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3,580,904

7-HALO-7-DEOXY-LINCOMYCIN DERIVATIVES

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The portion of the term of the patent subsequent to Feb. 4, 1986, has been disclaimed

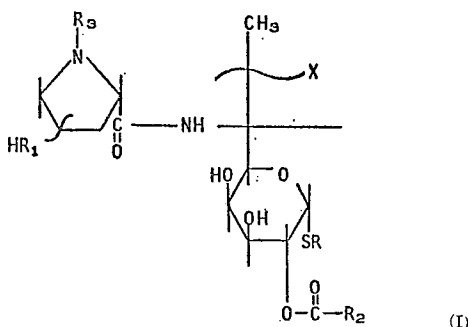
Int. Cl. C07c 47/18

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26 Claims

ABSTRACT OF THE DISCLOSURE

Antibacterial compounds of the formula:



and the salts thereof, and the 3,4-O-arylidene derivatives.

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of our copending application Ser. No. 637,358, filed May 10, 1967 now abandoned.

BRIEF SUMMARY OF THE INVENTION

The novel compounds of the invention are represented by Formula 1, wherein



is a carboxylic acid acyl radical, advantageously a hydrocarbon carboxylic acid acyl of not more than 18 carbon atoms; or a halo-, nitro-, hydroxy-, amino-, cyano-, thiocyno-, or loweralkoxy-substituted hydrocarbon carboxylic acid acyl radical advantageously of not more than 18 carbon atoms, X is chlorine, or bromine; R, and HR₁ are the same or different alkyl of not more than 20 carbon atoms, advantageously not more than 8 carbon atoms, or aralkyl of not more than 12 carbon atoms, advantageously not more than 8 carbon atoms; and R₃ is hydrogen, alkyl of not more than 20 carbon atoms, advantageously not more than 8 carbon atoms, cycloalkyl of from 3 to not more than 8 carbon atoms, and aralkyl of not more than 12 carbon atoms, advantageously not more than 8 carbon atoms.

Examples of alkyl of not more than 20 carbon atoms (R, HR₁, and R₃) 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 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 carboxylic acid acyl radicals are the acyl radicals of the following acids: (a) saturated or unsaturated, straight or branched chain aliphatic carboxylic acids, for example acetic, propionic, butyric, isobutyric,

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tert-butylacetic, valeric, isovaleric, caproic, caprylic, decanoic, dodecanoic, lauric, tridecanoic, myristic, pentadecanoic, palmitic, margaric, stearic, acrylic, crotonic, undecylenic, oleic, hexynoic, heptynoic, octynoic acids, and the like; (b) saturated or unsaturated, alicyclic carboxylic acids, for example, cyclobutanecarboxylic acid, cyclopentanecarboxylic acid, cyclohexanecarboxylic acid, methylcyclopentanecarboxylic acid, cyclohexanecarboxylic acid, dimethylcyclohexanecarboxylic acid, dipropylcyclohexanecarboxylic acid, and the like; (c) saturated or unsaturated, alicyclic aliphatic carboxylic acids, for example, cyclopentanepropionic acid, cyclohexanecarboxylic acid, methylcyclohexanecarboxylic acid, and the like; (d) aromatic carboxylic acids, for example, benzoic acid, toluic acid, naphthoic acid, ethylbenzoic acid, isobutylbenzoic acid, methylbutylbenzoic acid, and the like; and (e) aromatic-aliphatic carboxylic acids, for example, phenylacetic acid, phenylpropionic acid, phenylvaleric acid, cinnamic acid, phenylpropionic acid and naphthylacetic acid, and the like.

