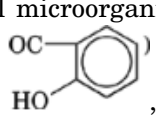
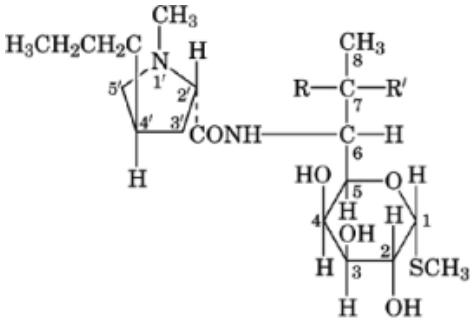
Kirk-Othmer Encyclopedia of Chemical Technology.

LINCOSAMINIDES

Lincomycin [154-21-2] (**1**, R = OH, R′ = H), $C_{18}H_{34}N_2O_6S$, the first lincosaminide antibiotic to which a structure was assigned, is defined chemically as methyl 6,8-dideoxy-6-(1-methyl-*trans*-4-propyl-L-pyrrolidin-2-ylcarbonylamino)-1-thio-D-erythro-D-galacto-octopyranoside. Both lincomycin and the semisynthetic clindamycin [18323-44-9] (**1**, R = H, R′ = Cl), $C_{18}H_{33}ClN_2O_5S$, are widely used in clinical practice. The trivial name of the sugar fragment of this antibiotic, methyl α-thiolincosaminide, has lent itself to the other members of this family, whether produced as secondary metabolites of soil microorganisms or derived semisynthetically by chemical modification. Thus celesticetin [2520-21-0] (**2**, R = ), $C_{24}H_{36}N_2O_9S$, and desalicetin [19246-70-9] (**2**, R = H), $C_{17}H_{32}N_2O_7S$, are also lincosaminides.



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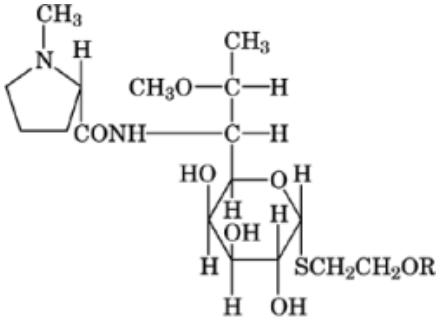


(**2**)

2 LINCOSAMINIDES

1. Lincomycin

The discovery and biological properties of lincomycin (**1**, R = OH, R′ = H) were described in 1962 (1). This antibiotic is active *in vitro* and *in vivo* against most of the common gram-positive pathogens. Resistance by Staphylococci is developed slowly in a stepwise manner, based on *in vitro* serial subculture experiments, and its activity is not influenced by body fluids up to concentrations of 50% in the assay medium (2).

Lincomycin was produced originally by the actinomycete *Streptomyces lincolnensis* var. *lincolnensis,* NRRL 2936. Subsequently, it has been produced by a variety of *Streptomyces* strains (3–8) and by strain 1146 of *Actinomyces roseolus* (9). Extraction by standard procedures using *Sarcina lutea* as the assay organism on agar trays (10) leads to a crystalline hydrochloride having molecular formula $C_{18}H_{34}N_2O_6S{\cdot}HCl{\cdot}1/2\ H_2O$ (11). A second, more dense form exists as the monohydrate (12), and this latter form of lincomycin hydrochloride is the Upjohn trademarked Lincocin available commercially. This salt is highly soluble in water, and moderately soluble in methanol and ethanol. It has one basic function, $pK_a = 7.5$, and the specific rotation $[\alpha]_D^{25} = +137^\circ$ (1.0 mg/mL in H_2O). The structure of lincomycin was determined by classical chemical degradation studies, together with the interpretation of proton magnetic resonance and mass spectra (13–18).

