbon atoms, advantageously not more than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

Novel compounds produced according to the present invention are represented by the above general formulae wherein halo is bromine.

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

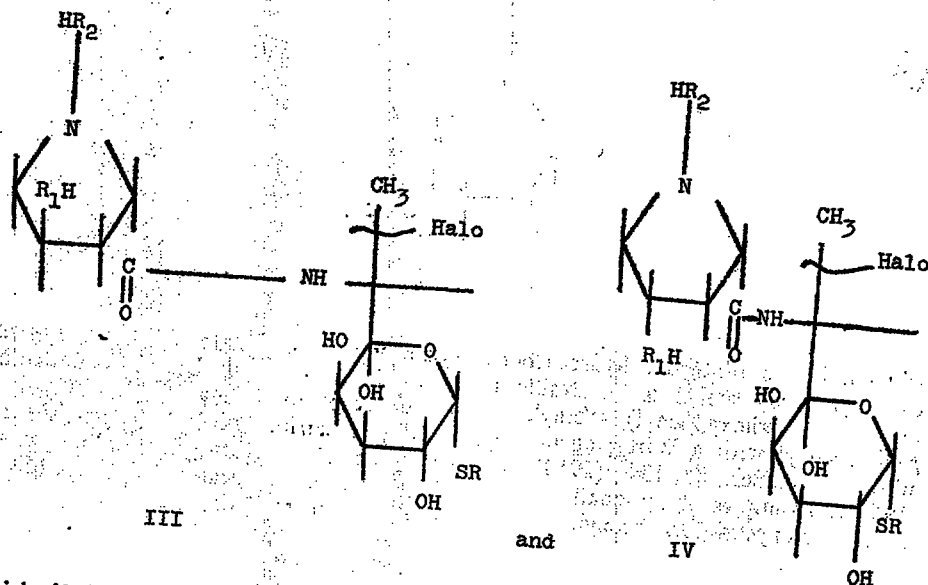
Examples of alkyl of not more than 20 carbon atoms (R , HR_1 , and HR_2) are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, and eicosyl and the isomeric forms thereof. Examples of cycloalkyl and cycloalkyl-alkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 2-methylcyclopentyl, 2,3-dimethylcyclobutyl, 4-methylcyclobutyl and 3-cyclopentylpropyl. Examples of aralkyl are benzyl, phenethyl, α -phenylpropyl and α -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 α -naphthylmethylene.

The compounds of Formula I can be prepared by replacing by halo as defined above, the 7-hydroxy of a compound of the formula



The replacement is effected by mixing the starting compound of Formula II with Rydon reagent in an inert solvent 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

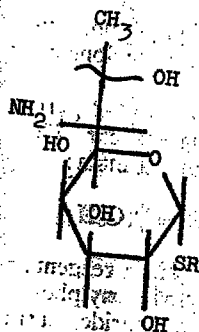
say when Ac in Formula I is that of the acid of Formula B) is obtained as a mixture of cis and trans epimers according to the formulas



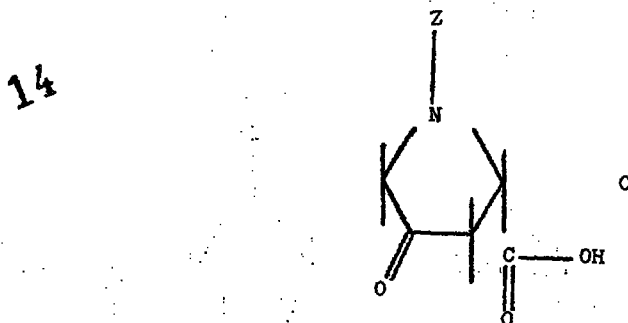
which, if desired, can be separated by counter current distribution or chromatography.

When R_2 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_2 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_1R_2CO where $R_1R_2C=$ is the same as R_2 given above. Examples of suitable oxo compounds are formaldehyde, acetaldehyde, propionaldehyde, butyraldehyde, acetone, isobutylmethyl ketone, benzaldehyde, phenylacetaldehyde, hydrocinnamaldehyde, acetophenone, propiophenone, butyrophenone, 3-methyl-4-phenyl-2-butanone, 2-methyl-5-phenyl-3-pentanone, 3-cyclopentanepropionaldehyde, cyclohexanecetaldehyde, cycloheptanecarboxaldehyde, 2,2-dimethylcyclopropylacetaldehyde, 2,2-dimethylcyclopropyl methyl ketone, cyclopentyl methyl ketone, cyclobutyl methyl ketone, cyclobutanone, cyclohexanone, and 4-methylcyclohexanone.

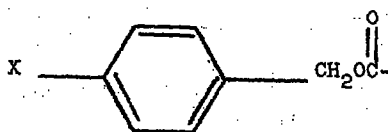
The starting compounds of Formula II are described in British Patent Specification No. 1,118,306. They are prepared by acylating a compound of the formula



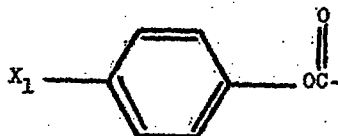
wherein R is as given above with a 4-substituted-L-2-pyrrolidinecarboxylic acid of Formula A or B. This acylation and like acylations referred to herein can be effected by procedures already well known in the art for acylating amino sugars. The starting acid of Formula A can be prepared by reacting a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



5 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



10 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



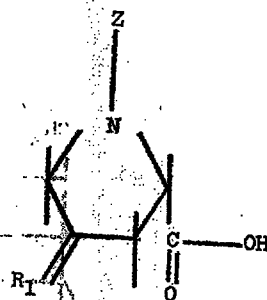
15 wherein X₁ is hydrogen, allyl, or alkyl of not more than 4 carbon atoms, such as phenyloxycarbonyl, *p*-tolyloxycarbonyl, *p*-ethylphenyloxycarbonyl, and *p*-allylphenyloxycarbonyl and the like.

