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[Price 5s. 0d. (25p)]

oxylic acids, for example, cyclopentaneacetic acid, cyclopentanepropionic acid, cyclopentaneacetic acid, cyclohexanebutyric acid, and methylcyclohexaneacetic acid; (d) aromatic carboxylic acids, for example, benzoic acid, toluic acid, naphthoic acid, ethylbenzoic acid, isobutylbenzoic acid, and methylbutylbenzoic acid; and (e) aromatic-aliphatic carboxylic acids, for example, phenylacetic acid, phenylpropionic acid, phenylvaleric acid, cinnamic acid, phenylpropionic acid and naphthylacetic acid. Suitable halo, nitro-, hydroxy-, amino, cyano-, thiocyano-, and lower alkoxy-hydrocarbon carboxylic acids include hydrocarbon carboxylic acids as given above which are substituted by one or more of halogen, nitro, hydroxy, amino, cyano, or thiocyano, or loweralkoxy, advantageously loweralkoxy of not more than 18 carbon atoms, for example, methoxy, ethoxy, propoxy, butoxy, amyloxy, hexyloxy, and isomeric forms thereof. Examples of such substituted hydrocarbon carboxylic acids are mono-, di-, and trichloroacetic acid; α - and β -chloropropionic acid; α - and γ -bromobutyric acid; α - and Δ -iodovaleric acid, mevalonic acid; 2- and 4-chlorocyclohexanecarboxylic acid; shikimic acid; 2-nitro-1-methyl-cyclobutanecarboxylic acid; 1,2,3,4,5,6-hexachlorocyclohexanecarboxylic acid; 3-bromo-2-methylcyclohexanecarboxylic acid; 4- and 5-bromo-2-methylcyclohexanecarboxylic acid; 6-bromo-2-methylcyclohexanecarboxylic acid; 2,3-dibromo-2-methyl-cyclohexanecarboxylic acid; 2,5-dibromo-2-methylcyclohexanecarboxylic acid; 4,5-dibromo-2-methylcyclohexanecarboxylic acid; 5,6-dibromo-2-methylcyclohexanecarboxylic acid; 3-bromo-3-methylcyclohexanecarboxylic acid; 6-bromo-3-methylcyclohexanecarboxylic acid; 1,6-dibromo-3-methylcyclohexanecarboxylic acid; 2-bromo-4-methylcyclohexanecarboxylic acid; 1,2-dibromo-4-methylcyclohexanecarboxylic acid; 3-bromo-2,2,3-trimethylcyclopentanecarboxylic acid; 1-bromo-3,5-dimethylcyclohexanecarboxylic acid; homogentisic acid, *o*-, *m*-, and *p*-chlorobenzoic acid; anisic acid; salicylic acid; *p*-hydroxybenzoic acid; β -resorcylic acid; gallic acid; veratric acid; a trimethoxybenzoic acid; a trimethoxycinnamic acid; 4,4'-dichlorobenzilic acid; *o*-, *m*-, and *p*-nitrobenzoic acid; cyanoacetic acid; 3,4- and 3,5-dinitrobenzoic acid; 2,4,6-trinitrobenzoic acid; thiocynoacetic acid; a cyano-propionic acid; lactic acid; ethoxyformic acid (ethyl hydrogen carbonate); butyloxyformic acid; pentyloxyformic acid; hexyloxyformic acid; dodecyloxyformic acid; and hexadecyloxyformic acid.

The compounds of the invention have essentially the same antibacterial spectrum *in vivo* as the antibiotic lincomycin and can be used for the same purposes as lincomycin. The compounds of the invention are more

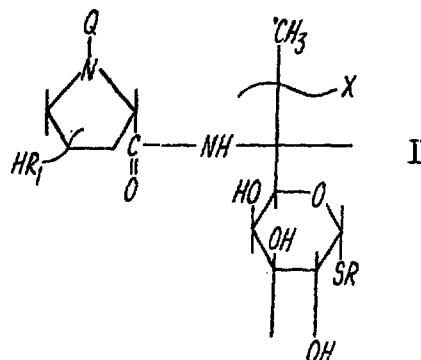
active and can advantageously be used for oral administration to animals, including mammals.

Also according to the invention there is provided an antibacterial composition comprising as the active ingredient a compound of Formula I together with a carrier.

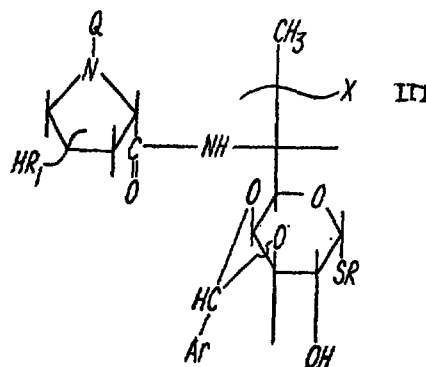
Preferably the active ingredient is a com-

pound of Form I wherein $R_2-\overset{\text{O}}{\parallel}{C}$ is alkanoyl of from 12 to not more than 18 carbon atoms. Such formulations are advantageously used in pediatrics.

The novel compounds of this invention are prepared by condensing a 7-halo-7-deoxylincomycin of the formula:



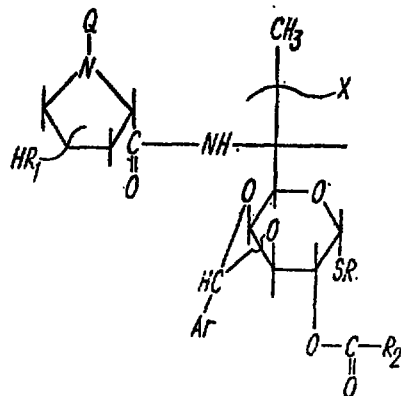
wherein Q is R_3 other than hydrogen, or a protective group, with an aromatic aldehyde to produce a 3,4-O-acetal of a 7-halo-7-deoxylincomycin of the formula:



wherein Ar is aryl optionally substituted or heterocyclic optionally substituted directly linked to the CH or an optionally substituted

aryl group indirectly linked to the CH through one to four vinylene groups, acylating this

compound to form a 3,4-O-acetal of a 7-halo-7-deoxy-lincomycin-2-acylate of the formula:



IV

5 and, when necessary or desired, removing the protective groups to form a lincomycin-2-acylate of Formula I.