1.1. Biosynthesis

The terminal *C*-methyl of the propyl side chain, the *S*-methyl, and the *N*-methyl groups are derived from methionine (19). *trans*-4-Propyl-L-proline [31101-27-6] was shown to accumulate when *Streptomyces lincolnensis* is grown in media deficient in sulfur, and the addition of L-tyrosine or L-dihydroxyphenylalanine (DOPA) was shown to stimulate this production. From a comparison of the incorporation of label from L-[1-^{14}C]tyrosine and L[U-^{14}C]tyrosine, it was demonstrated that all of the carbon atoms of the propylproline other than the *C*-terminal methyl group were derived from tyrosine and, by the use of L-[^{15}N]tyrosine, it was determined that the proline nitrogen atom was derived from the amino—nitrogen atom of tyrosine (20).

Later work (21), using ^{2}H- and ^{13}C-labeled precursors, in combination with ^{13}C nmr and mass spectral analyses, showed that glucose is converted into tyrosine and thence into DOPA which, via an initial 2,3-extradiol cleavage, cyclization, loss of two carbon atoms, and introduction of a *C*-methyl group from *S*-adenosylmethionine, gives propylproline. The biosynthesis of methyl α-thiolincosaminide [14810-93-6], $C_9H_{19}NO_5S$, has also been demonstrated to proceed from glucose via a C-5 and a C-3 unit, using both specifically ^{13}C-labeled substrates and uniformily labeled D-(^{13}C) glucose followed by the analysis of the ^{13}C spin coupling patterns (22).

1.2. Mechanism of Action

The earliest studies on the mechanism of action of lincomycin showed that lincomycin had the immediate effect on *Staphylococcus aureus* of complete inhibition of protein synthesis (23). This inhibition results from the blocking of the peptidyltransferase site of the 50S subunit of the bacterial ribosome (24). Little effect on DNA and RNA synthesis was observed.

1.3. Resistance to Lincomycin

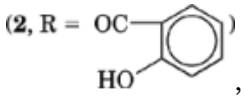
Resistance to lincomycin is developed slowly, and is usually caused by modification of 23S ribosomal RNA, which leads to co-resistance to macrolide, lincosaminide, and streptogramin B antibiotics (25). Inactivation of lincomycin by clinical isolates of strains of *Staphylococcus aureus* and *Staphylococcus haemolyticus*, though retention of sensitivity to macrolides (see Antibiotics, macrolides) and streptogramins (see Antibiotics, peptides), has been found to be the consequence of the conversion of the antibiotic into its 3-(5′-adenylate) (26).

1.4. Pharmacology and Uses

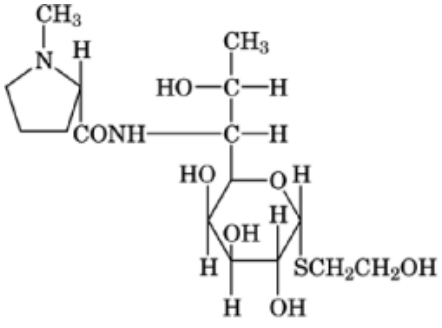
Lincomycin hydrochloride (Lincocin) is available in oral dosage forms and as a sterile solution for injection. After oral administration to adults, mean peak serum levels were achieved between 2 and 6 h. Single 500 and 1000 mg doses gave peak levels of 1.8–5.3 and 2.5–6.7 μg/mL, respectively (27–31). The half-life is 4.2–5.4 h (32). Intramuscular administration gave peak levels at 0.5–2 h. After 300 and 600 mg doses, mean peak levels were 11.7–15 and 9.3–18.5 μg/mL, respectively (27, 28, 31, 33). Lincomycin activity is widely distributed in human body tissues and fluids. Significant concentrations were found in bile, peritoneal fluid, pleural fluid, the eye, bone, and brain (31, 34–37). It is excreted both in the urine and in the feces (27–31).

Lincomycin has found use in the treatment of diseases of the ear, throat, nose, respiratory tissue, skin and soft tissue, bone, joint, dental, and septicemic infections caused by staphylococci, pneumonococci, and streptococci (other than enterococci). It has also been used in the treatment of diphtheria and a variety of anaerobic infections, including actinomycosis (38).

