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3,598,806

PROCESS FOR PREPARING LINCOMYCIN-3-MONOACYLATES

Walter Morozowich, Kalamazoo, Mich., assignor to The Upjohn Company, Kalamazoo, Mich.

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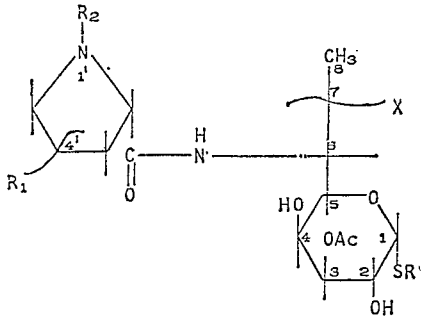
ABSTRACT OF THE DISCLOSURE

This invention relates to a novel process for the manufacture of lincomycin-3-monoacylate compounds, including novel 7-halogenated lincomycin-3-monoacylate compounds, selected from the group consisting of the free bases and acid addition salts of the formula:



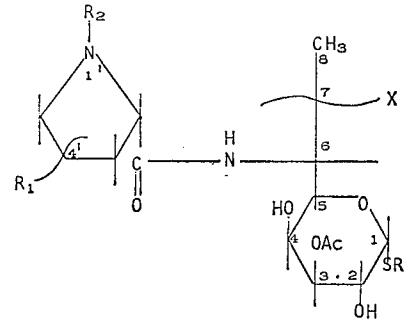
(I)

wherein R is alkyl of 1 to 6 carbon atoms, inclusive; R_1 is alkyl of 2 to 8 carbon atoms, inclusive; R_2 is alkyl of 1 to 8 carbon atoms, inclusive, or hydrogen; X is hydroxy, chlorine, bromine or iodine; and Ac is the acyl radical of a hydrocarbon carboxylic acid containing 1 to 18 carbon atoms, inclusive. In the above Formula I, the vertical wavy line ∫ is used to indicate that the group R_1 can be in the cis position (below the plane of the ring) or in the trans position (above the plane of the ring), with respect to the carbonyl group. The horizontal wavy line ~ is used to indicate that both epimers are to be included in the group, the 7(R) (or D-erythro) configuration and the 7(S) (or L-threo) configuration. These lincomycin-3-monoacylate compounds can be used as antibacterial agents, for example to inhibit the growth of *Staphylococcus aureus* and *Sarcina lutea* on dental and medical equipment contaminated with these organisms. The novel 7-halogenated 3-monoacylate esters are particularly advantageous in having greater antibacterial activity than the 7-hydroxy esters.

The novel process for selective 3-monoacylation of lincomycin compounds of this invention comprises mixing a solution of the lincomycin compound or its acid addition salt with the acid anhydride or acyl halide of a hydrocarbon carboxylic acid and a sterically hindered strongly basic tertiary amine and reacting under mild conditions.

BRIEF SUMMARY OF THE INVENTION

The novel process of this invention can be used to manufacture lincomycin-3-monoacylate compounds, including novel 7-deoxy - 7 - halolincomycin-3-monoacylate compounds, given by the Formula I



(I)

wherein R is alkyl of 1 to 6 carbon atoms, inclusive; R_1 is alkyl of 2 to 8 carbon atoms inclusive, situated below the plane of the pyrrolidine ring as drawn to give the cis configuration with respect to the carbonyl, or above the ring to give the trans configuration; R_2 is alkyl of 1 to 8 carbon atoms, inclusive, or hydrogen; X is hydroxy, chlorine, bromine or iodine, situated to the left of the vertical line as drawn to give the 7(R) configuration, or to the right to give the 7(S) configuration; and Ac is the acyl radical of a hydrocarbon carboxylic acid containing 1 to 18 carbon atoms, inclusive. Typical alkyl groups of 1 to 8 carbon atoms include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and octyl, and isomeric forms thereof. Suitable hydrocarbon carboxylic acid acyl radicals include radicals of (a) saturated or unsaturated straight or branched chain aliphatic carboxylic acids, for example, formic, acetic, propionic, butyric, isobutyric, tert-butylacetic, valeric, isovaleric, caproic, caprylic, decanoic, dodecanoic, acrylic, crotonic, undecylenic, hexynoic, heptynoic, octynoic acids and the like; (b) saturated or unsaturated, substituted, alicyclic carboxylic acids, for example, cyclobutanecarboxylic acid, cyclopentanecarboxylic acid, cyclopentenecarboxylic acid, methylcyclopentenecarboxylic acid, cyclohexanecarboxylic acid, dimethylcyclohexenecarboxylic acid, dipropylcyclohexanecarboxylic acid and the like; (c) saturated or unsaturated, substituted, alicyclic aliphatic carboxylic acids, for example, cyclopentaneacetic acid, cyclopentanepropionic acid, cyclopenteneacetic acid, cyclohexanebutyric acid, methylcyclohexaneacetic 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, phenylpropiolic acid and naphthylacetic acid, and the like.