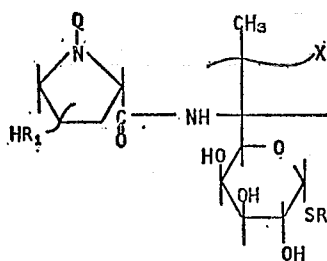
Suitable halo-, nitro-, hydroxy-, amino-, cyano-, thiocyno-, and lower alkoxyhydrocarbon carboxylic acids include hydrocarbon carboxylic acids as given above which are substituted by one or more of halogen, nitro, hydroxy, amino, cyano, or thiocyno, or loweralkoxy, advantageously lower-alkoxy of not 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;
 trimethoxybenzoic acid;
 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;
 cyanopropionic acid;
 lactic acid;
 ethoxyformic acid (ethyl hydrogen carbonate);
 butyloxyformic acid;
 pentyloxyformic acid;

hexyloxyformic acid;
dodecyloxyformic acid;
hexadecyloxyformic acid, and the like.

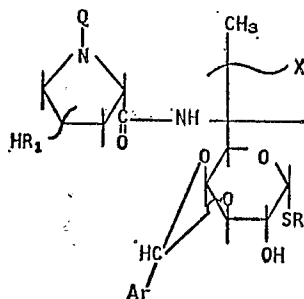
The compounds of the invention have essentially the same antibacterial spectrum in vivo as the antibiotic lincomycin and can be used for the same purposes as lincomycin. The compounds of the invention are more active and can advantageously be used for oral administration to animals, including mammals.

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



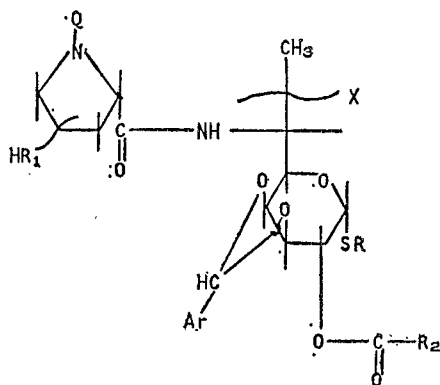
(II)

wherein Q is R₃ other than hydrogen, or a protective group, with an aromatic aldehyde to produce a 3,4-O-arylidene 7-halo-7-deoxy-lincomycin of the formula:



(III)

wherein Ar is aryl, acylating this compound to form a 3,4-O-arylidene 7-halo-7-deoxy-lincomycin-2-acylate of the formula:



(IV)

and removing the protective groups to form a lincomycin-2-acylate of Formula I.

When R₃ is hydrogen it is replaced by a protective group before acylation. Advantageously this group is a protective group removable by hydrogenolysis or mild acid hydrolysis. Suitable such groups are carbobenzoxy, t-butoxycarbonyl, and like hydrocarboxycarbonyl groups, benzyl, trityl, diphenylmethyl, and nitrobenzyl.

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 form a 3,4-O-arylidene 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 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 reaction mixture with 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 organic solvent, for example, benzene, toluene, chloroform, ethylene chloride, and the like. The azeotrope-forming solvent can be eliminated if water is removed by some other means, such as by evacuation, vaporization with an 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-dimethylacetamide, dimethylsulfoxide, N-methyl pyrrolidone, and the like, in order to solubilize 7-halo-7-deoxy-lincomycin hydrochloride and thus produce a homogeneous solution.

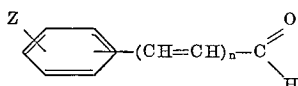
The condensation reaction can be conducted between temperatures of about 70° to 180° C.; the preferred temperature being about 90°-110° C. The optimum temperature depends on the ratio of polar to non-polar solvent, and on the specific properties of the non-polar solvent, such as the boiling temperature 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, phthalaldehyde, m-nitrobenzaldehyde, p-nitrobenzaldehyde, β-naphthalaldehyde, p-bromobenzaldehyde, o-

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bromobenzaldehyde, 2,4-dichlorobenzaldehyde, vanillin, methaldehyde, terephthaldehyde, protocatechualdehyde, and cinnamaldehyde.