2. Celesticetin and other Lincosaminide Metabolites



The production (39) and isolation (40) of the antibiotic celesticetin , a salicylate ester of the β-hydroxyethylthio-substituent was reported as early as the 1950s, although its structure was not determined until 1968 (41). Reexamination of the fermentation showed the presence of desalicetin (**2**, R = H) and a variety of other β-hydroxyethylthio esters, together with similar esters of 7-de-*O*-methyldesalicetin [39032-07-0], (**3**) $C_{16}H_{30}N_2O_7S$ (42, 43). One auxotrophic mutant of *S. caelestis* produced 7-de-*O*-methylcelesticetin [39032-05-8] (**4**, R = CH_3, R′ = H), $C_{23}H_{34}N_2O_9S$ (44), whereas a second produced both de-*N*-methylcelesticetin [40736-31-0] (**4**, R = H, R′ = CH_3), $C_{23}H_{34}N_2O_9S$, and de-*N*-methyl-7-de-*O*-methylcelesticetin, (**4**, R = R′ = H), $C_{22}H_{32}N_2O_9S$ (45).



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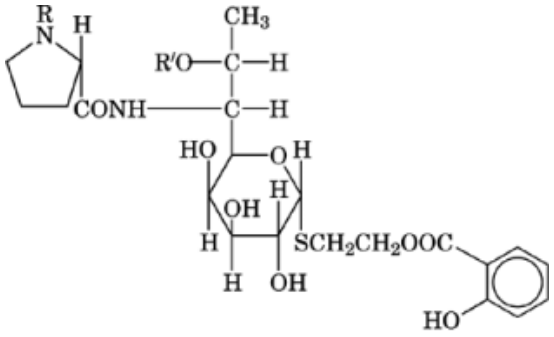
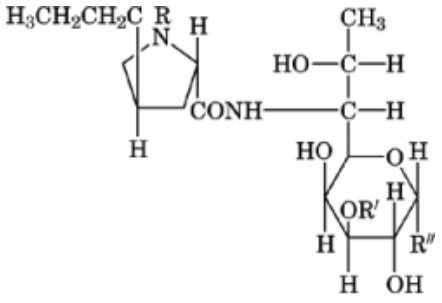


(**4**)

Antibiotic Bu-2545, 7-*O*-methyl-4′-depropyllincomycin [75007-09-9] (**1**, R = OCH_3, R′ = H but lacking the 4′-propyl group), $C_{16}H_{30}N_2O_6S$, produced by *Streptomyces* strain No. H 230-5, possesses structural features in common with both celesticetin and lincomycin (46, 47).

Accompanying lincomycin in *S. lincolnensis* fermentations is a small amount of the analogue 4′-depropyl-4′-ethyllincomycin [2520-24-3], $C_{17}H_{32}N_2O_6S$ (48), which has considerably lower antibacterial activity than the parent compound. Extension of the normal six-day fermentation to twelve days resulted in the formation of lincomycin sulfoxide [23444-78-2], $C_{18}H_{34}N_2O_7S$, and 1-demethylthio-1-hydroxylincomycin [22099-01-0], (lincomycose) $C_{17}H_{32}N_2O_7$, (**5**, R = CH_3, R″ = H, R = OH) (49), both of which have greatly reduced antibacterial activity. The addition of D,L-ethionine and of methyl α-thiolincosaminide, the sugar fragment of lincomycin, produces the *S*-ethyl analogue of lincomycin, [14042-43-4], $C_{19}H_{36}N_2O_6S$ (50, 51) and de-*N*-methyllincomycin [16843-70-2] (**5**, R = R′ = H, R″ = SCH_3), $C_{17}H_{32}N_2O_6S$, (52) respectively, whereas the addition of ethyl α-thiolincosaminide [6734-39-0], $C_{10}H_{21}NO_5S$, the sugar fragment of the *S*-ethyl analogue, produces the de-*N*-methyl-*S*-ethyl analogue (**5**, R = R′ = H, R″ = SC_2H_5), $C_{18}H_{34}N_2O_6S$ (50).