The novel lincomycin-3-monoacylate compounds of the above formula exist either in the non-protonated (free base) form or in the protonated (acid addition salt) form, depending on the pH of the environment. They form stable protonates, i.e., acid addition salts, on neutralization of the free base with suitable acids. Salts of lincomycin-3-monoacylate compounds can be made 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, sulfuric, phosphoric, thiocyanic, fluosilicic, acetic, succinic, citric, lactic, maleic, fumaric, pamoic, cholic, palmitic, mucic, camphoric, glutaric, glycolic, phthalic, tartaric, lauric, stearic, salicyclic, 3-phenylsalicyclic, 5-phenylsalicyclic, 3-methyl glutaric, orthosulfobenzoic, cyclohexane-

sulfamic, cyclopentanepropionic, 1,3 - cyclohexanedicarboxylic, 4 - cyclohexenecarboxylic, octadecenylsuccinic, octenylsuccinic, methanesulfonic, benzenesulfonic, helianthic, Reinecke's, azobenzenesulfonic, octadecylsulfuric, picric, pamoic and like acids.

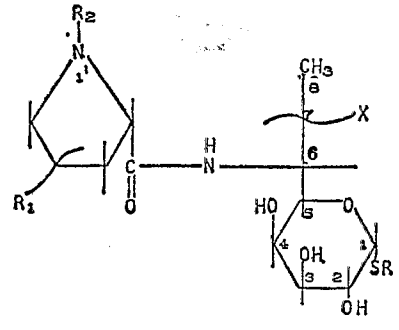
Addition salts of lincomycin-3-monoacylate compounds of this invention can be used for the same purpose as the free bases. They can also be used to upgrade the free bases, namely, by making acid addition salts of the free bases, subjecting them to purification procedures, and then converting the salts back to the free bases by neutralizing with an alkali or contacting with an anionic resin, advantageously to about pH 7.5 to 8.5, the free bases are upgraded.

In general, the acid addition salts of lincomycin-3-monoacylate compounds are the preferred forms for use, especially where alkaline aqueous solutions of the compounds are involved. This is because there is a tendency for the 3-monoacylates in the free base form to be somewhat unstable in mildly alkaline solutions, and pH values greater than about 6.5 to 7 should be avoided. At the other extreme, pH values of less than about 2 should be avoided in aqueous solutions of lincomycin-3-monoacylate compounds in either the free base or acid addition salt form, to minimize acid-catalyzed instability.

Monacylate esters of lincomycin itself are described in U.S. Pat. 3,326,891. The novel process of the present invention also affords novel lincomycin-3-monoacylate compounds in which the hydroxyl group at carbon 7 is substituted by halogen, including chlorine, bromine or iodine. Such novel 3-monoacylate compounds, especially those in which the 7-hydroxyl is substituted to give 7(S)-chloro, have increased antibacterial potency over the 7-hydroxy compound and can be used for the same purposes as the corresponding 7-hydroxy compound but in lesser amounts. The lincomycin-3-monoacylate compounds of Formula I in which R_2 is hydrogen have like antibacterial properties and, moreover, have improved gram-negative activity.

Lincomycin itself (methyl 6,8-dideoxy-6-(1-methyl-4-propyl-L-2-pyrollidinecarboxamido)-1-thio - D - erythro-D-galacto-octapyranoside) is an antibiotic obtained as an elaboration product of a lincomycin-producing actinomycete. Methods for the production, recovery and purification of lincomycin and its acid addition salts are described in U.S. Pat. 3,086,912. Other unacylated lincomycin starting compounds, i.e., wherein there is an OH group at the 3-position, as in Formula II, below, can be prepared by procedures disclosed in various patents, publications and patent applications as follows:

With reference to compounds of Formula II,



(II)

wherein:

R=alkyl to 6 carbon atoms, U.S. Pat. 3,380,992 (specification and Example 12)

R_1=cis or trans alkyl to 8 carbon atoms, U.S. Pat. 3,380,992 (specification and Example 1)

R_2=hydrogen or alkyl to 8 carbon atoms, U.S. Pat. 3,380,992 (specification and Examples 1E and IG+H)

X=(S)-OH, U.S. Pat. 3,380,992 (specification and Example 11D)