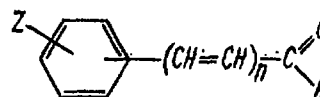
10 When R_3 is hydrogen it is replaced by a protective group before acylation. Advantageously this group is a protective group removable by hydrogenolysis. Suitable such groups are carbobenzoxy and like hydrocarboxycarbonyl groups, benzyl, and nitrobenzyl.

15 In carrying out the process of the subject invention, a 7-halo-7-deoxy-lincomycin of Formula II, advantageously as the hydrochloride salt, is first condensed with an aromatic aldehyde, with the aid of mild heat, to
20 form a 3,4-O-acetal of a 7-halo-7-deoxy-lincomycin of Formula III. Acid catalysis of the reaction is unnecessary if the hydrochloride salt of the 7-halo-7-deoxy-lincomycin is used as this provides sufficient catalysis of the reaction. When the hydrogen group at
25 position 1' is substituted by a protective group which renders the molecule non-basic, e.g., by a carbobenzoxy group, it is advantageous to supplement the reaction mixture with
30 catalytic amounts of mineral acids or, preferably, of acidic salts such as ammonium chloride, to facilitate the condensation reaction. The reaction is forced to completion through azeotropic removal of water by an
35 organic solvent, for example, benzene, toluene, chloroform, or ethylene chloride. The azeotrope-forming solvent can be eliminated if water is removed by some other means, such as by evacuation, vaporization with an
40 inert gas, or merely by co-distillation with a solvent which has a higher boiling point than water. The azeotrope-forming solvent is used in admixture with a highly polar solvent, such as N,N-dimethylformamide, N,N-dimethyl-
45 acetamide, dimethylsulphoxide, or N-methyl pyrrolidone, in order to solubilize 7-halo-7-deoxy-lincomycin hydrochloride and thus produce a homogeneous solution.

The condensation reaction can be conducted between temperatures of about 70° to 180° C.; the preferred temperature being about 90°—110° C. The optimum temperature depends on the ratio of polar to non-polar solvent, and on the specific properties of the non-polar solvent, such as the boiling temperature of the azeotrope formed with water as well as the boiling point of the non-polar solvent itself. The non-polar solvent containing moisture can be continuously removed by distillation and replaced periodically with fresh, dry solvent. The water also can be removed by condensation and separation with a water trap or a desiccant can be used, thus permitting the dried solvent to return to the reaction vessel.

The time for complete condensation of the 7-halo-7-deoxy-lincomycin hydrochloride with an aromatic aldehyde, as disclosed above, varies with the solvent composition, and the efficiency of removal of the water. When azeotrope-forming solvents are used, as described above, the course of the reaction can be followed by measuring the amount of water liberated. Alternatively, the reaction vessel can be sampled periodically and chromatographed. With solvent combinations of benzene and dimethylformamide, reaction times of about 1—16 hours can be used, with 2—3 hours being optimum. If anhydrous 7-halo-7-deoxy-lincomycin hydrochloride is used, the reaction time required is reduced by approximately a factor of 1/2 since only one-half of the amount of water is liberated, compared with 7-halo-7-deoxy-lincomycin hydrochloride monohydrate. A variety of aromatic aldehydes can be used in the process of the invention, for example, furfural, 5-methylfurfural, benzaldehyde, salicylaldehyde, *m*-tolualdehyde, *o*-tolualdehyde, *p*-tolualdehyde, *o*-chlorobenzaldehyde, *m*-chlorobenzaldehyde, *m*-bromobenzaldehyde, *p*-bromobenzaldehyde, *p*-methoxybenzaldehyde, *m*-methoxybenzaldehyde, *o*-methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde (veratric aldehyde), salicylaldehyde, *p*-hydroxybenzaldehyde, 3,4,5-trimethoxybenzaldehyde, piperonal, *o*-nitrobenzaldehyde, *p*-chlorobenzaldehyde, phthaldehyde, *m*-nitrobenzaldehyde, *p*-nitrobenzaldehyde, β -naphthaldehyde, *o*-bromobenzaldehyde, 2,4-dichlorobenzaldehyde, vanillin, terephthaldehyde and protocatechualdehyde.

Also useful are aldehydes in which the carbonyl group is separated from the aromatic moiety by one or more double bonds giving a conjugated structure of:



wherein n is an integer of from 1—4 and Z

is one of the following substituents on the aromatic moiety:

	CH ₃	PO ₃ H [⊖]	
	CH ₂ CH ₃	AsO ₃ H [⊖]	
	CH(CH ₃) ₂	OCH ₃	
5	C(CH ₃) ₃	OC ₂ H ₅	
	3,4-(CH ₂) ₄	O(CH ₂) ₂ CH ₃	
	C ₆ H ₅	OCH(CH ₃) ₂	
	CF ₃	O(CH ₂) ₃ CH ₃	
	CN	O(CH ₂) ₄ CH ₃	
10	COCH ₃	OC ₆ H ₅	
	CO ₂ C ₂ H ₅	OCOCH ₃	
	CO ₂ H	OH	
	CO ₂ [⊖]	SCH ₃	
	CH ₂ Si(CH ₃) ₃	SC ₂ H ₅	
15	Si(CH ₃) ₃	SCH(CH ₃) ₂	
	Si(C ₂ H ₅) ₃	SH	
	Ge(CH ₃) ₃	SCOCH ₃	
	Ge(C ₂ H ₅) ₃	SCN	
	Sn(CH ₃) ₃	SOCH ₃	F
20	Sn(C ₂ H ₅) ₃	SO ₂ CH ₃	Cl
	N ₃ ⁺	SO ₂ NH ₂	Br
	NHCOCH ₃	S(CH ₃) ₂ ⁺	I
	N(CH ₃) ₃ ⁺	SO ₃ [⊖]	IO ₂
	NO ₂	SeCH ₃	CH=CHNO ₂

25 The acetals formed by the above-disclosed process are initially isolated as crystalline hydrochloride salts. With stable acetals, for example, 3,4 - benzylidene - 7 - halo - 7 - deoxy - lincomycin, and 3,4 - *p* - chlorobenzylidene - 7 - halo - 7 - deoxy - lincomycin, recrystallization of the hydrochlorides can be brought about with hot Methyl Cello-solve (Registered Trade Mark), or dimethyl-formamide, or chloroform. The less stable acetals, for example, 3,4 - *p* - anisylidene - 7 - halo - 7 - deoxy - lincomycin, 3,4 - cinnamylidene, and 3,4 - toluylidene - 7 - halo - 7 - deoxy - lincomycin, must be converted to the free base form before isolation of the acetal.