Rapid inactivation of added lincomycin was found to result from the growth of *Streptomyces rochei* in a synthetic medium; the antibiotic was converted into lincomycin 3-phosphate [23670-99-7] (**5**, R = CH_3, R′ = PO_3H_2, R″ = SCH_3), $C_{18}H_{35}N_2O_9PS$, readily cleaved back to the antibiotic upon treating with alkaline phosphatase (53).



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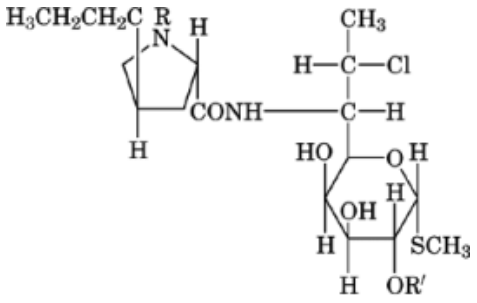


(**6**)

3. Clindamycin

Clindamycin, 7(*S*)-7-chloro-7-deoxylincomycin [18323-44-9], (**1**, R = H, R′ = Cl), also known as Cleocin, first resulted from the reaction of lincomycin and thionyl chloride (54); improved synthetic methods involve the reaction of lincomycin and triphenylphosphine dichloride or triphenylphosphine in carbon tetrachloride (55). Clindamycin is significantly more active than lincomycin against gram-positive bacteria *in vitro,* and is absorbed rapidly following oral administration. Clindamycin 2-palmitate [36688-78-5], (**6**, R = CH_3, R′ = $OC(CH_2)_{14}CH_3$), $C_{34}H_{63}ClN_2O_8S$, the 2-palmitate ester of clindamycin, is tasteless and antibacterially inactive. However, following oral administration, esterase cleavage occurs to give good blood levels of clindamycin (56), and this ester has been developed as a pediatric formulation of the antibiotic (Cleocin Pediatric). Given intramuscularly, clindamycin hydrochloride causes pain at the site of injection; the 2-phosphate ester (**6**, R = CH_3, R′ = PO_3H_2) (57) (Cleocin Phosphate), antibacterially inactive, is much better tolerated on injection, and is hydrolyzed by phosphatase, giving good levels of clindamycin.

3.1. Pharmacology and Uses

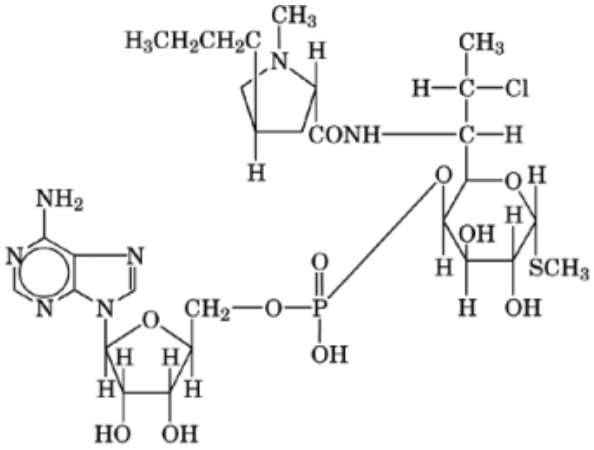
Oral administration of clindamycin hydrochloride gives peak serum levels of 1.9–2.7, 3.6, and 5.6 μg/mL one hour after single doses of 150, 300, and 450 mg, respectively. The half-life is 2.0–3.8 h (58–61). Clindamycin palmitate was also absorbed rapidly, following oral administration, but serum concentrations were lower than after clindamycin hydrochloride (58). Intramuscular injection of single 300, 450, and 600 mg doses of clindamycin phosphate gave mean peak serum levels of 3.8–4.9, 5.3, and 6.2–6.3 μg/mL respectively, 2–4 h after administration (59, 62, 63). Applied topically, clindamycin 2-phosphate [24729-96-2] (Cleocin T), $C_{18}H_{34}ClN_2O_8PS$, is effective in the treatment of acne vulgaris (64). Clindamycin, like lincomycin, is distributed widely in human body tissues, except that no significant levels are found in the brain or eye (38).