X=(R)- or (S)-Cl, -Br or -I, Belgium Pat. 676,202

A previous process for manufacture of lincomycin monocylates, including lincomycin-3-monoacylates, is described in U.S. Pat. 3,326,891. It consists of reacting lincomycin with the acyl halide or anhydride of the selected carboxylic acid in the presence of an acid-binding agent, for example a tertiary amine such as pyridine (preferred) or a trialkyl amine (as opposed to a hindered trialkylamine in the present invention) at a temperature not greater than about 100°, to complete the reaction. At molar ratios of acyl halide or acid anhydride to lincomycin of less than 4:1 the reaction product is described normally to be a mixture of variously acylated compounds, i.e., various positionally isomeric mono-, di-, and triacylates. From such a mixture is desired 3-monoacylate must be separated by tedious and expensive means such as counter-current distribution or partition chromatography. Monoacylates are also described in U.S. Pat. 3,326,891 to be producible by first forming a higher acylate, e.g., a tetraacylate, hydrolyzing with acid, and separating the desired monoacylate from amongst the various related hydrolytic products. This alternative procedure is thus a two-step process, non-specific for 3-mono-acylates, and also requires tedious separation of the desired 3-monoacylate from amongst other acylates and other products.

Direct monoacylation of lincomycin compounds of Formula II to yield almost exclusively the 3-monoacylate would be unexpected, since the 3-hydroxyl group of the compound is only one of three or four secondary hydroxyl groups in the molecule, and it would commonly be expected that the other secondary hydroxyl groups, namely the 2-, 4-, and (if present) 7-hydroxyl groups, would need to be protected by a suitable protective group. It has, however, unexpectedly been found in the present invention that highly selective direct monoesterification at the 3-position of lincomycin compounds can be effected under controlled mild conditions without the use of protective groups, in high yield.

Selective direct monoacylation of a lincomycin compound of Formula II, wherein R, R_1, R_2 and X are as previously defined, or its acid addition salt, is achieved by mixing a solution of the lincomycin compound or an acid addition salt thereof with an acid anhydride or an acyl halide of a hydrocarbon carboxylic acid and a sterically hindered strongly basic tertiary amine. The preferred solvent for bringing the lincomycin into solution is N,N-dimethylformamide. Other solvents can be used, such as N,N-dimethylacetamide, N-methylpyrrolidine or any solvent that will dissolve the lincomycin compound acid addition salt. The choice of solvents can be extended by the use of the free base form of the lincomycin compound, since this form is more soluble in common solvents than the acid addition salts.

By "sterically hindered strongly basic tertiary amine" is meant a strongly basic amine in which groups around the nitrogen atom are of sufficient size or are oriented in space in a manner which hinders the approach of an attacking molecule to the nitrogen atoms in the subsequent acyl-ammonium complex, to be described. The subject of steric hindrance in this general sense is discussed in Astle, M. J. and Shelton, J. R., "Organic Chemistry," Harper and Brothers, 2nd edition, page 580. The preferred sterically hindered tertiary amine base is tripropylamine. Other, e.g., trimethyl, triethyl, tripropyl, tributyl, triisobutyl, butyldimethyl, tripentyl, etc., amines can be used to provide selectivity in the 3-monoacylation of the lincomycin compound. Pyridine is definitely not acceptable since random esterification occurs when it is employed. However, sterically hindered pyridine derivatives such as 2-methylpyridine or 2,6-dimethylpyridine, are acceptable bases although, being weaker bases, slower reaction re-

sults. The use of derivatives of the morpholines, such as the N-methyl and N-cyclohexyl analogs, allows some random esterification because of their minimal steric hindrance. The best tertiary amine bases are the straight chain trialkylamine bases. The rate of reaction decreases in the order: triethylamine>tripropylamine>tributylamine. Amine bases with chains longer than that of tributylamine are not desirable, since the reaction time becomes impractically long at room temperature, although excellently selective 3-monoacylation is still achieved with longer chain trialkylamines.

The best 3-monoacylating agents are the anhydrides of hydrocarbon carboxylic acids. Selective 3-monoacylation can also be achieved with sterically hindered acyl halides, such as trimethylacetyl chloride (pivalyl chloride), triethylacetyl chloride, trimethylpropionyl chloride, trimethylbutyryl chloride, 2,2-, 2,3- and 3,3 - dimethylbutyryl chloride, tributylpropionyl bromide, triethylbutyryl fluoride, tripropylpropionyl fluoride and the like.

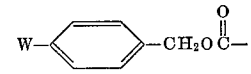
Selectively in 3-monoacylation is increased by operating at relatively low temperatures. For example, in selective 3-monoacylation by use of acid anhydrides, about room temperature is preferred. In the case of the use of acid halides, lower temperatures, of from about —20° C. to 0° C., are beneficial. Higher temperatures, e.g., from about 40° C. to about 100° C. promote more rapid acylation, but with some loss of selectivity toward 3-monoacylation.