30 The hydrochloride salts of the 3,4 - O - acetals of 7 - halo - 7 - deoxy - lincomycins are usually of a high degree of purity and can be used in acylation as such or they can be converted to the free base by mixing the salts with a basic material, for example, aqueous sodium hydroxide, a quaternary ammonium hydroxide, ammonium hydroxide, or a strong amine base. Basic ion exchange resin can be used. The insoluble 3,4 - O - acetal of the 7 - halo - 7 - deoxy - lincomycin base can be removed by filtration, or it can be extracted with water-immiscible solvents, for example, chloroform, methylene chloride, ethylene dichloride, or ether. Alternatively, the hydrochloride salts of the 3,4 - O - acetal of the 7 - halo - 7 - deoxy - lincomycin can be converted to the free base by first neutralizing the salt with a base after placing the salt in solution in a solvent such as chloroform, dimethyl-

formamide, dimethylacetamide, or propylene glycol. The base can be an alkoxide, an amine, ammonia, or a solid inorganic base, for example, sodium hydroxide, or potassium hydroxide. The resulting solutions of the 3,4 - O - acetal of the 7 - halo - 7 - deoxy - lincomycin base can be recovered from water-miscible solvents by dilution with water to the cloud point resulting in slow crystallization of the acetals. The solutions of 3,4 - O - acetal of the 7 - halo - 7 - deoxy - lincomycin base in water-immiscible solvents can be recovered by dilution of the solution with a nonpolar solvent, for example, hexane, or isomeric hexanes, or by simply evaporating the solvent. The latter procedure for forming the free base from the hydrochloride salts of the 3,4 - O - acetal of the 7 - halo - 7 - deoxy - lincomycin is suitable for isolating the very labile acetals of 7 - halo - 7 - deoxy - lincomycin, since a nonaqueous procedure can be employed.

Most of the 3,4 - O - acetals of the 7 - halo - 7 - deoxy - lincomycin bases can be purified by solution of the compound in acetone, diluting the solution with ether, and then adding hexane to the cloud point to induce spontaneous crystallization.

The 3,4 - O - acetal of the 7 - halo - 7 - deoxy - lincomycin can be acylated by processes already well known in the art, for example, by reacting it with an acylating agent in the presence of an acid-binding agent, for example, a tertiary amine, to produce a 3,4 - O - acetal of a 7 - halo - 7 - deoxy - lincomycin - 2 - acylate. Suitable acylating agents include acid halides and acid anhydrides. Suit-

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able tertiary amines include heterocyclic amines such as pyridine, quinoline, and isoquinoline; trialkylamines such as trimethylamine, triethylamine, triisopropylamine, and the like; N,N-dialkylanilines such as dimethylaniline, diethylaniline, and the like; and N-alkylpiperidines such as N-ethylpiperidine, N-methylpiperidine, and the like. The preferred base is pyridine.

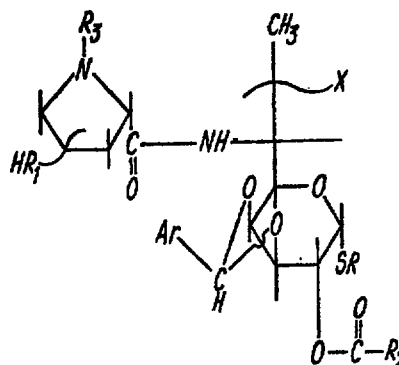
The acylation is advantageously conducted by treating a solution of a 3,4 - O - acetal of the 7 - halo - 7 - deoxy - lincomycin or a suspension of the hydrochloride in a mixture of an inert solvent and a tertiary amine, for example, pyridine, with an acylating agent, for example, an acyl chloride, and cooling the reaction mixture to prevent side reactions. Advantageously, the reaction is conducted in pyridine at low temperature, preferably - 20° to 80° C. However higher or lower temperatures can be used. Suitable inert solvents include chloroform, dimethylformamide, dimethylacetamide, acetonitrile, methylene chloride, acetone, and dioxane.

The 3,4 - O - acetal protective group can be removed by hydrolysis, preferably, a mild acid hydrolysis. For example, a 3,4 - O - anisylidene - 7 - chloro - 7 - deoxy - lincomycin - 2 - acylate on being heated with 80% acetic acid at 100° C. for 10 to 15 min. yields a 7 - chloro - 7 - deoxy - lincomycin - 2 - acylate. Acids such as formic, propionic, dilute hydrochloric and dilute sulphuric can also be used.

The protective group Q can be removed by hydrogenolysis over a palladium catalyst. For example, a 3,4 - O - anisylidene - 7 - chloro - 7 - deoxy - N - carbobenzoxy - lincomycin - 2 - acylate, either before or after the hydrolytic removal of the 3,4 - O - anisylidene group, is hydrogenated using palladium as catalyst. The hydrogenolysis also removes the 3,4 - O - anisylidene group. The palladium is usually deposited on a carrier, for example, carbon. The hydrogenolysis, advantageously, is effected in a solvent at a temperature between about 10°C. and 50°C., and at a pressure not above about 60 lbs. per square inch gauge. Suitable solvents include methanol, acetic acid, ethyl acetate, chloroform, and dioxane.

The desired 2-acylate can be isolated from the reaction mixture by various techniques well known in the art. The 2-acylates so prepared are easily isolated as the hydrochloride salt by precipitation with a non-solvent such as acetone or ether. The compounds are usually isolated in a pure state by this method although if necessary recrystallization may be achieved from water or acetone plus a small amount of water,

According to one feature of the invention there is provided a compound of the general formula:—

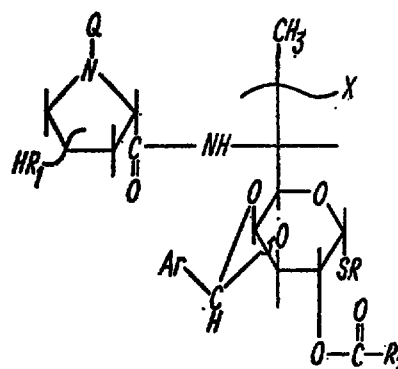


and the salts thereof wherein X, R, HR₁,

R₂—C(=O)—, and R₃ are as given above except R₃ does not represent hydrogen and Ar is an optionally substituted aryl group or an optionally substituted heterocyclic group

directly linked to the CH or an optionally substituted aryl group indirectly linked to the CH group through one to four vinylene groups.