Antibacterial activity of clindamycin is found both in urine and feces after administration of clindamycin. This activity is a consequence of the presence of both clindamycin and its metabolite, de-*N*-methylclindamycin [22431-45-4] (**6**, R = R′ = H). Unlike de-*N*-methyllincomycin, the de-*N*-methyl analogue is as active *in vitro* as clindamycin. The analogue has been isolated from the urine of humans who had received clindamycin, and its presence in serum has been detected (65).

Clindamycin has found use in the treatment of common infections caused by gram-positive cocci. It is also efficacious in the treatment of anaerobic infections, including actinomycosis (38). Clindamycin has been shown to be active against strains of *Plasmodium* in animals (66–68).

4. Resistance to Clindamycin

Cross-resistance between lincomycin and clindamycin is complete (64), and co-resistances of lincomycin also apply to clindamycin. However, the inactivation of clindamycin by clinical isolates of *Staphylococcus haemolyticus* and *Staphylococcus aureus* is caused by adenylylation at the 4-position to form clindamycin 4-(5′-adenylate) [29752-38-3] (**7**) in contrast to the lincomycin 3-(5′-adenylate) [117785-83-8] (**8**) that forms (26).



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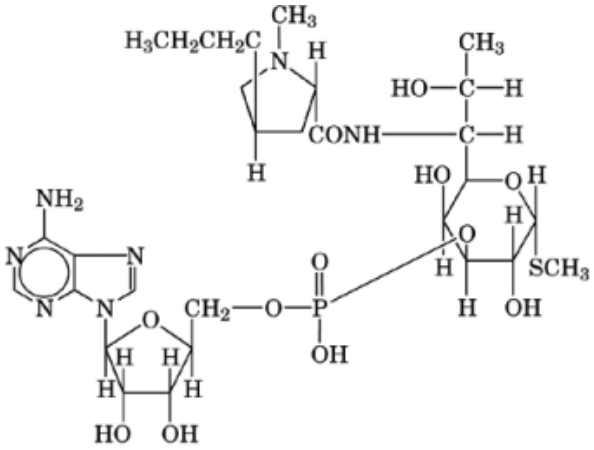


(**8**)

5. Biomodification of Clindamycin

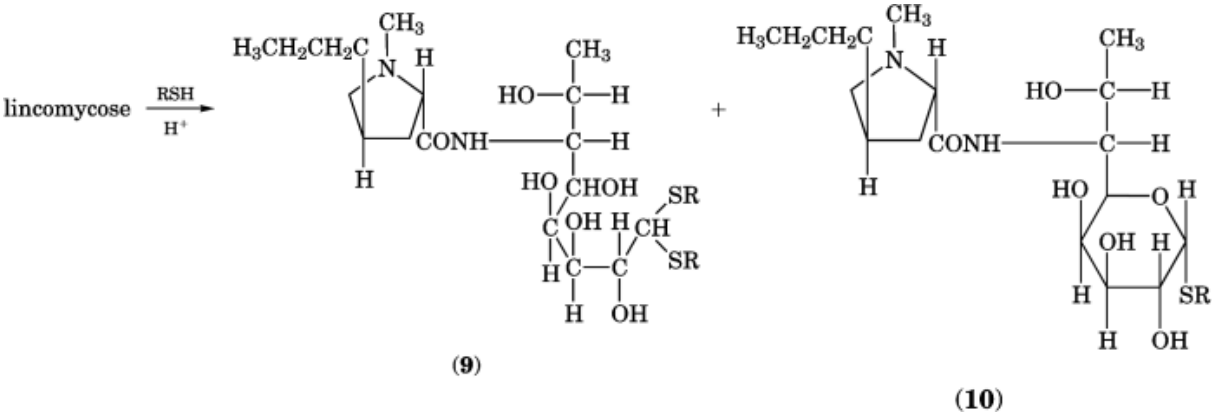
When added to fermentations of *Streptomyces punipalus*, clindamycin is converted into de-*N*-methylclindamycin (**6**, R = R′ = H). However, when clindamycin is incubated with *Streptomyces armentosus*, clindamycin sulfoxide [68366-52-9], $C_{18}H_{33}ClN_2O_6S$, which has low antibacterial activity, is formed (69). Clindamycin 3-phosphate [28708-34-1], antibacterially inactive *in vitro,* and the ribonucleotides clindamycin 3-(5′-cytidylate) [31186-90-0], clindamycin 3-(5′-adenylate) [31186-91-1], clindamycin 3-(5′-uridylate) [36010-69-2],