The time required for completion of the reaction depends upon such factors as the reaction temperature, the particular reactants employed, the relative amounts of reactants, thoroughness of mixing and the like. Therefore, it will be understood that the optimum reaction time will vary for each set of reaction conditions, and particularly for the hindered tertiary amine and 3-monoacylating agent used. For example, in the reaction of lincomycin hydrochloride with hexanoic anhydrides and tripropylamine in N,N-dimethylformamide, the following weight ratio is optimum; 2 parts lincomycin hydrochloride, 5 parts hexanoic anhydride, 3 parts tripropylamine and 10 parts N,N-dimethylformamide. For the aforesaid ratio the time required for completion of the reaction is 24 hours at room temperature. The progress of a given 3-monoacylation reaction can, if desired, be followed by periodic sampling and examination of the reaction mixture, for example by gas or thin layer chromatography or other appropriate method in the art.

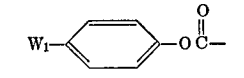
In addition to the marked selectivity of monoacylation toward 3-acylation, a pronounced advantage of the process of this invention is in the ease of recovery of the 3-monoacylate product. In general, the product in essentially pure form as free base or acid addition salt is afforded by direct crystallization upon evaporation of the reaction mixture, or by preliminary extraction of the 3-monoacylate product into a suitable solvent such as ether or chloroform. Thus, the tedious and expensive separation of a minor amount of desired product from a major amount of structurally related impurity is avoided. The product can then be recrystallized from a suitable solvent or mixture of solvents. In the relatively infrequent instances when the reaction mixture contains excessive amounts of other monoacylates or higher acylates, due to decreased selectivity in 3-monoacylation, the selectivity toward 3-monoacylation can be increased by use of lower reaction temperature or by use of a more suitable hindered tertiary amine.

In general, the corresponding lincomycin-3 - acylate compound acid addition salt is obtained as product of the invention process if the unesterified lincomycin compound starting material is in the acid addition salt form; and a monoacylate free base product is obtained where the starting lincomycin compound is in the free base form. Under such circumstances, alkaline process solutions of the monoacylate free base should be avoided, pH values of about pH 2 to 6 being preferred, to minimize base-catalyzed degradation as discussed previously. Another method for affording the free base form, when needed, is to freeze-dry a lincomycin-3-monoacylate acid addition salt formed from a volatile addition acid, for example a lincomycin-3-monoacylate formate salt, bicarbonate salt or acetate salt. Such salts of volatile addition acids, as well as other salts, are prepared easily, among other means, by passing a lincomycin-3-monoacylate acid addition salt, for example a hydrochloride, through an ion exchange resin column previously loaded with the appropriate volatile acid. The lincomycin-3-monoacylate salt of the volatile acid can then be isolated from the column eluate by concentration and addition of a non-solvent for the salt, such as acetone. Lincomycin-3-monoacylate salts of non-volatile acids can, of course, be isolated directly from the ion exchange column eluate by freeze-drying.

In the instances where the desired lincomycin 3-monoacylate compound of Formula I is a member of the group in which R_2 is hydrogen, i.e., in the case of 1'-desmethyl lincomycin compounds, simultaneous undesirable acylation at 1'-N is prevented by first protecting the 1'-N atom with a protective group removable by hydrogenolysis. Suitable such groups are trityl, i.e., triphenylmethyl, diphenyl-(p-methoxyphenyl)methyl, bis - (p-methoxyphenyl)-phenylmethyl, benzyl, or p-nitrobenzyl and hydrocarbyloxycarbonyl groups. Examples of the latter are tertiary-butoxycarbonyl; benzyloxycarbonyl groups of the formula

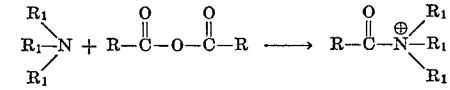


wherein W is hydrogen, nitro, methoxy, chloro, or bromo, for example, carbobenzoxy, p-nitrocarbobenzoxy, p-bromo-, and p-chlorocarbobenzoxy; and phenyloxycarbonyl groups of the formula



wherein W_1 is hydrogen, allyl, or alkyl of not more than 4 carbon atoms, such as phenyloxycarbonyl, p-tolyloxyoxycarbonyl, p-ethylphenyloxycarbonyl, and p-allylphenyloxycarbonyl and the like. After 3-monoacylation of the 1'-protected lincomycin compound by the process of this invention, the protective group is replaced by hydrogen by hydrogenolysis, according to the art, to yield the 3-monoacylate ester of the 1'-hydrogen lincomycin compound.