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 can be an integer of from 1-4, and Z can be one of the following substituents on the aromatic moiety:

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

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 Cellosolve, dimethylformamide, chloroform, and the like. 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.

The 3,4-O-arylidene-7-halo-7-deoxy-lincomycin hydrochloride salts 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 arylidene-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, ether and the like. Alternatively, the 3,4-O-arylidene-7-halo-7-deoxy-lincomycin hydrochloride salts 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, dimethylformamide, dimethylacetamide, propylene glycol, and the like. The base can be an alkoxide, an amine, ammonia, or a solid inorganic base, for example, sodium hydroxide, potassium hydroxide, and the like. The resulting solutions of the 3,4-O-arylidene-7-halo-7-deoxy-lincomycin base

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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-arylidene-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, isomeric hexanes, and the like, or by simply evaporating the solvent. The latter procedure for forming the free base from the 3,4-O-arylidene-7-halo-7-deoxy-lincomycin hydrochloride salts 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-arylidene-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-arylidene-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-arylidene-7-halo-7-deoxy-lincomycin-2-acylate. Suitable acylating agents include acid halides and acid anhydrides. Suitable tertiary amines include heterocyclic amines such as pyridine, quinoline, and isoquinoline; trialkylamines such as trimethylamine, triethylamine, trisopropylamine, and the like; N,N-di-alkylanilines 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-arylidene-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, 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.

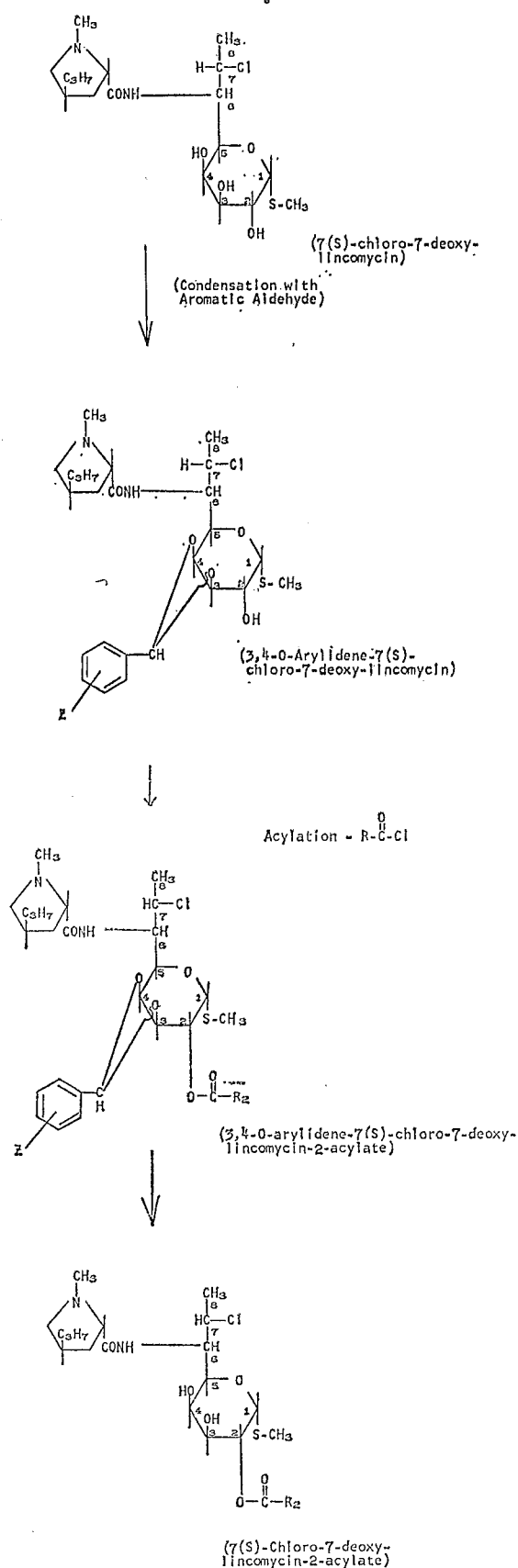
The 3,4-O-arylidene protective group can be removed by hydrolysis, preferably, a mild acid hydrolysis. For example, 3,4-O-anisylidene-7-chloro-7-deoxy-lincomycin-2-acylate on being heated with 80% acetic acid at 100° C. for 10 to 15 min. yields 71-chloro-7-deoxy-lincomycin-2-acylate. Acids such as formic, propionic, dilute hydrochloric and dilute sulfuric can also be used. When the Q group is removable by acid hydrolysis, for example when Q is t-butoxycarbonyl, trityl, or diphenylmethyl, it can be removed at the same time.