and clindamycin 3-(5′-guanylate) [36010-70-5], all inactive *in vitro,* can be generated (70). All of these derivatives protect mice infected with *Staphylococcus aureus*, however, presumably because of biotransformation into clindamycin (71–73).

6. Other Chemically Modified Lincosaminides

6.1. Modification of the Thioglycoside

Reaction of lincomycin (**1**, R = OH, R′ = H) and bromine in aqueous solution results in the replacement of the methylthio moiety with a hydroxy group producing lincomycose (**5**, R = CH_3, R′ = H, R = OH). Treatment of lincomycose with alkanethiols in the presence of strong acids affords a mixture of dialkyl dithioacetals (**9**) which are inactive and de-*S*-methyl-*S*-alkyllincomycins (**10**), which are equivalent to lincomycin in activity if the alkyl groups are small, but are less active when larger alkyl substituents are present (54). Inversion of the configuration of the methylthio-substituent from α- to β-results in the total loss of activity (74).



6.2. Modification of the Carbohydrate Ring Substituents

Replacement of lincomycin's 2-hydroxy group by methoxy or by hydrogen (74), or inversion of the configuration of the hydroxy group at C-4 or at C-2 destroys activity (75).

6.3. Modification of the Carbohydrate Side Chain

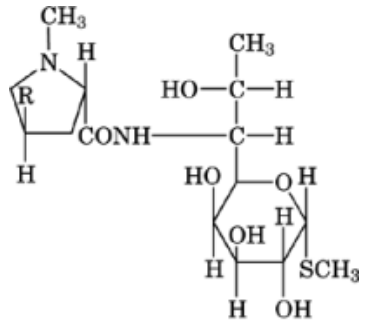
The importance to the antibacterial activity of the C-7 substituents in lincosaminides has been shown not only by the increased activity of the 7(*S*)-chloro-analogue, clindamycin, (**1**, R = H, R′ = Cl) and of the corresponding 7(*S*)-bromo-7-deoxylincomycin [18464-22-7] (**1**, R = H, R′ = Br), $C_{18}H_{33}BrN_2O_5S$, and iodo, $C_{18}H_{33}IN_2O_5S$ [26390-05-6] (**1**, R = H, R′ = I) analogues, but also by the minimal activity of 7-deoxylincomycin [72496-56-1] (**1**, R = R′ = H), $C_{18}H_{34}N_2O_5S$, and 7-deoxy-7-ketolincomycin [17057-59-9] (**1**, R = R′ = O), $C_{18}H_{32}N_2O_6S$, and the diminished activity of 7-epilincomycin [17017-22-0] (**1**, R = H, R′ = OH), $C_{18}H_{34}N_2O_6S$, and of the 7(*R*)-7-chloro-deoxylincomycin [78788-75-7] (**1**, R = Cl, R′ = H), $C_{18}H_{33}ClN_2O_5S$, derived from it (76). 7-*O*-Methyllincomycin [39679-82-8] (**1**, R = OCH_3, R′ = H), $C_{19}H_{36}N_2O_6S$, possesses somewhat enhanced activity (77) and the 7(*S*)-methoxy analogue (**1**, R = H, R′ = OCH_3) is significantly more active than lincomycin, albeit with the same spectrum of activity, but activity decreases rapidly as the size of the alkoxy-substituent increases (78).