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:

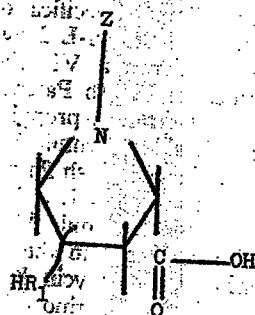


20 wherein R₁ is as given above. These Wittig reagents are prepared by reacting an alkyl, cycloalkyl, cycloalkyl-alkyl or aralkyltriphenylphosphonium halide with a base such as sodamide, or sodium or potassium hydride, or the sodium or potassium metalate of dimethylsulphoxide and the like. For example, 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

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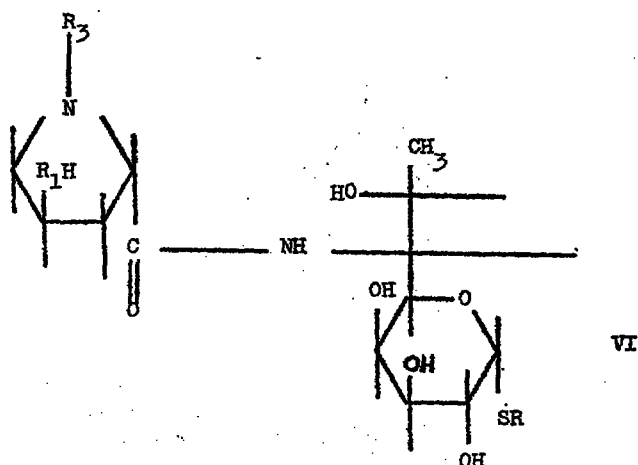


is recovered from the reaction mixture in a conventional manner, generally by extraction from aqueous solutions of the reaction mixture. The crude product can be purified by conventional means, such as recrystallization, chromatography, or formation and recrystallization of easily formed derivatives 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



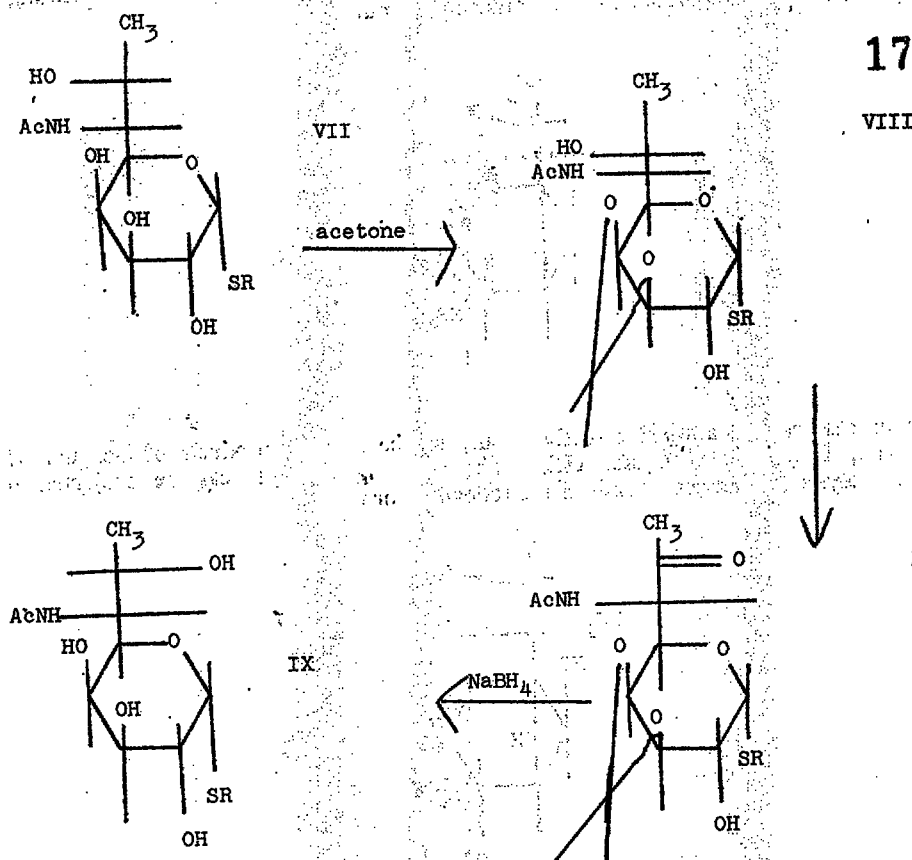
is obtained. Platinum deposited on a carrier, e.g., carbon or an anion exchange resin like Dowex—1 (Registered Trade Mark), a cross-linked polystyrene trimethyl benzyl ammonium resin in the hydroxide cycle is suitable. If desired, the starting compounds of Formula II can be acylated with acids of Formula 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 of chromatography. The starting acids of Formula B in which R₃ 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 R₃ is hydrogen by the same process. The starting acids of Formula B in which R₃ is hydrogen as well as compounds of Formula IIB in which R₃ is hydrogen can be converted respectively to compounds of Formulas B and IIB in which R₃ is HR₂ by the procedures given above. The starting acids of Formula A are obtained by treating an acid of Formula D or Formula E with hydrogen bromide in acetic acid to remove the Z group and then replacing the N-hydrogen with an HR₂ group by the procedure given above. Compounds of Formula IID and IIE are converted to compounds of Formula IIB 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 structure formula:



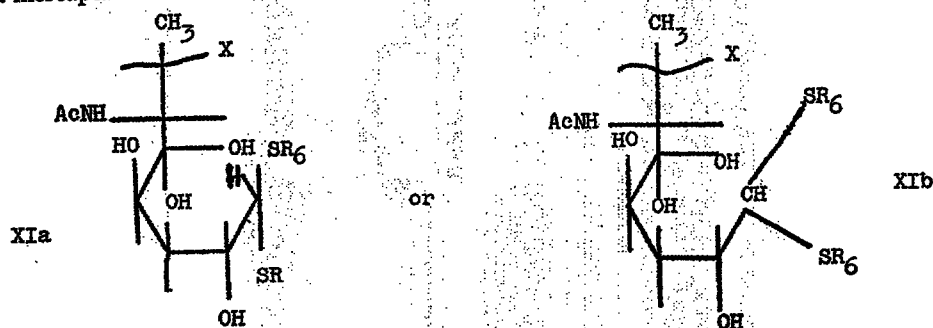
wherein R and R₃ are methyl and R₁H is propyl. Lincomycin B, methyl 6,8-dideoxy-6-(trans-1-methyl-4-ethyl-L-2-pyrrolidinecarboxamido)-1-thio-D-erythro-α-D-galacto-octopyranoside (Formula VI wherein R and R₃ are methyl and —R₁H is ethyl) is described in British Patent Specification No. 1,096,841. Lincomycin C, 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, —R₁H is propyl, and R₃ 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-D-galacto-octopyranoside (Formula VI wherein R is methyl, —R₁H is propyl, and R₃ is hydrogen) is described in British Patent Specification No. 1,102,835. 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, —R₁H is ethyl and R₃ 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, —R₁H is propyl, and R₃ is hydrogen) is produced when the fermentation of British Patent Specification No. 978,765 is carried out in the presence of added α-ETL, ethyl 6-amino-6,8-dideoxy-D-erythro-α-thio-D-galacto-octopyranoside, a compound obtained by the hydrazinolysis of lincomycin C. 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, —R₁H is ethyl, and R₃ is hydrogen) is also obtained when α-ETL is added to the fermentation of British Patent Specification No. 976,765. The above-described N-desmethyl products are examples of starting compound IIB wherein R₃ is hydrogen which, by the procedure described above can have the N-hydrogens replaced when it is desired for R₃ to equal HR₃, e.g., when it is desired to produce methyl 6,8-dideoxy-6-(trans-1-ethyl-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-D-erythro-α-D-galacto-octopyranoside or ethyl 6,8-dideoxy-6-(trans-1-methyl-4-ethyl-L-2-pyrrolidinecarboxamido)-1-thio-D-erythro-α-D-galacto-octopyranoside or ethyl 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 oxidising the 7-hydroxy group to a 7-oxo group and then reducing the latter to a 7-hydroxy group. A suitable procedure for this purpose is illustrated in the following sequence:

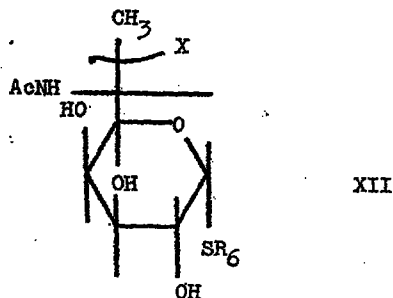


For example, lincomycin on treatment with acetone in the presence of *p*-toluene sulphonic acid is converted to 3,4-O-isopropylidenelincomycin which on oxidation with chromic oxide gives 7-dehydro-3,4-O-isopropylidenelincomycin (methyl 6,8-dideoxy-3,4-O-isopropylidene-6-(trans-1-methyl-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-D-glycero-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

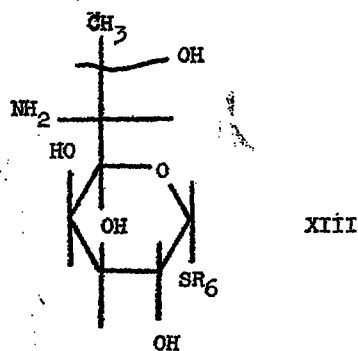
As the biosynthetic-produced lincomycins, as well as the amino sugars derived therefrom, are either methyl or ethyl thioglycosides, it is sometimes desirable to convert them to higher or lower glycosides. It is also sometimes desirable to convert any of the compounds of Formulas I, II, or V to higher or lower glycosides. This can effectively be accomplished by reacting the compound to be converted with a mercaptan of the Formula R₆SH wherein R₆ is an alkyl group of not more than 20 carbon atoms, but one different from R₁, for example, compounds of Formula I and II on reaction with a mercaptan of Formula R₆SH produce dithioacetals of the formula



wherein X is hydroxy or halogen, which on treatment with acid and/or on heating is recycled to give 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:



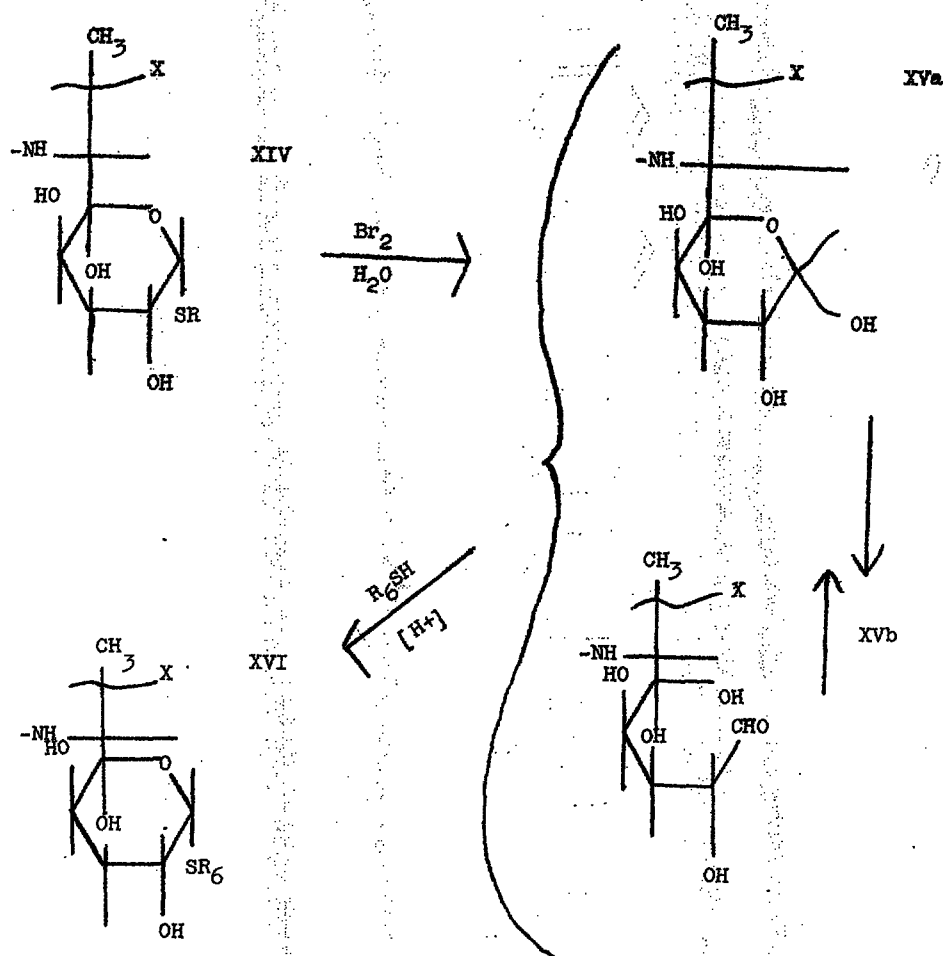
10 which can be N-acylated as described above with acids of Formula A, B, C, D, and E to provide compounds according to Formula XII wherein X is hydroxy. The process can also be applied to the starting compounds of Formula V. For example, α -MTL on treatment with ethyl mercaptan followed by recyclization 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. 1,008,447.