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-carbobenzoxo-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, ethylacetate, 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.

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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, sulfuric, 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, ortho-sulfobenzoic, cyclopentanepropionic, 1,2 - cyclohexanedicarboxylic, 4 - cyclohexanecarboxylic, octadecenylsuccinic, octenylsuccinic, methanesulfonic, benzenesulfonic, helianthic, Reinecke's, dimethyldithiocarbamic, cyclohexylsulfamic, hexadecylsulfamic, octadecylsulfamic, sorbic, monochloroacetic, undecylenic, 4' - hydroxyazobenzene-4-sulfonic, octyldecylsulfuric, 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 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 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 inhibitors according to U.S. Pats. 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. Pats. 1,915,334 and 2,075,359, and the hexafluoroarsenic acid and hexafluorophosphoric acid addition salts are useful as parasiticides according to U.S. Pats. 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 (Belgian Pat. 676,154) or with a Rydon reagent (Belgian Pat. 676,154).

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 hydrochloride in 60 ml. anisaldehyde and 50 ml. of di-

methylformamide 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 200 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° (dec.).

Analysis.—Calc'd for $C_{34}H_{54}N_2O_6SCl_2$ (percent): C, 58.35; H, 9.22; N, 4.00; S, 4.58; Cl, 10.13. Found (percent): C, 58.66; H, 9.30; N, 3.60; S, 4.23; Cl, 10.82; H_2O , 0.76. (Analysis 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.

Analysis.—Calc'd for $C_{30}H_{56}N_2O_6SCl_2$ (percent): C, 55.97; H, 8.77; N, 4.35; S, 4.98; Cl, 11.02. Found (percent): C, 56.11; H, 8.66; N, 4.36; S, 4.91; Cl, 9.96; H_2O , 0.88. (Analysis 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 hydrochloride 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.

Analysis.—Calc'd for $C_{24}H_{44}N_2O_6SCl_2$ (percent): C, 51.51; H, 7.93; N, 5.01; S, 5.73; Cl, 12.67. Found (per-

cent): 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.

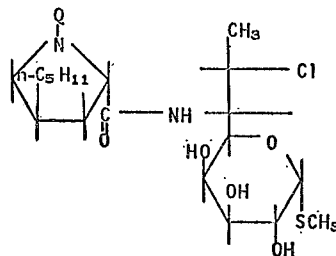
This compound and other 3,4-O-arylidene compounds as indicated above can be substituted for the 3,4-O-anisylidene-7(S)-chloro-7-deoxy-lincomycin in the foregoing examples.

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, 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 on 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:



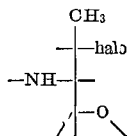
wherein Q is carbobenzoxy, there are obtained 3,4-O-anisylidene-7-chloro - 6,7,8 - trideoxy - 6 - (trans-1-carbobenzoxy)-4-pentyl-L-2-pyrrolidine-carboxamido)-1-thio-L-threo- α -D-galacto-octopyranoside and the 2-palmitate, 2-laurate, and 2-hexanoate esters thereof which on hydrolysis yield 7-chloro-6,7,8-trideoxy-6-(trans-1-carbobenzoxy-L-2-pyrrolidine-carboxamido) - 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-pyrrolidine-carboxamido) - 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-arylidene group is also removed.