The principle responsible for the selectivity in 3-monoacylation on reaction of a hindered tertiary amine and an anhydride of a hydrocarbon carboxylic acid is believed to be formation of an activated sterically hindered acylammonium complex, which serves as the acylating agent, viz:



Because of steric considerations, this hindered acyl-ammonium complex can attack only unhindered, reactive hydroxyl groups. In the lincomycin compounds of Formula II, the 2-, 4-, and (if present) 7-hydroxyl groups can themselves be considered to be hindered by what can be considered to be isopropyl-type substituents on adjacent carbons. These substituents tend effectively to prevent the reactive approach of the hindered acyl-ammonium complex. On the other hand, the hydroxyl at carbon 3 is relatively unhindered. The successful reactive approach of the acylating, hindered acyl-ammonium complex to the 3-hydroxyl carbon is further fostered by the equatorial position of the 3-hydroxyl, which provides minimal steric hindrance. As a consequence, the monoacylation product tends to be solely the 3-monoacylate.

Lincomycin-3-monoacylate compounds of Formula I, herein defined, and their acid addition salts are valuable antibacterial agents. The compounds, for example lincomycin-3-hexanoate hydrochloride inhibit the growth of *S. lutea* and *S. aureus* and therefore are useful as disinfectants on various dental and medical equipment contaminated with these organisms. Similarly, for example 1'-desmethyllincomycin-3-butyrate, they can be used to disinfect washed and stacked food utensils contaminated with such organisms. The novel 7-halogenated lincomycin-3-monoacylate compounds afforded by the present invention process have the additional advantages noted previously.

DETAILED DESCRIPTION

It is to be understood that the invention is not to be limited to the exact details of operation or exact compounds shown and described herein, as obvious modifications and equivalents will be apparent to one skilled in the art, and the invention is therefore to be limited only by the scope of the appended claims.

Example 1.—Lincomyin-3-hexanoate hydrochloride

A solution of 50 g. of lincomycin hydrochloride in 200 ml. of N,N-dimethylformamide is mixed with 60 ml. of tripropylamine and 50 ml. of hexanoic anhydride. After about 24 hours at room temperature, gas chromatographic analysis shows that about 91% of lincomycin-3-hexanoate hydrochloride is formed. The reaction is terminated by the addition of 20 ml. of water and after about 30 minutes the solution is concentrated to a viscous liquid under high vacuum at about 40° C. The resulting brown residue is dissolved in 1000 ml. of water and the solution extracted with 100 ml. of ether. The aqueous phase is mixed with 200 ml. of water containing 56.3 g. of disodium hydrogen phosphate and 20.4 g. of citric acid (monohydrate). The aqueous phase is extracted with 1000 ml. of chloroform. The chloroform extract is washed three times with 2 liter portions of water containing 57.2 g. of disodium hydrogen phosphate and 20.4 g. of citric acid (monohydrate) per liter. The chloroform layer is dried over sodium sulfate and the solvent removed under vacuum. The clear viscous residue is dissolved in 800 ml. of ether and the product precipitated by the addition of gaseous hydrogen chloride. It is isolated by filtration, washed with ether and dried by passing nitrogen through the filter to give 25.1 g. of lincomycin-3-hexanoate hydrochloride. The identity of the product compound is confirmed by its nuclear magnetic resonance (NMR) spectrum.

Analysis.— Calcd. for $C_{24}H_{45}N_2O_7SCl$ (percent): C, 53.27; H, 8.38; N, 5.18; S, 5.93; Cl, 6.55. Found (corrected for H_2O content) (percent): C, 53.67; H, 8.60; N, 5.12; S, 5.73; Cl, 6.34, (H_2O, 2.40).

Lincomycin-3-hexanoate hydrochloride is converted to lincomycin-3-hexanoate by treatment with a strongly basic anion exchange resin. Suitable anion exchange resins for this purpose are obtained by chlormethylating by the procedure given on pages 88 and 97 of Kunin, Ion Exchange Resins, 2nd ed. (1958), John Wiley and Sons, Inc., polystyrene crosslinked, if desired, with divinylbenzene prepared by the procedure given on page 84 of Kunin, supra, and quaternizing with trimethylamine, or dimethylethanolamine by the procedure given on page 97 of Kunin, supra. Anion exchange resins of this type are marketed under the trade names Dowex 2, Dowex 20, Amberlite IRA–400, Duolite A–102, and Permutit S–1. The lincomycin-3-hexanoate is converted to other salts by contacting with other acids as previously disclosed or by percolating the hydrochloride salt through an anion exchange resin loaded with the appropriate acid.

Following the procedure of Example 1 but substituting lincomycin for its hydrochloride, yields lincomycin-3-hexanoate.

Lincomycin - 3-hexanoate hydrochloride was found to have a plate antibacterial activity equivalent to 490 μg. lincomycin base per mg. using *S. lutea* in the assay. Its relative molar CD_{50} was determined to be 0.5 times lincomycin when administered subcutaneously and 1.27 times lincomycin when given orally to mice infected with *S. aureus*.