15 An alternative process for making compounds of Formula XI or Formula XIII is to brominate the starting material and then react it with the mercaptan according to the following sequence:

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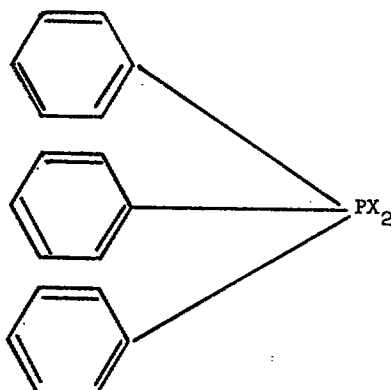


The starting compound, XIV, is dissolved in water as a soluble salt, e.g., the hydrochloride and bromine added with cooling advantageously to between about -10 and 20°C . It is sufficient if the aqueous solution is cooled to about 0°C . and the bromine added dropwise. The stoichiometric amount of bromine 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*-toluene sulfonic acid, and sulfonic acid type anion exchange resins, the mercaptan R_6SH reacts with the sugar XV to form the thioglycoside XVI. Concomitantly some diacetal of Formula XI may be formed which after separation can be cyclized as described above to form more of the desired thioglycoside XVI.

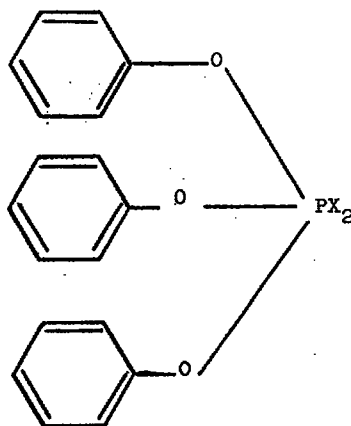
The mechanism by which Rydon reagent effects the substitution of the 7-hydroxy by halogen is not fully understood. The mechanism is such that a change in configuration results. Thus, a 7-hydroxy compound of the *D-erythro* configuration would yield a 7-halo compound of the *L-threo* configuration.

Rydon reagents are formed by the addition of halogen to triphenylphosphine or triphenylphosphite or addition of an alkyl halide to triphenylphosphite and can be represented, when alkyl is methyl, by the formula:

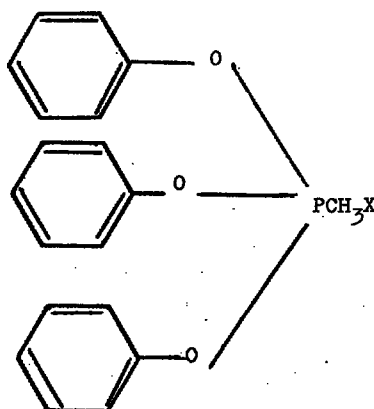
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I



II



III

5 wherein X is halogen, e.g., chlorine, bromine, and iodine. Rydon et al., J. Chem. Soc.,
 2224 (1953); Ibid, 2281 (1954); Ibid, 3043 (1956). The Rydon reagent can be formed
 in situ by addition of halogen or methyl halide to a solution of the triphenylphosphine
 or triphenylphosphite in an inert solvent such as acetonitrile or dimethylformamide, or
 it can be isolated as a separate entity. In either case the reaction with the lincomycin
 or related compound is effected by contacting the Rydon reagent therewith in an inert
 10 solvent, e.g., acetonitrile or dimethylformamide, until the desired substitution of the
 7-hydroxy is obtained. The reaction takes place at ordinary temperature, though gentle
 heating can be effected if desired. Advantageously the temperature is maintained
 between about 20° C. and about 55° C. The product can be recovered from the

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reaction mixture by well known techniques such as filtration, solvent extraction, etc. The reaction mixture advantageously is treated with methanol to destroy any excess Rydon reagent, filtered to remove any solid such as triphenylphosphine oxide, formed in the reaction, and then treated to recover the product. The methanol can be added either before or after the filtration. Advantageously the treated and filtered reaction mixture is evaporated to dryness and purified by solvent extraction and/or chromatography.

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 refers to the acid-addition salt and the non-protonated form to 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, orthosulfobenzoic, cyclopentanepropionic, 1,2-cyclohexanedicarboxylic, 4-cyclohexanecarboxylic, octadecenylsuccinic, octenylsuccinic, methanesulphonic, benzenesulphonic, helianthic, Reinecke's, dimethyldithiocarbamic, cyclohexylsulphamic, hexadecylsulphamic, octadecylsulphamic, sorbic, monochloroacetic, undecylenic, 4'-hydroxyazobenzene-4-sulphonic, octyldecylsulphuric, 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 an 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 sulfate 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 a buffer or as an antacid. 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-halo-7-deoxy lincomycin, i.e., where $\text{—R}_1\text{H}$ is cis or transalkyl of not more than 8 carbon atoms; R_2 is methyl or ethyl; R is alkyl of not more than 8 carbon atoms have antibacterial properties and some are comparable or superior to lincomycin and can be used for the same purposes as lincomycin. 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