According to another feature of the invention there is provided a compound of the general formula:—

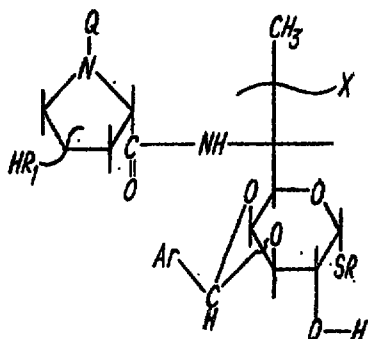


wherein Q is hydrocarboxycarbonyl, benzyl or nitrobenzyl and X, R, HR₁, Ar and R₂—C(=O)— are as previously defined.

Also according to another feature of the invention there is provided a compound of the general formula:—

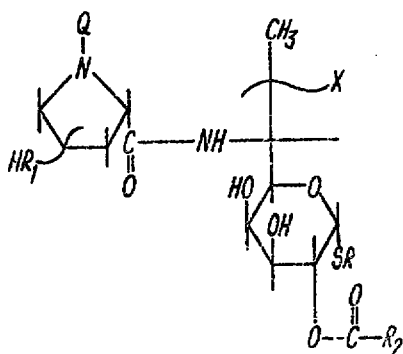
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wherein X, R, HR₁, and Ar are as previously defined; and Q is as defined above. Preferably ArCH< in the above formulae represents anisylidene.

According to a still further feature of the invention there is also provided a compound of the general formula:—



wherein X, R, HR₁, R₂—C=O and Q are all as defined above.

The novel compounds of the invention are nitrogenous bases and can exist in a protonated or a non-protonated form according to the pH of the environment. When the protonated form is intended the compound is qualified as the acid addition salt; when the non-protonated form is intended it is qualified 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 6.0 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, pamoic, 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, octyldecylsulphuric, picric, benzoic, and cinnamic 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 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 can be used as a buffer or as an antacid. They also react with isocyanates to form urethanes and can be used to modify polyurethane resins. The long chain compounds, i.e., where HR₂ 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 inhibitors according to U.S. Patents 2,425,320 and 2,606,155 in the acid pickling of steel. 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 free bases also form salts with penicillins. These salts retain the antibacterial activity of the penicillins but have different solubility characteristics which make them useful in situations indicated by the special solubility characteristics and in the isolation and purification of the penicillins, particularly benzyl penicillin. Said salts can be formed either by neutralization of the free base form of a compound with the free acid form of a penicillin, or by a metathetical exchange of the anion of an acid addition salt of the compound, for example, the chloride ion of a hydrochloride, with the anionic form of a penicillin.

The starting 7 - halo - 7 - deoxy - lincomycins of Formula II can be prepared by reacting the corresponding lincomycin with thionyl chloride or with a Rydon reagent (British Patent Specifications Nos. 1,140,663 and 1,140,833).

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

EXAMPLE 1

7(S) - Chloro - 7 - Deoxy - lincomycin - 2 - Palmitate

A—1 3,4 - O - Anisylidene - 7(S) - chloro - 7 - deoxy - lincomycin hydrochloride

A solution of 30 g. of 7(S) - chloro - 7 - deoxy - lincomycin in 60 ml. anisaldehyde and 50 ml. of dimethylformamide was warmed to 45° C. and then diluted with 200 ml. of benzene. The reaction mixture was set up for distillation and after collection of each 100 ml. solvent an additional 100 ml. portion of fresh benzene was added. Crystallization slowly occurred during distillation. After collecting 1000 ml. of distillate by this process, 150 ml. of benzene was added and the reaction mixture was allowed to cool to room temperature. The product was isolated by filtration and washed with acetone. The yield was 30 g. of white crystalline 3,4 - O - anisylidene - 7(S) - chloro - 7 - deoxy - lincomycin hydrochloride.

B—1 3,4 - O - Anisylidene - 7(S) - chloro - 7 - deoxy - lincomycin - 2 - palmitate hydrochloride

A partial solution of 23.18 g. of 3,4 - O - anisylidene - 7(S) - chloro - 7 - deoxy - lincomycin hydrochloride in 200 ml. of pyridine and 40 ml. of chloroform was treated dropwise with a solution of 12.19 g. palmitoyl chloride in 50 ml. chloroform over a 20 min. period. After 1 hr. at room temperature the clear orange reaction solution was concentrated to a viscous residue under high vacuum at 60° C. The residue was dissolved in 100 ml. isopropyl alcohol and the solvent was removed as above leaving a residue of 3,4 - O - anisylidene - 7(S) - chloro - 7 - deoxy - lincomycin - 2 - palmitate hydrochloride.

C—1 7(S) - Chloro - 7 - deoxy - lincomycin - 2 - palmitate hydrochloride

The residue of part B—1 was dissolved in 300 ml. of acetic acid and diluted with 40 ml. of water. After heating on a steam bath at 90° C. for 5 min., the solvents were removed under high vacuum at 60° C. The orange residue was dissolved in 100 ml. of isopropyl alcohol and the solvent was removed as before. The residue was dissolved in 150 ml. of acetone and the resulting solution was poured into 1500 ml. of acetonitrile to precipitate 7(S) - chloro - 7 - deoxy - lincomycin - 2 - palmitate hydrochloride. The compound was isolated by filtration under nitrogen and then dried by slowly passing nitrogen through the filter for 10 min. Final drying was achieved by drawing air through the filter cake for 1

hr. The yield was 23.5 g. (84%) of 7(S) - chloro - 7 - deoxy - lincomycin - 2 - palmitate hydrochloride, m.p. 126° C. (dec.).

Anal. Calc'd for $C_{34}H_{46}N_2O_6SCl_2$:

C, 58.35; H, 9.22; N, 4.00; S, 4.58; Cl, 10.13

Found: C, 58.66; H, 9.30; N, 3.60; S, 4.23; Cl, 10.82; H_2O , 0.76

(Analyses corrected for H_2O content)

EXAMPLE 2

3,4 - O - Anisylidene - 7(S) - chloro - 7 - deoxy - lincomycin - 2 - laurate Hydrochloride and 7(S) - Chloro - 7 - deoxy - lincomycin - 2 - laurate hydrochloride

By substituting the palmitoyl chloride of part B—1 by lauroyl chloride (10.5 g.), there was obtained 3,4 - O - anisylidene - 7(S) - chloro - 7 - deoxy - lincomycin - 2 - laurate hydrochloride which on hydrolysis by the procedure of part C—1 yielded 7(S) - chloro - 7 - deoxy - lincomycin - 2 - laurate hydrochloride, m.p. 145—160° C.