Example 2.—Lincomycin-3-propionate hydrochloride

A solution of 50 g. of lincomycin hydrochloride monohydrate in 200 ml. of N,N-dimethylformamide is diluted with 75 ml. of tripropylamine and 125 ml. of propionic anhydride. After about 24 hours at room temperature the solvent of the solution is evaporated under high vacuum at about 60° C. to give a viscous residue. The residue is dissolved in 200 ml. of water and the pH adjusted to 6.5 with 6.6 N sodium hydroxide solution. The water phase is extracted three times with 200 ml. of chloroform. The extracts are combined, dried with sodium sulfate and the chloroform removed under vacuum. The brown viscous residue is dissolved in 200 ml. of ether and hydrogen chloride gas is bubbled into the solution to precipitate lincomycin-3-propionate hydrochloride. The precipitate is isolated by filtration, washed with ether and dried under high vacuum to give 25.5 g. of crude lincomycin-3-propionate hydrochloride. This material is dissolved in 150 ml. of N,N-dimethylformamide and the solution diluted with 1 liter of chloroform. Crystallization of the product occurs rapidly. It is isolated by filtration, washed with chloroform and dried by passing nitrogen through the filter for about 15 minutes. It is dried at about 100° C. for about 4 hours under a high vacuum and finally air is drawn through the lincomycin-3-propionate hydrochloride on a filter for about 6 hours.

Analysis.—Calcd. for $C_{21}H_{39}N_2O_7SCl$ (percent): C, 50.54; H, 7.88; N, 5.61; S, 6.43; Cl, 7.10. Found (corrected for H_2O content) (percent): C, 50.06; H, 7.79; N, 5.94; S, 6.29; Cl, 7.18. (H_2O, 3.42).

The relative CD_{50} of lincomycin-3-propionate hydrochloride was established to be 0.29 times that of lincomycin base, on a molar basis, when administered orally to mice infected with *S. aureus,* and 0.22 times when administered subcutaneously.

Treatment of lincomycin-3-propionate hydrochloride with a strongly basic ion exchange resin (prepared in the manner described following Example 1) gives the free base, which can be converted to other salt forms by contacting with other acids as previously disclosed.

Following the procedure of Example 2 but substituting lincomycin for its hydrochloride, yields lincomycin-3-propionate.

Example 3.—Lincomycin-3-propionate hydrochloride

A solution of 20 g. of anhydrous lincomycin hydrochloride in 20 ml. of propionic anhydride and 20 ml. of t-butylamine is kept at room temperature for about 64 hours. A gas chromatogram of a sample of the reaction mixture shows about an 80% conversion to the desired lincomycin-3-propionate hydrochloride. The crude product is isolated and purified in the manner described in Examples 1 and 2, with a yield approximately the same as obtained therein.

Example 4.—7-deoxy-7(S)-chlorolincomycin 3-palmitate hydrochloride

52 g. of 7-deoxy-7(S)-chlorolincomycin hydrochloride is dissolved in 200 ml. of N,N-dimethylformamide and 60 ml. of tributylamine and 107 g. of palmitic anhydride are added. After about 30 hours at room temperature the reaction is terminated by addition of 100 mls. of water. The resulting diluted reaction mixture is extracted with 100 ml. ether. The aqueous phase is mixed with 200 ml. of water containing 56.3 g. of disodium hydrogen phosphate and 20.4 g. of citric acid (monohydrate). The aqueous phase is extracted with 1000 ml. of ether. The ether extract is washed three times with 2 liter portions of water containing 57.2 g. of disodium hydrogen phosphate and 20.4 g. of citric acid (monohydrate) per liter. The ether layer is dried over sodium sulfate and the solvent re-

moved under vacuum. The residue is dissolved in 800 ml. of ether and the product precipitated by the addition of gaseous hydrogen chloride. It is isolated by filtration, washed with ether and dried by passing nitrogen through the filter to give 7-deoxy-7(S)-chlorolincomycin-3-palmitate hydrochloride.

Example 5.—1'-desmethyl - 7 - deoxy-7(S)-chlorolincomycin-3-hexanoate hydrochloride

55 g. of 1' - desmethyl-1'-carbobenzoxy-7-deoxy-7(S)-chlorolincomycin (prepared according to Belgium Pat. 676,202) is dissolved in 200 ml. of N,N-dimethylformamide, and 60 ml. of tripropylamine and 50 ml. of hexanoic anhydride are added. The reaction mixture is held at room temperature for about 24 hours. About 100 ml. of water is added and the reaction mixture is concentrated to a viscous liquid by evaporation at about 40° C. under vacuum. The liquid is dissolved in about 1 liter of methanol. This solution is shaken over about 10 g. of 10%-palladium-on-carbon catalyst under 40 lbs. of hydrogen pressure for about 17 hours. The catalyst is filtered off and the solution is concentrated under vacuum. The residue is dissolved in about 1 liter of water and, if necessary, quickly adjusted to pH 5 to 6. This solution is extracted with ether, diluted with phosphate-citrate buffer, and extracted into chloroform as in Example 1. The chloroform extract is dried and evaporated. The residue is dissolved in about 100 ml. of acetone and about 10 ml. of water and acidified slowly with 6 N hydrochloric acid. The desired product, 1'-desmethyl-7-deoxy-7(S)-chlorolincomycin-3-hexanoate hydrochloride precipitates as crystals; or if it remains in solution, it is induced to precipitate by cautious addition of more acetone or hexane.