A. 7-Bromo-7-deoxylincomycin and its hydrobromide

A solution of Rydon reagent was prepared by stirring a dry solution of 52.6 g. (0.2 M) of triphenylphosphine and 800 ml. of acetonitrile at 30° under nitrogen and 10 ml. (0.19 M) of bromine added over a 20-min. period. After stirring for 10 min. more, 8.2 g. of lincomycin was added and the reaction stirred at 30° for 18 hr. A white solid was then present. The reaction was filtered and the solid discarded. Methanol (100 ml.) was added to the filtrate and the solvents then evaporated under vacuum. The viscous residue was dissolved in 100 ml. methanol, diluted with 1800 ml. of water and extracted six times with 200 ml. portions of ether. The ether extracts were

discarded, the aqueous phase made basic (pH 11) with aqueous KOH and then extracted four times with 200 ml. portions of methylene chloride. The extracts were dried and evaporated, leaving 11 g. of a yellow solid which was chromatographed over 1 kg. of silica gel using methanol:chloroform 1:9 (v/v) as the solvent system. After a forerun of 1200 ml., 22 fractions of 56 ml. were collected. The last 6 (fractions 17-22) were pooled and evaporated to dryness yielding 2.8 g. of 7-bromo-7-deoxylincomycin. This was converted to the hydrobromide by dissolving in water, adding HBr to pH 1, filtering and lyophilizing the filtrate. The hydrobromide had an $\alpha_D + 114^\circ$ (c; 0.9314, H₂O) and the following analysis:

Calcd. for C₁₈H₃₄Br₂N₂O₅S:

C, 39.28; H, 6.23; N, 5.09; S, 5.83; Br, 29.04.

Found: C, 39.64; H, 6.19; N, 5.07; S, 6.04; Br, 28.59.

In place of bromine, there can be substituted chlorine, which yields 7-chloro-7-deoxylincomycin which is identical with the product obtained by chlorinating lincomycin with thionyl chloride. In place of triphenylphosphine there can be substituted triphenyl phosphite. Also, in that case a methyl halide can be used in place of halogen. In place of the lincomycin, there can be substituted other lincomycins and analogs thereof. Thus, when lincomycin C is substituted for lincomycin 7-bromo-7-deoxylincomycin C there is obtained.

Lincomycin C can be obtained by the fermentation process of British Patent Specification No. 1,087,882 or by reacting lincomycin with ethane thiol as described in British Patent Specification No. 1,127,139 followed by heating in the presence of *p*-toluenesulphonic acid or by fusion.

Other alkyl, cycloalkyl, cycloalkyl-alkyl and aralkyl, 7-halo-6,7,8-trideoxy-6-(trans-1-methyl-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio- α -D-galactooctopyranosides.

By substituting the lincomycin by the appropriate alkyl, cycloalkyl, cycloalkyl-alkyl and aralkyl 6,8-dideoxy-6-(trans-1-methyl-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-D-erythro- α -D-galactooctopyranoside, 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; by 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 α -naphthylmethyl, there are obtained the corresponding alkyl, cycloalkyl, cycloalkyl-alkyl and aralkyl 7-halo-6,7,8-trideoxy-6-(trans-1-methyl-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio- α -D-galactooctopyranosides. The compounds thus obtained (both the 6,8-dideoxy and the 7-halo-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.

Also, when the lincomycin is substituted by methyl 6,8-dideoxy-6-(trans-1-methyl-4-butyl-L-2-pyrrolidinecarboxamido)-1-thio-D-erythro- α -D-galactooctopyranoside, the corresponding 7-bromo-7-deoxy compound, methyl 7-bromo-6,7,8-trideoxy-6-(trans-1-methyl and 1-ethyl-4-butyl-L-2-pyrrolidinecarboxamido)-1-thio- α -D-galactooctopyranosides are obtained having the same antibacterial spectrum as lincomycin and equal or greater activity.

On substituting the cis epimers, there are obtained methyl 7-bromo-6,7,8-trideoxy-6-(cis-1-methyl and 1-ethyl-4-butyl-L-2-pyrrolidinecarboxamido)-1-thio- α -D-galactooctopyranosides having the same antibacterial spectrum.

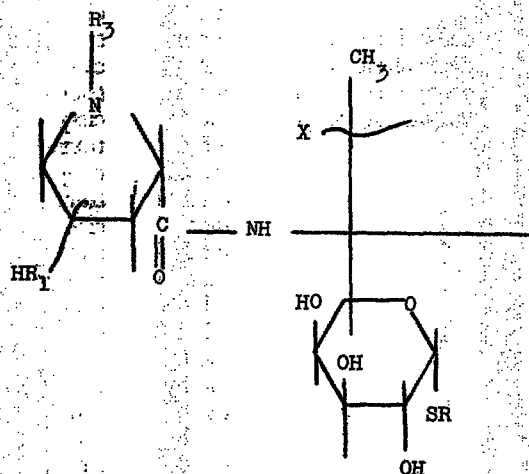
The cis and trans epimers used as starting materials in the above examples are described in British Patent Specification No. 1,118,306.

If desired the above procedure can be applied to the S analogs of a α -MTL obtained by the hydrazinolysis of the lincomycin C or the S-analogues thereof described acylating the resulting alkyl, cycloalkyl, cycloalkyl-alkyl or aralkyl-6-amino-6,7,8-trideoxy-7-halo-1-thio-D-erythro- α -D-galactooctopyranoside with an acid of Formula A, B, D, D or E by the procedures 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 Formula IIa, IIb, IIc, IIc and IIe where R₃ is hydrogen to produce the same compounds. The resulting 7-halo 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 represented by the formula: —



XXIV

wherein *X* is chlorine or bromine and *R*, *HR*₁, and *R*₃ are alkyl of not more than six carbon atoms, advantageously of not more than twelve carbon atoms and the configuration to *L-threo* in the aggregate are obtained on treatment with Rydon reagent by the procedure of Part A if compounds according to Formula XXIV where *X* is hydroxy and *R*, *HR*₁, and *R*₃ are alkyl as given above and the configuration is *L-erythro*. The 6,8-dideoxy compounds of Formula XXI as characterized above are active antibacterials comparable with lincomycin. The 7-halo-6,7,8-trideoxy compounds of Formula XXIV as characterized above have the same spectrum of antibacterial activity but are substantially more active. Representative compounds of Formula XXIV wherein *X* is bromine and the configuration is *L-threo* are given in the following table:

24

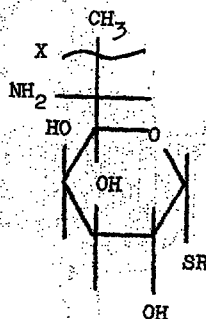
TABLE I

Compounds of Formula XXIV where X is Bromine

		R	HR ₁	R ₂
4A		methyl	trans-ethyl	methyl
4B		methyl	cis-ethyl	methyl
4C	(7-bromo-7-deoxylincomycin)	methyl	trans-propyl	methyl
4D	(7-bromo-7-deoxyallolincomycin)	methyl	cis-propyl	methyl
4E	(7-bromo-7-deoxylincomycin E)	methyl	trans-propyl	ethyl
4F	(7-bromo-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-propyl	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 bromine 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 bromine, 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 bromine, 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 bromine and HR₁ and H in the 4-position are replaced by the ylidene group, R₁.

When the lincomycin in the above Example is replaced by alkyl, cycloalkyl, cycloalkyl-alkyl or aralkyl 6-amino-6,8-dideoxy-1-thio-D-erythro-α-D-galacto-octopyranosides there are obtained compounds of the formula



XXV

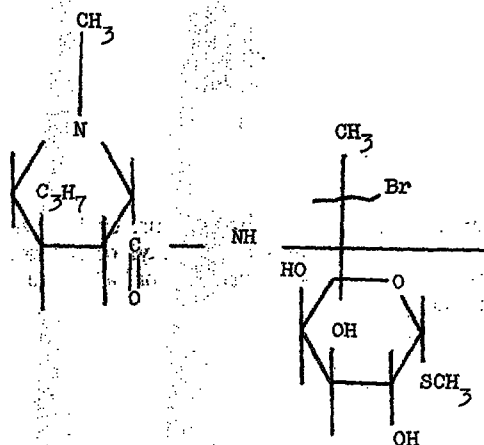
wherein R is, for example, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, and eicosyl, or any of the isomeric forms thereof, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 2-methylcyclopentyl, 2,3-dimethylcyclobutyl, 2-methylcyclobutyl, and 3-cyclopentylpropyl; benzyl, phenethyl, 3-phenylpropyl, and α -naphthylmethyl which can be acylated by the procedures described in our copending application No. 5299/66 (Serial No. 1,140,663) to form the corresponding 7-halo-7-deoxylincomycin analogues, for example, the compounds of Formula XXIV as given and illustrated above, as well as the intermediates therefor.

By substituting the lincomycin by epilincomycin, there is obtained methyl 7-bromo-6,7,8-trideoxy-6-(trans-1-methyl-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio- α -octopyranoside (7-bromo-7-deoxy-epilincomycin) which has the same antibacterial spectrum as lincomycin. The epilincomycin is prepared according to the following example:

EXAMPLE 2

A. 7-Bromo-7-deoxyepilincomycin

The procedure of Example 1 substituting the lincomycin by epilincomycin yields 7-bromo-7-deoxyepilincomycin of the formula

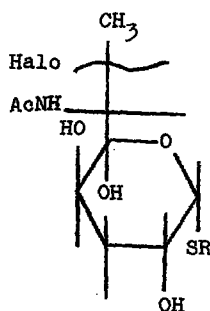


XXVII

as the free base and as the hydrochloride.

By substituting epilincomycin in this example by epilincomycin analogs of Formula II wherein Z, R, R₁, R₂, R₃ of the Ac group are as given and illustrated above, the corresponding 7-halo-7-deoxyepilincomycin analogs of the formula

26

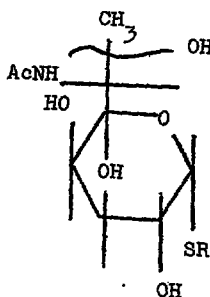


XXVIII

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

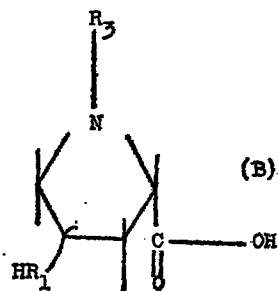
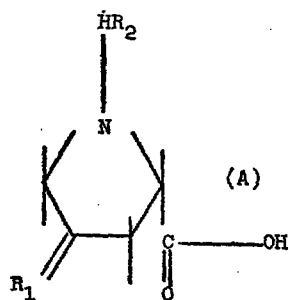
WHAT WE CLAIM IS:—

1. A compound of the formula:

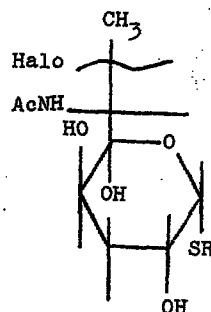


I

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 pyrrolidine-carboxylic acid of the formula:



26

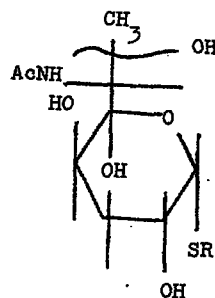


XXVIII

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

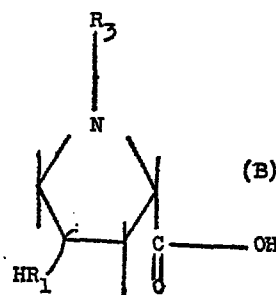
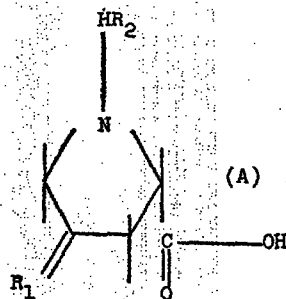
WHAT WE CLAIM IS:—