Anal. Calc'd for $C_{30}H_{40}N_2O_6SCl_2$:

C, 55.97; H, 8.77; N, 4.35; S, 4.98; Cl, 11.02

Found: C, 56.11; H, 8.66; N, 4.36; S, 4.91; Cl, 9.96; H_2O , 0.88

(Analyses corrected for H_2O content)

EXAMPLE 3

3,4 - O - anisylidene - 7(S) - chloro - 7 - deoxy - lincomycin - 2 - hexanoate hydrochloride and 7(S) - chloro - 7 - deoxy - lincomycin - 2 - hexanoate hydrochloride

By substituting the palmitoyl chloride of part B—1 by hexanoic acid anhydride, there was obtained 3,4 - O - anisylidene - 7(S) - chloro - 7 - deoxy - lincomycin - 2 - hexanoate which on hydrolysis by the procedure of part C—1 and recrystallization from hot water yielded 7(S) - chloro - 7 - deoxy - lincomycin - 2 - hexanoate hydrochloride, m.p. 171—175° C.

Anal. Calc'd for $C_{24}H_{34}N_2O_6SCl_2$:

C, 51.51; H, 7.93; N, 5.01; S, 5.73; Cl, 12.67

Found: C, 50.92; H, 8.14; N, 4.68; S, 5.77; Cl, 12.45; H_2O , 2.41

(Analyses corrected for H_2O content)

EXAMPLE 4

3,4 - O - (p - Acetamidobenzylidene) - 7(S) - chloro - 7 - deoxy - lincomycin hydrochloride

A solution of 10 g. 7(S) - chloro - 7 - deoxy - lincomycin hydrochloride in 20 ml. dimethylformamide was mixed with a solution of 15 g. p-acetamidobenzaldehyde in 150 ml. of benzene. The reaction mixture was set up for distillation and after collection of 50 ml. of distillate an additional 50 ml. of fresh benzene was added. A total of 500 ml. of benzene was collected by distillation.

The reaction vessel was cooled and a small

amount of 7(S) - chloro - 7 - deoxy - lincomycin hydrochloride was removed by filtration. The filtrate was diluted with ether to precipitate 7.4 g. of 3,4 - O - p - acetamidobenzylidene - 7(S) - chloro - 7 - deoxy - lincomycin hydrochloride.

The compound was shaken with a mixture of 50 ml. water and 10 ml. concentrated ammonium hydroxide. The resulting 3,4 - O - p - acetamidobenzylidene - 7(S) - chloro - 7 - deoxy - lincomycin base was isolated by filtration to give 5.2 g. of white compound.

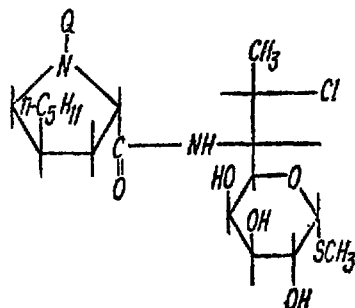
This compound and other 3,4 - O - acetals as indicated above can be substituted for the 3,4 - O - anisylidene - 7(S) - chloro - 7 - deoxy - lincomycin in the foregoing examples.

EXAMPLE 5

By substituting the 7(S) - chloro - 7 - deoxy - lincomycin of Examples 1, 2, and 3 by 7(S) - chloro - 7 - deoxy - N - carbobenzoxy - lincomycin there are obtained 3,4 - O - anisylidene - 7(S) - chloro - 7 - deoxy - N - carbobenzoxy - lincomycin, 3,4 - O - anisylidene - 7(S) - chloro - 7 - deoxy - N - carbobenzoxy - lincomycin - 2 - palmitate, 2 - laurate, and 2 - hexanoate, and 7(S) - chloro - 7 - deoxy - N - carbobenzoxy - lincomycin - 2 - palmitate, 2 - laurate, and 2 - hexanoate. On removal of the carbobenzoxy group by hydrogenolysis over palladium or charcoal, there are obtained 7(S) - chloro - 7 - deoxy - N - demethyl - lincomycin - 2 - palmitate, 2 - laurate, and 2 - hexanoate. If desired, the hydrogenolysis can be effected to remove both the carbobenzoxy and the anisylidene groups.

EXAMPLE 6

By substituting the 7(S) - chloro - 7 - deoxy - lincomycin of Examples 1, 2, and 3 by 7 - chloro - 6,7,8 - trideoxy - 6 - (trans - 1 - carbobenzoxy - 4 - pentyl - L - 2 - pyrrolidinecarboxamido) - 1 - thio - L - threo - α - D - galacto - octopyranoside of the formula:



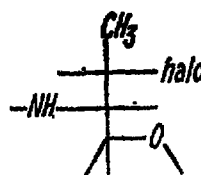
wherein Q is carbobenzoxy, there are obtained 3,4 - O - anisylidene - 7 - chloro - 6,7,8 - trideoxy - 6 - (trans - 1 - carbobenzoxy - 4 - pentyl - L - 2 - pyrrolidinecarboxamido) - 1 - thio - L - threo - α - D - galacto - octopyranoside and the 2 - palmitate,

2 - laurate, and 2 - hexanoate esters thereof which on hydrolysis yield 7 - chloro - 6,7,8 - trideoxy - 6 - (trans - 1 - carbobenzoxy - L - 2 - pyrrolidine - carboxamido) - 1 - thio - L - threo - α - D - galacto - octopyranoside - 2 - palmitate, 2 - laurate, and 2 - hexanoate. On removal of the carbobenzoxy group by hydrogenolysis over palladium on charcoal, there are obtained 7 - chloro - 6,7,8 - trideoxy - 6 - (trans - 4 - pentyl - L - 2 - pyrrolidinecarboxamido) - 1 - thio - L - threo - α - D - galacto - octopyranoside - 2 - palmitate, 2 - laurate, and 2 - hexanoate. If desired, the hydrogenolysis can be effected before the hydrolysis in which case, the 3,4 - O - acetal group is also removed.