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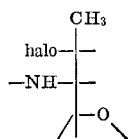
By substituting the 7(S)-chloro-7-deoxy-lincomycin hydrochloride in Examples 1, 2, and 3 by 7(S)-bromo-7-deoxy-lincomycin there are obtained the hydrochloride of 3,4-O-arylidene-7(S)-bromo-7-deoxy-lincomycin 2-laurate and the 2-palmitate, 2-hexanoate thereof which esters on hydrolysis yield the hydrochloride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



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

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

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.

Methylparaben, U.S.P.—7.5 gm.

Propylparaben, U.S.P.—2.5 gm.

Sorbic acid—10 gm.

Saccharin sodium—12.5 gm.

Cyclamate sodium—2.5 gm.

Glycerin—3000 ml.

Tragacanth powder—100 gm.

Orange oil flavor—10 gm.

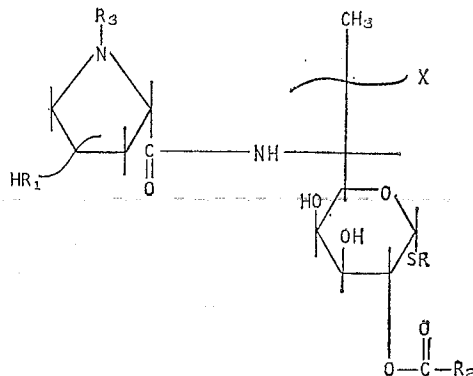
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F.D. & C. orange dye—7.5 gm.
Deionized water q.s.—10,000 ml.

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

We claim:

1. A compound of the formula

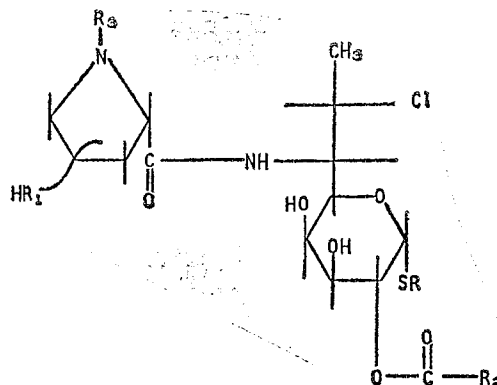


or the acid addition salts thereof, wherein



is a hydrocarbon carboxylic acid or alkoxyformic acid acyl of not more than 18 carbon atoms; or a chloro- and bromo-, iodo-, nitro-, hydroxy-, amino-, cyano-, thiocyno-, or lower alkoxy-substituted hydrocarbon carboxylic acid acyl radical of not more than 18 carbon atoms; 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 of not more than 12 carbon atoms.

2. A compound or the acid addition salts thereof according to claim 1 having the formula:



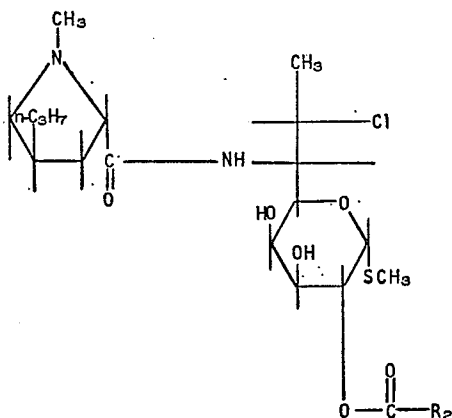
wherein R, HR₁,



and R₃ are as given in claim 1.

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3. A compound or the acid addition salts thereof according to claim 2 having the formula:



wherein



is as given in claim 1.

4. A compound or the acid addition salts thereof according to claim 1 wherein



is palmitoyl, lauroyl, or hexanoyl.

5. A compound or the acid addition salts thereof according to claim 2 wherein



is palmitoyl lauroyl, or hexanoyl.