Example 6.—1'-desmethyl-4'-despropyl-4'-trans-pentyl-7-deoxy-7(S)-chlorolincomycin - 3 - palmitate hydrochloride

57 g. of 1'-desmethyl-1'-carbobenzoxy-4'-despropyl-4'-trans-pentyl-7-deoxy-7(S)-chlorolincomycin (prepared according to Belgium Pat. 672,202) is dissolved in about 200 ml. of N,N-dimethylformamide and 60 mls. of tripropylamine and 107 g. of palmitic anhydride is added. The reaction is terminated after about 24 hours by the addition of 10 mls. of water. The reaction mixture is evaporated at less than 40° C. under vacuum to a thick syrup. The syrup is dissolved in methanol and treated with hydrogen and paladium-on-carbon catalyst, and concentrated as in Example 5. The residue (in about 100 mls. of water) is extracted with ether, and the aqueous phase diluted with phosphate-citrate buffer and extracted into chloroform as in Example 1, to afford the desired product 1'-desmethyl - 4' - despropyl - 4'-trans-pentyl-7-deoxy-7(S)-chlorolincomycin-3-palmitate hydrochloride.

Example 7.—Lincomycin-3-acylate acid addition salts and free bases

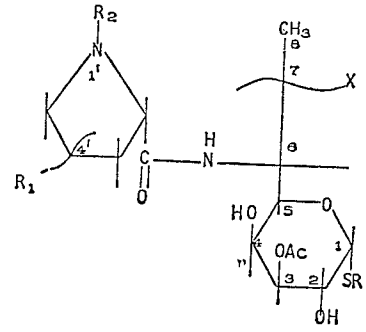
The corresponding lincomycin-3-monoacylate acid addition salts and free bases are obtained by substituting for the hexanoic anhydride in Example 1 (and in the second paragraph thereafter) the anhydrides of the following hydrocarbon carboxylic acids: acetic, butyric pentanoic, hexanoic, heptanoic, octanoic, nonanoic, decanoic, dodecanoic, tetradecanoic, hexadecanoic (palmitic), octadecanoic, and isomers thereof: acrylic, crotonic, undecylenic, hexynoic, heptynoic, octynoic acids and the like; saturated or unsaturated, substituted, alicyclic carboxylic acids, for example, cyclobutanecarboxylic acid, cyclopentanecarboxylic acid, cyclopentenecarboxylic acid, methylcyclopentenecarboxylic acid, cyclohexanecarboxylic acid, dimethylcyclohexenecarboxylic acid, dipropylcyclohexanecarboxylic acid and the like; cyclopentaneacetic acid, cyclopentanepropionic acid, cyclopenteneacetic acid, cyclohexanebutyric acid, methylcyclohexaneacetic acid, and the like; benzoic acid, toluic acid, naphthoic acid, ethylbenzoic acid, isobutylbenzoic acid, methylbutylbenzoic acid and the like; phenylacetic acid, phenylpropionic acid, phenylvaleric acid, cinnamic acid, phenylpropiolic acid and naphthylacetic acid, and the like; cyclohexanecarboxylic acid, 2,6-dimethyl-3-cyclohexane-1-carboxylic acid, 3,4-dipropylcyclohexanecarboxylic acid, cyclopentaneacetic acid, 3-cyclopentylpropionic acid, 4-cyclohexylbutrylic acid, (2-methylcyclohexyl) acetic acid, p-ethylbenzoic acid, p-isobutylbenzoic acid, 3-methyl-4-butylbenzoic acid, 3-phenylpropionic acid, 5-phenylvaleric acid, cinnamic acid, 3-phenylpropiolic acid, (1-naphthyl)-acetic acid, and the like.

Example 8.—Lincomycin-3-acylate acid addition salts and free bases

The corresponding lincomycin-3-monoacylate acid addition salts and free bases are obtained by substituting for the hexanoic anhydride in Example 1 (and in the second paragraph thereafter) the following halides of hydrocarbon carboxylic acids (i.e., acyl halides): trimethylacetyl chloride (pivalyl chloride), triethylacetyl chloride, trimethylpropionyl chloride, trimethylbutyryl chloride, 2,2-, 2,3- and 3,3-dimethylbutyryl chloride, tributylpropionyl bromide, triethylbutyryl fluoride, tripropylpropionyl fluoride and the like.