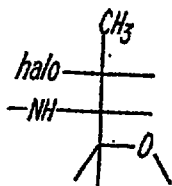
By substituting the 7(S) - chloro - 7 - deoxy - lincomycin hydrochloride in Examples 1, 2, and 3 by 7(S) - bromo - 7 - deoxy - lincomycin there are obtained the hydrochloride of 3,4 - O - anisylidene - 7(S) - bromo - 7 - deoxy - lincomycin and the 2 - palmitate, 2 - laurate and 2 - hexanoate thereof which esters on hydrolysis yield the hydrochloride of 7(S) - bromo - 7 - deoxy - lincomycin - 2 - palmitate, 2 - laurate, and 2 - hexanoate.

By substituting the 7(S) - chloro - 7 - deoxy - lincomycin hydrochloride in Examples 1, 2, and 3 by 7(S) - bromo - 7 - deoxy - N - carbobenzoxylincomycin, there are obtained 3,4 - O - anisylidene - 7(S) - bromo - 7 - deoxy - N - carbobenzoxylincomycin and the 2 - palmitate, the 2 - laurate, and the 2 - hexanoate thereof which esters on hydrolysis yield 7(S) - bromo - 7 - deoxy - N - carbobenzoxylincomycin - 2 - palmitate, 2 - laurate, and 2 - hexanoate. On removal of the carbobenzoxy group by hydrogenolysis over palladium on charcoal, there are obtained 7(S) - bromo - 7 - deoxy - N - demethyl - lincomycin - 2 - palmitate, 2 - laurate, and 2 - hexanoate. If desired, the hydrogenolysis can be effected without the hydrolysis in which case 7(S) - bromo - 7 - deoxy - N - demethyl - lincomycin - 2 - palmitate, 2 - laurate, and 2 - hexanoate is obtained directly.

By substituting the 7(S) - chloro - and - bromo - 7 - deoxy - lincomycin hydrochlorides or the 7(S) - chloro - and bromo - 7 - deoxy - N - carbobenzoxylincomycin by the 7 - epimers thereof, there are obtained the corresponding 7(R) - compounds. The 7(S) - epimers have the L - threo configuration in the side chain



and the 7(R)-epimers have the D-erythro configuration in the side chain



- 5 By substituting for anisaldehyde the other aromatic aldehydes listed above, there are obtained the corresponding 3,4-O-acetals.

- 10 By substituting the acid chlorides and anhydrides, by the acid chlorides or anhydride of the other acids listed above, there are obtained the corresponding 2-acylates.

EXAMPLE 7

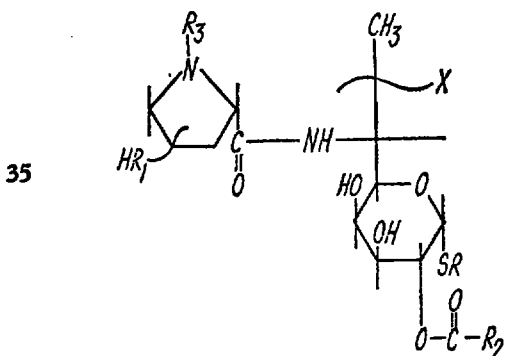
Syrup

- 15 An aqueous oral preparation containing 400 mg. of 7(S) - chloro - 7 - deoxy - lincomycin - 2 - palmitate hydrochloride in each five milliliters is prepared from the following ingredients:

- | | | |
|----|--|------------|
| 20 | 7(S) - chloro - 7 - deoxy - lincomycin - 2 - palmitate hydrochloride | 800 gm. |
| | Methylparaben, U.S.P. | 7.5 gm. |
| | Propylparaben, U.S.P. | 2.5 gm. |
| | Sorbic acid | 10 gm. |
| | Saccharin sodium | 12.5 gm. |
| 25 | Cyclamate sodium | 2.5 gm. |
| | Glycerin | 3000 ml. |
| | Tragacanth powder | 100 gm. |
| | Orange oil flavor | 10 gm. |
| | F.D. & C. orange dye | 7.5 gm. |
| 30 | Deionized water q.s. | 10,000 ml. |
- The final preparation should be adjusted to pH 4.0-4.5.

WHAT WE CLAIM IS:—

1. A compound of the formula



and the acid-addition salts thereof, wherein

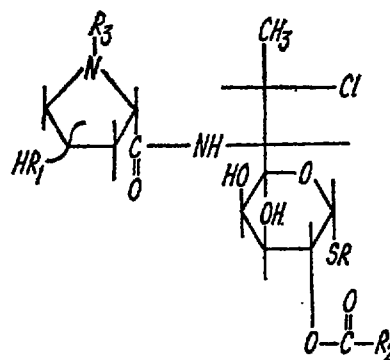
$R_2-C(=O)-$ is a hydrocarbon carboxylic acid acyl radical of not more than 18 carbon atoms; or a halo-, nitro-, hydroxy-, amino-,

40 cyano-, thiocyano-, or alkoxy-substituted hydrocarbon carboxylic acid acyl radical of not more than 18 carbon atoms; or an alkoxy-carbonyl radical; X is chlorine or bromine; R and HR_1 are the same or different alkyl of not more than 20 carbon atoms, cycloalkyl of 45 from 3 to not more than 8 carbon atoms, or aralkyl of not more than 12 carbon atoms; and R_3 is hydrogen, alkyl of not more than 20 carbon atoms, cycloalkyl of from 3 to not more than 8 carbon atoms, or aralkyl or nitro-aralkyl of not more than 12 carbon atoms.

2. A compound according to claim 1 wherein R_3 is benzyl or nitrobenzyl.

3. A compound according to claim 1 having the formula:

55

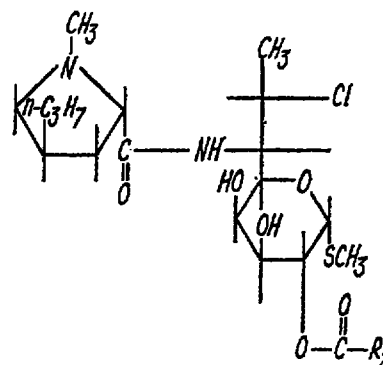


and the acid-addition salts thereof, wherein

$R_2-C(=O)-$, and R_3 are as given in claim 1.

4. A compound according to claim 3 having the formula:

60



and the acid-addition salts thereof wherein

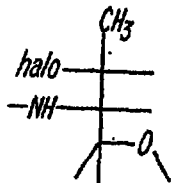
$R_2-C(=O)-$ is as given in claim 1.