6. A compound or the acid addition salts thereof according to claim 2 wherein R_3 is hydrogen, HR_1 is propyl, R is methyl, and



is palmitoyl lauroyl, or hexanoyl.

7. A compound or the acid addition salts thereof according to claim 2 wherein R_3 is hydrogen, HR_1 is pentyl, R is methyl, and



is palmitoyl lauroyl, or hexanoyl.

8. A compound or the acid addition salts thereof according to claim 3 wherein



is palmitoyl lauroyl, or hexanoyl.

9. A compound or the acid addition salts thereof according to claim 3 wherein



is palmitoyl.

10. 7(S)-chloro-7-deoxylincomycin-2-palmitate hydrochloride.

11. A compound or the acid addition salts thereof according to claim 1 wherein



is hexadecyloxy carbonyl.

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12. A compound or the acid addition salts thereof according to claim 2 wherein



is hexadecyloxy carbonyl.

13. A compound or the acid addition salts thereof according to claim 2 wherein R_3 is hydrogen or methyl, HR_1 is propyl or pentyl, R is methyl, and



is hexadecyloxy carbonyl.

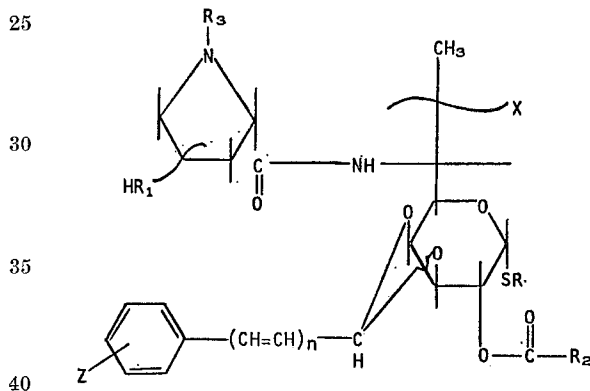
14. A compound or the acid addition salts thereof according to claim 3 wherein



is hexadecyloxy carbonyl.

15. 7(S)-chloro-7-deoxylincomycin-2-hexadecylcarbonate hydrochloride.

16. A compound of the formula:



or the acid addition salts thereof wherein X , R , HR_1 ,



and R_3 are as given in claim 1; n is an integer of 0 to not more than 4, and Z is hydrogen or

50	CH_3	OC_2H_5
	CH_2CH_3	$\text{O}(\text{CH}_2)_2\text{CH}_3$
	$\text{CH}(\text{CH}_3)_2$	$\text{OCH}(\text{CH}_3)_2$
	$\text{C}(\text{CH}_3)_3$	$\text{O}(\text{CH}_2)_3\text{CH}_3$
	$3,4-(\text{CH}_2)_4$	$\text{O}(\text{CH}_2)_4\text{CH}_3$
55	C_6H_5	OC_6H_5
	CF_3	OCOCH_3
	CN	OH
	COCH_3	SCH_3
	$\text{CO}_2\text{C}_2\text{H}_5$	SC_2H_5
60	CO_2H	$\text{SCH}(\text{CH}_3)_2$
	CO_2^-	SH
	$\text{CH}_2\text{Si}(\text{CH}_3)_3$	SCOCH_3
	$\text{Si}(\text{CH}_3)_3$	SCN
	$\text{Si}(\text{C}_2\text{H}_5)_3$	SOCH_3
65	$\text{Ge}(\text{CH}_3)_3$	SO_2XH_3
	$\text{Ge}(\text{C}_2\text{H}_5)_3$	SO_2NH_2
	$\text{Sn}(\text{CH}_3)_3$	$\text{S}(\text{CH}_3)_2$
	$\text{Sn}(\text{C}_2\text{H}_5)_3$	SO_3^+
	N_2^+	SeCH_3
70	NHCOCH_3	F
	$\text{N}(\text{CH}_3)_3^+$	Cl
	NO_2	Br
	PO_3H^-	I
	AsO_3H^-	IO_2
75	OCH_3	$\text{CH}=\text{CHNO}_2$

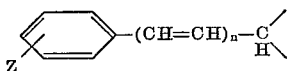
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17. A compound or the acid addition salts thereof according to claim 16 wherein R and R₃ are methyl and HR₁ is trans-propyl, X is chlorine, and



is palmitoyl.