Whereas introducing a thiol moiety at C-7 markedly reduced the antibacterial activity relative to lincomycin (79), the 7(*S*)-7-deoxy-7-alkylthiolincomycins exhibited considerably enhanced antibacterial activity without apparent regard for the size of the alkyl group (80–82). A marked increase in gram-negative activity was shown when the 7(*S*)-substituent contained a 2- or 3-hydroxy or amino group, but this activity was insufficient to be effective in infected mice (83–85).

6.4. Modification of the Proline Fragment

Besides the 4′-ethyl analogue of lincomycin, co-produced in fermentations of *S. lincolnensis* (48), other 4′-alkyl analogues were chemically synthesized. A peak of activity is reached with the *trans*-4′-pentyl and hexyl analogues (**11**), the cis-epimers (**12**) possessing about one-half of the activity of the trans-. Equivalent activities are shown by *N*-ethyl lincosaminides, but larger *N*-alkyl substituents show decreased activity (86).

Similar structure activity relationships were found in the 4′-alkyl analogues of clindamycin (87). The de-*N*-methylclindamycin intermediates including de-*N*-methylclindamycin itself, but unlike de-*N*-methyllincomycin, are also highly active antibacterially. In addition, they are active *in vivo* as antimalarial agents (66–68).



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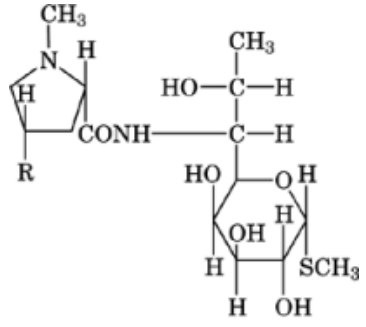

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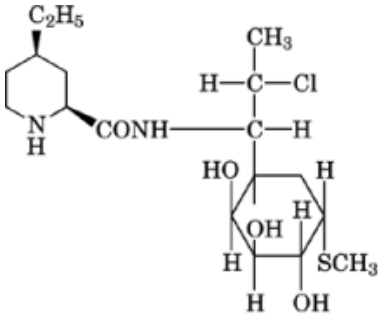

(13)

7. Other Changes in the Amino Acid Fragment

The influence of the size of the cyclic amino acid in analogues of clindamycin has been examined. The (2-(*S*)-*cis*)-4-ethylpipecolic acid analogue (6-ring), $C_{17}H_{31}ClN_2O_5S$, [78822-40-9] (**13**) was highly active both *in vitro* and *in vivo,* but the *cis*-(*R*)-isomer [80081-63-6] had minimal activity. Significant activity was shown for the azepine (7-ring) analogue, $C_{16}H_{29}ClN_2O_5S$, [88015-22-9], but the azetidine (4-ring) analogue, $C_{13}H_{23}ClN_2O_5S$ [88000-11-7], showed little activity (88).

7.1. Synthesis of the Carbohydrate Fragment of Lincomycin

The first formal synthesis of methyl α-thiolincosaminide started with D-galactose and was reported in 1970 (89). Other syntheses beginning with carbohydrates may also be found in the literature (90–96). Additionally, the total synthesis of methyl β-lincosaminide, albeit racemic, has been reported, utilizing the cyclocondensation of activated dienes and aldehydes, catalyzed by Lewis acids, to yield functionalized pyran rings (97). The synthesis of methyl 1-thio-α-lincosaminide from methyl α-D-galactopyranoside involving an elegant stereocontrolled introduction of the amino-alcohol substituents at C-6 and C-7 has also been reported (98).

8. Economic Aspects

It is estimated (99) that U.S. sales of clindamycin in 1989 were $45 million. Clindamycin was the seventh most widely used of all prescription products in U.S. hospitals (100). Figures are not available for worldwide sales of clindamycin, or for sales of lincomycin, which are virtually all outside the United States.

The composition of matter patents in the United States issued to The Upjohn Company on clindamycin phosphate and hydrochloride expired at the end of 1986 and in early 1987, respectively. Since then, these compounds have been available generically from more than two dozen companies in the United States alone (101, 102).

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