5. A compound according to claim 1 where-

65

in $R_2-C(=O)-$ is palmitoyl, lauroyl, hexanoyl or hexadecyloxy-carbonyl.

and the 7(R)-epimers have the D-erythro configuration in the side chain



- 5 By substituting for anisaldehyde the other aromatic aldehydes listed above, there are obtained the corresponding 3,4-O-acetals.

- 10 By substituting the acid chlorides and anhydrides, by the acid chlorides or anhydride of the other acids listed above, there are obtained the corresponding 2-acylates.

EXAMPLE 7

Syrup

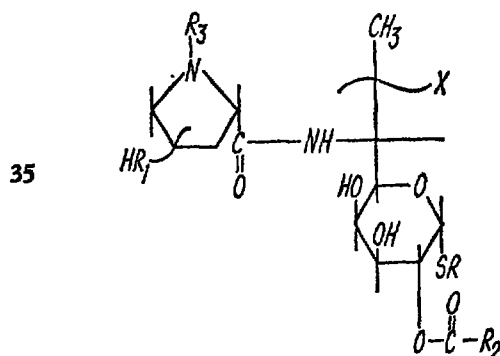
- 15 An aqueous oral preparation containing 400 mg. of 7(S) - chloro - 7 - deoxy - lincomycin - 2 - palmitate hydrochloride in each five milliliters is prepared from the following ingredients:

	7(S) - chloro - 7 - deoxy - lincomycin - 2 - palmitate hydrochloride	800 gm.
20	Methylparaben, U.S.P.	7.5 gm.
	Propylparaben, U.S.P.	2.5 gm.
	Sorbic acid	10 gm.
	Saccharin sodium	12.5 gm.
25	Cyclamate sodium	2.5 gm.
	Glycerin	3000 ml.
	Tragacanth powder	100 gm.
	Orange oil flavor	10 gm.
	F.D. & C. orange dye	7.5 gm.
30	Deionized water q.s.	10,000 ml.

The final preparation should be adjusted to pH 4.0-4.5.

WHAT WE CLAIM IS:—

1. A compound of the formula



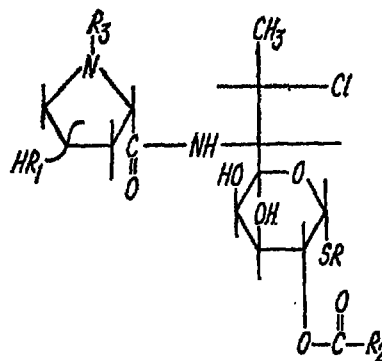
and the acid-addition salts thereof, wherein

$R_2-C(=O)-$ is a hydrocarbon carboxylic acid acyl radical of not more than 18 carbon atoms; or a halo-, nitro-, hydroxy-, amino-,

cyano-, thiocyano-, or alkoxy-substituted hydrocarbon carboxylic acid acyl radical of not more than 18 carbon atoms; or an alkoxy-carbonyl radical; X is chlorine or bromine; R and HR₁ are the same or different alkyl of not more than 20 carbon atoms, cycloalkyl of from 3 to not more than 8 carbon atoms, or aralkyl of not more than 12 carbon atoms; and R₃ is hydrogen, alkyl of not more than 20 carbon atoms, cycloalkyl of from 3 to not more than 8 carbon atoms, or aralkyl or nitro-aralkyl of not more than 12 carbon atoms.

2. A compound according to claim 1 wherein R₃ is benzyl or nitrobenzyl.

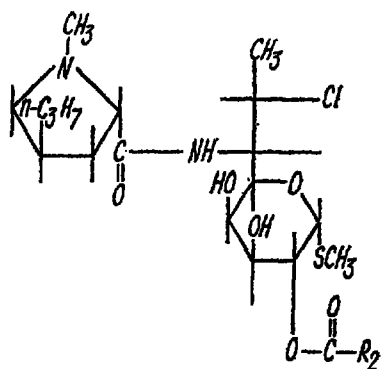
3. A compound according to claim 1 having the formula:



and the acid-addition salts thereof, wherein

R, HR₁, $R_2-C(=O)-$, and R₃ are as given in claim 1.

4. A compound according to claim 3 having the formula:



and the acid-addition salts thereof wherein

$R_2-C(=O)-$ is as given in claim 1.

5. A compound according to claim 1 where-

in $R_2-C(=O)-$ is palmitoyl, lauroyl, hexanoyl or hexadecyloxy-carbonyl.



6. A compound according to claim 3 where-

in $R_2-C(=O)-$ is palmitoyl, lauroyl, or hexanoyl.

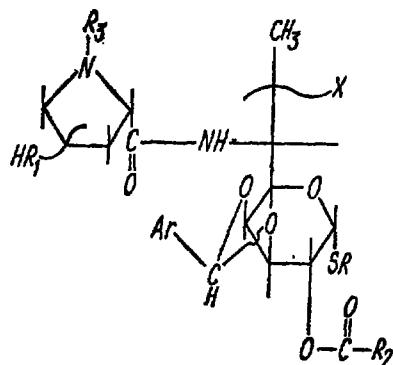
7. A compound according to claim 6 where-
in R_3 is hydrogen, HR_1 is propyl, and R is methyl.

8. A compound according to claim 6 where-
in R_3 is hydrogen, HR_1 is pentyl, and R is methyl.

9. A compound according to claim 4 where-

10 in $R_2-C(=O)-$ is palmitoyl, lauroyl, hexanoyl or hexadecyloxy carbonyl.

10. A compound of the formula:—



and the salts thereof wherein X , R , HR_1 ,

15 $R_2-C(=O)-$, and R_3 are as given in claim 1 except R_3 does not represent hydrogen and Ar is an optionally substituted aryl group or an optionally substituted heterocyclic group

directly linked to the CH or an optionally

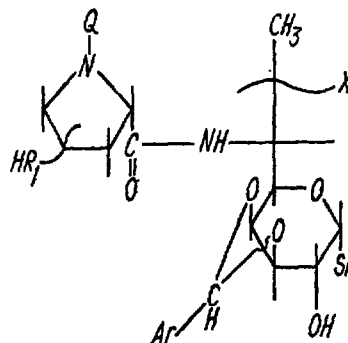
20 substituted aryl group indirectly linked to the CH group through one to four vinylenes groups.

11. A compound according to claim 10 wherein R_3 is benzyl or nitrobenzyl.

12. A compound according to claim 10
25 wherein R and R_3 are methyl and HR_1 is

trans-propyl, X is chlorine, and $R_2-C(=O)-$ is palmitoyl.