18. A compound or the acid addition salts thereof according to claim 16 wherein

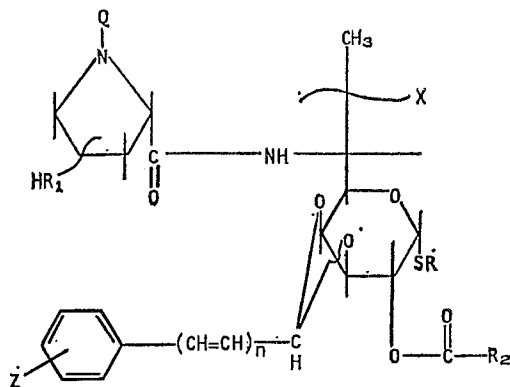


is anisylidene.

19. 3,4-O-anisylidene-7(S)-chloro-7-deoxylincomycin-2-palmitate or the acid addition salts thereof.

20. The hydrochloride salt of the compound according to claim 19.

21. A compound of the formula:

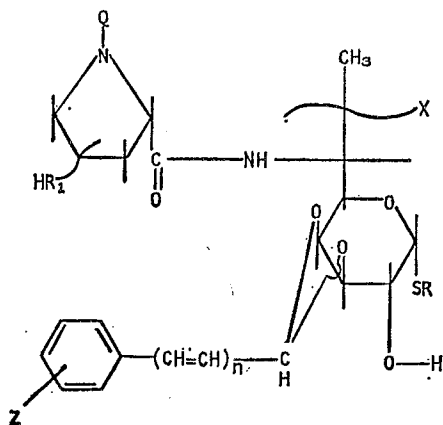


wherein Q is hydrocarboxycarbonyl, trityl, benzyl, diphenylmethyl, or nitrobenzyl, X, R, HR₁, and



are as given in claim 1; n is an integer of 0 to not more than 4, and Z is as given in claim 16.

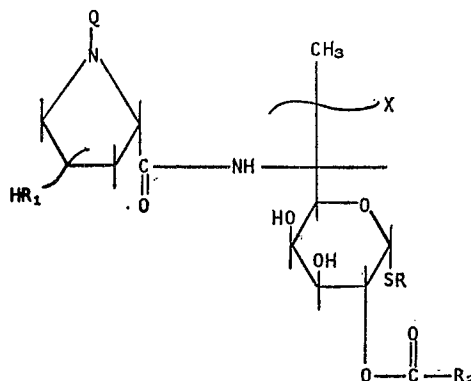
22. A compound of the formula:



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wherein X, R, and HR₁ are as given in claim 1; n is an integer of 1 to not more than 4; Z is as given in claim 16; and Q is as given in claim 22.

23. A compound of the formula:

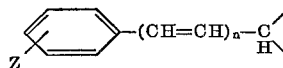


wherein X, R, HR₁, and



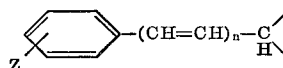
are as given in claim 1, and Q is hydrocarboxycarbonyl, benzyl or nitrobenzyl.

24. A compound according to claim 21 in which



is anisylidene.

25. A compound according to claim 22 in which



is anisylidene.

26. A compound or the acid addition salts thereof according to claim 1 in which R₃ is hydrogen.

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ELBERT L. ROBERTS, Primary Examiner

J. R. BROWN, Assistant Examiner

U.S. Cl. X.R.

252—357; 260—2.5, 999