What is claimed is:

1. A process for preparing a compound selected from the group consisting of the free bases and acid addition salts of a lincomycin-3-monoacylate compound of the formula



(I)

wherein R is alkyl of 1 to 16 carbon atoms, inclusive, R_1 is alkyl of 2 to 8 carbon atoms, inclusive; R_2 is alkyl of 1 to 8 carbon atoms, inclusive; X is selected from the group consisting of hydroxy, chlorine, bromine and iodine; and Ac is the acyl radical of a hydrocarbon carboxylic acid containing 1 to 18 carbon atoms, inclusive, which comprises: mixing the corresponding 3-hydroxy compound with a compound selected from the group consisting of an acyl halide and anhydride of a hydrocarbon carboxylic acid of not more than 18 carbon atoms, in the presence of a sterically hindered strongly basic tertiary aliphatic amine.

2. A process according to claim **1** in which the tertiary amine is tripropylamine.

3. A process according to claim **1** in which the tertiary amine is tributylamine.

4. A process according to claim **1** in which the starting lincomycin compound is lincomycin or its acid addition salt.

5. A process according to claim **1** in which the starting lincomycin compound is lincomycin hydrochloride, the tertiary amine is tripropylamine, and the acid anhydride is hexanoic anhydride.

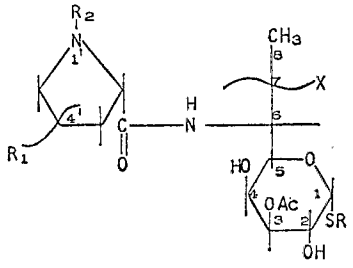
6. A process according to claim **1** in which the starting lincomycin compound is lincomycin hydrochloride, the tertiary amine is tributylamine and the acid anhydride is propionic anhydride.

7. A process according to claim **1** in which the starting lincomycin compound is 7-deoxy-7(S)-chlorolincomycin or its acid addition salt.

8. A process according to claim **1** in which the starting compound is 7-deoxy-7(S)-chlorolincomycin or its acid

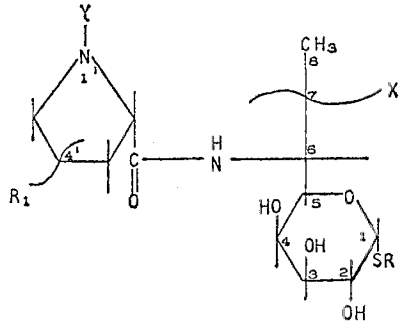
addition salt an the acid anhydride is palmitic anhydride.

9. A process for preparing a compound selected from the group consisting of the free bases and acid addition salts of a lincomycin-3-monoacylate compound of the formula



(I)

wherein R is alkyl of 1 to 6 carbon atoms, inclusive, R_1 is alkyl of 2 to 8 carbon atoms, inclusive; R_2 is hydrogen; X is selected from the group consisting of hydroxy, chlorine, bromine and iodine; and Ac is the acyl radical of a hydrocarbon carboxylic acid containing 1 to 18 carbon atoms, inclusive, which comprises: mixing a compound of the formula



(II)

wherein R, R_1, and X are as in claim **1**, and Y is a protective group removable by hydrogenolysis, with a compound selected from the group consisting of the acyl halide and the acid anhydride of a hydrocarbon carboxylic acid of not more than 18 carbon atoms, in the presence of a sterically hindered basic tertiary aliphatic amine, and removing the protective group by hydrogenolysis, to obtain the corresponding 3-monoacylate compound.

10. A process according to claim **9** in which the starting compound is 1' - desmethyl - 1'-protected-7-dexoy-7(S)-chlorolincomycin or its acid addition salt and the acid anhydride is hexanoic anhydride.

11. A process according to claim **9** in which the starting compound is 1' - desmethyl - 1'-protected-7-deoxy-7(S) chlorolincomycin or its acid addition salt and the acid anhydride is palmitic anhydride.

12. A process according to claim **9** in which the starting compound is 1-desmethyl-1'-protected-4'-despropyl-4'-trans-pentyl-7-deoxy-7-chlorolincomycin or its acid addition salt and the acid anhydride is hexanoic anhydride.

13. A process according to claim **9** in which the starting compound is 1'-desmethyl-1'-protected-4'-despropyl-4'-trans-pentyl-7-deoxy-7-chlorolincomycin or its acid addition salt and the acid anhydride is palmitic anhydride.

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LEWIS GOTTS, Primary Examiner

J. R. BROWN, Assistant Examiner

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