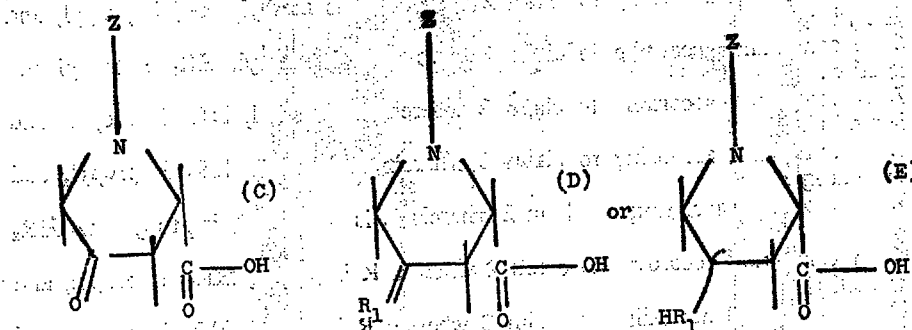
1. A compound of the formula:



I

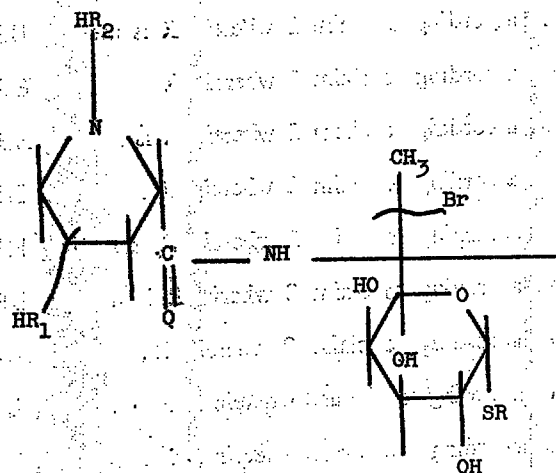
wherein R is alkyl of not more than 20 carbon atoms, cycloalkyl or cycloalkyl-alkyl of from 3 to not more than 8 carbon atoms or aralkyl of not more than 12 carbon atoms and Ac is hydrogen or the acyl radical of a 4-substituted pyrrolidine-carboxylic acid of the formula:





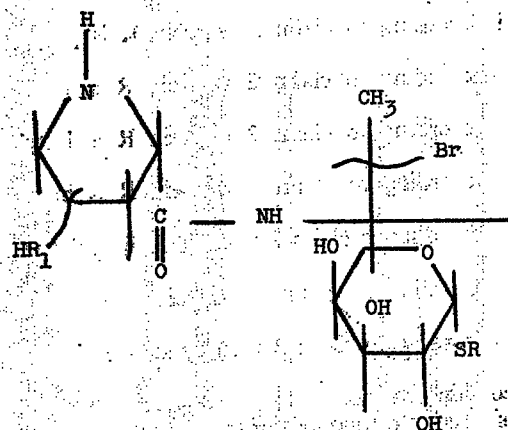
wherein R_1 and R_2 are alkylidene of not more than 20 carbon atoms, cycloalkylidene or cycloalkyl-alkylidene of from 3 to not more than 8 carbon atoms, or aralkylidene of not more than 12 carbon atoms, R_3 is hydrogen or HR_2 and Z is a protective hydro-carbonyloxy-carbonyl or substituted hydrocarbonyloxy-carbonyl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

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:

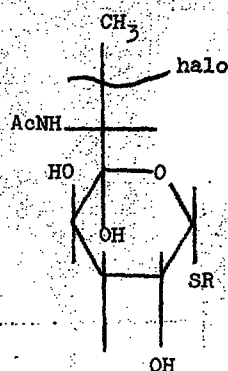


wherein R and HR_1 are lower alkyl of not more than 8 carbon atoms.
wherein R , HR_1 , and HR_2 are lower alkyl of not more than 8 carbon atoms.

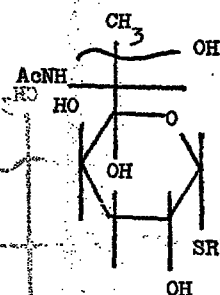
4. A compound according to claim 2 wherein R is methyl, HR_1 is propyl, and HR_2 is methyl.

5. A compound according to claim 2 wherein R is methyl, HR₁ is propyl, and HR₂ is hydrogen.
6. A compound according to claim 2 wherein R is methyl, HR₁ is propyl and HR₂ is ethyl.
- 5 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.
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.
- 15 13. A compound according to claim 2 wherein R is butyl, HR₁ is propyl, and HR₂ is methyl.
14. A compound according to claim 2 wherein R is butyl, HR₁ is propyl, and HR₂ is hydrogen.
- 20 15. A compound according to claim 2 wherein R is butyl, HR₁ is propyl, and HR₂ is ethyl.
- 20 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.
- 25 18. A compound according to claim 2 wherein R is methyl, HR₁ is pentyl, and HR₂ is ethyl.
19. A compound according to claim 2 wherein R is methyl, HR₁ is butyl, and HR₂ is methyl.
- 30 20. A compound according to claim 2 wherein R is methyl, HR₁ is butyl, and HR₂ is hydrogen.
- 30 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.
- 35 23. A compound according to claim 2 wherein R is ethyl, HR₁ is butyl, and HR₂ is hydrogen.
24. A compound according to claim 2 wherein R is ethyl, HR₁ is butyl, and HR₂ is ethyl.
- 40 25. A compound according to claim 2 wherein R is propyl, HR₁ is butyl, and HR₂ is methyl.
- 40 26. A compound according to claim 2 wherein R is propyl, HR₁ is butyl, and HR₂ is hydrogen.
- 45 27. A compound according to claim 2 wherein R is propyl, HR₁ is butyl, and HR₂ is ethyl.
- 45 28. A compound according to claim 2 wherein R is butyl, HR₁ is butyl, and HR₂ is methyl.
29. A compound according to claim 2 wherein R is butyl, HR₁ is butyl, and HR₂ is hydrogen.
- 50 30. A compound according to claim 2 wherein R is butyl, HR₁ is butyl, and HR₂ is ethyl.
- 50 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.
- 55 33. A compound according to claim 2 wherein R is cyclohexyl, HR₁ is butyl, and HR₂ is ethyl.
34. 7-bromo-7-deoxylincomycin.
- 60 35. The process of making compounds of the formula
- 60