13. A process which comprises acylating the
30 2-hydroxy group of a compound of the formula:

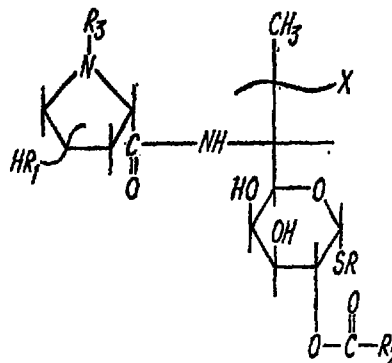


wherein Q is R_3 , other than hydrogen, or a protective group removable by hydrogenolysis and R , HR_1 , R_3 and X are as given in claim 1 and Ar is as defined in claim 10 with a reagent producing the acyl radical R_2CO .

14. A process according to claim 13 wherein $ArCH_2-$ is anisylidene.

15. A process according to claims 13 or 14 which comprises removing the 3,4-O-acetal group by acid hydrolysis and when necessary or desired the Q -group by hydrogenolysis to form a compound according to claim 1.

16. An aqueous composition comprising a
45 compound of the formula:

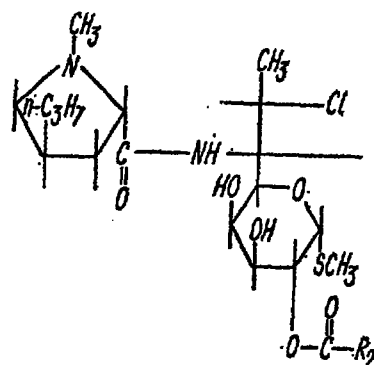
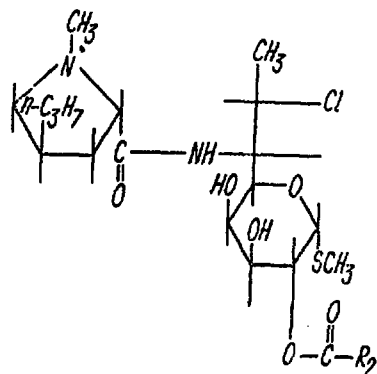


of the acid-addition salts thereof wherein X , R , HR_1 , and R_3 are as given in claim 1, and

$R_2-C(=O)-$ is alkanoyl of from 12 to not more than 18 carbon atoms.

17. A composition according to claim 16 in which the compound is a compound of the formula:





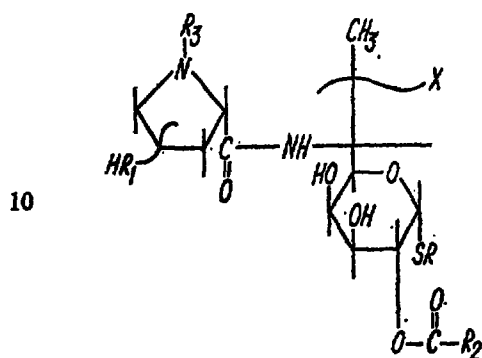
or an acid-addition salt thereof wherein

$R_2-C(=O)-$ is as given in claim 16.

18. A pediatric formulation according to

5 claim 17 in which $R_2-C(=O)-$ is palmitoyl.

19. A process for control of bacteria in animals (excluding humans) which comprises orally administering a compound of the formula:



10

or an acid-addition salt thereof wherein X,

R_2 , HR_1 , $R_2-C(=O)-$, and R_3 are as given in claim 1.

20. A process for control of bacteria in animals (excluding humans) according to claim 19 in which the compound is a compound of the formula:

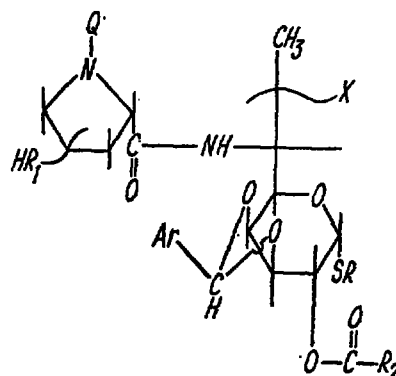
15

or an acid-addition salt thereof wherein

$R_2-C(=O)-$ is palmitoyl.

21. A compound of the formula:

20

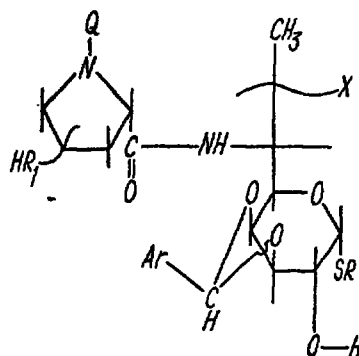


wherein Q is hydrocarbonoxycarbonyl, benzyl

or nitrobenzyl, X, R, HR_1 , and $R_2-C(=O)-$, are as given in claim 1 and Ar is as given in claim 10.

25

22. A compound of the formula:



18 5

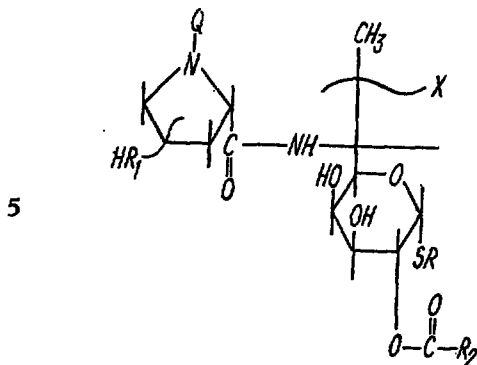
12

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12

wherein X, R, and HR₁ are as given in claim 1; Ar is as given in claim 10; and Q is hydro-carboxycarbonyl, benzoyl or nitrobenzyl.

23. A compound of the formula:



wherein X, R, HR₁, and R₂-C(=O)- are as given in claim 1, Q is as given in claim 21.

24. A compound according to claims 10 to 12, 21 or 22 wherein ArCH< is anisylidene.

25. A process for the preparation of a compound as claimed in any of claims 1 to 12 or 21 to 24 substantially as herein described with reference to Examples 1 to 6.

26. A compound as claimed in any of claims 1 to 12 or 21 to 24 when prepared by a process as claimed in claims 13 to 15 or 25.

27. An antibacterial composition comprising as the active ingredient a compound of Formula I as claimed in any of claims 1 to 9 or 26 together with a carrier.

28. An antibacterial composition substantially as herein described with reference to Example 7.

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