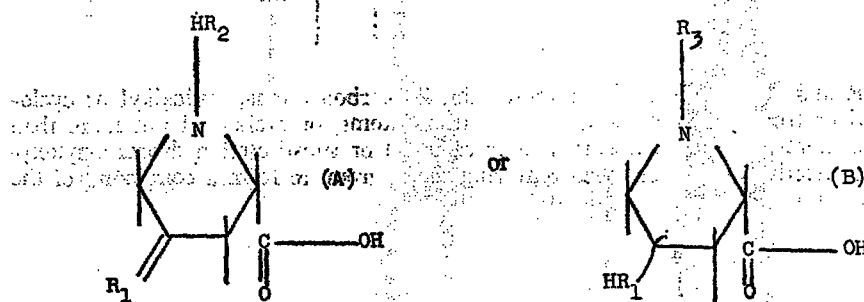


wherein halo is chlorine or bromine and R and Ac are as defined in claim 1 which comprises reacting a compound of the formula



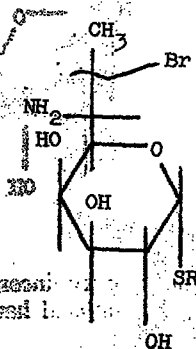
with Rydon reagent at an elevated temperature in an inert solvent.

36. A process according to claim 35 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 .

37. A process for making 7-bromo-7-deoxylincomycin D and analogues and isomers thereof which comprises acylating a compound of the general formula:

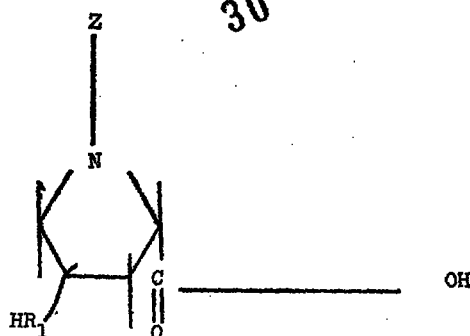




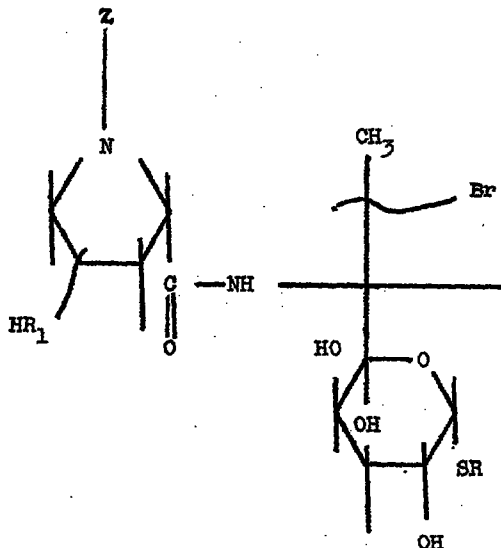
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with a compound of the general formula:



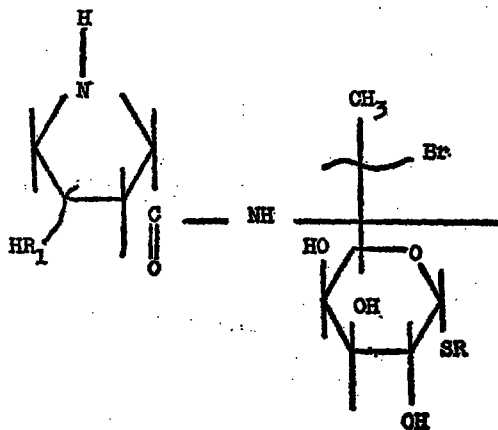
to a compound of general formula:



5 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 hydrocarbonyloxy-carbonyl or substituted hydrocarbonyloxy-carbonyl protective group, and then removing the Z group to form a compound of the general formula:

5

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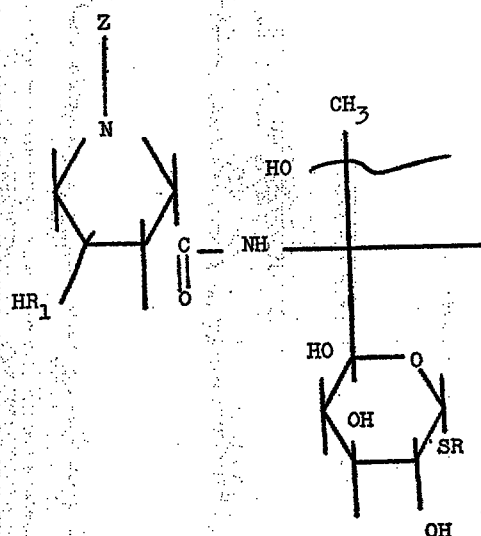


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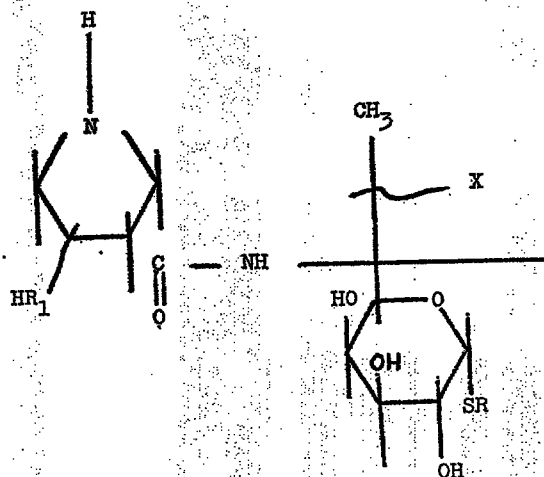
where R, R₁ are as given above.

38. The process for preparing 7-halo-7-deoxy-lincomycin D and analogues and isomers thereof which comprises reacting a compound having the general formula:

31



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 hydrocarbonyloxy-carbonyl or substituted hydrocarbonyloxy-carbonyl protective group, with a chlorinating or brominating Rydon reagent at a temperature effective to replace the 7-hydroxy group with chlorine or bromine then removing the Z group to form a compound of the general formula:



wherein R and R₁ are as given above and X is chlorine or bromine.

39. A process for the preparation of a compound as claimed in any of claims 1 to 34 substantially as herein described with reference to the Examples.

40. A compound as claimed in any of claims 1 to 34 when prepared by a process as claimed in claims 35 to 39.

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