added at 0 to −5°. After stirring for 30 min, $MeNH_2$ was slowly bubbled for 3 hr in the mixture maintained from 0 to 5°.

The mixed anhydride, which had separated, slowly redissolved and the clear solution was allowed to stand overnight at room temperature and then evaporated. The residue was crystallized from EtOAc and weighed 1.25 g, mp 171–172°.

N,N-Dimethyl-2-nitro-5-ethyl-1-imidazoleacetamide (59). Method I. To a solution of 5 g of ethyl 2-nitro-5-ethylimidazoleacetate in 150 ml of MeOH, 68 g of Me_2NH was added. The mixture was heated 8 hr at 40° and, after one night at room temperature, refluxed for 6 hr. Evaporation of the solvent afforded an oily residue which solidified on standing. After crystallization (MeOH–i-Pr_2O) 3.5 g of yellow crystals was obtained, mp 94–95°.

1-Methyl-2-nitro-4-ethylimidazole and 1-Methyl-2-nitro-5-ethylimidazole (60–31). Method M. A suspension of 1.6 g of silver 4(5)-ethyl-2-nitroimidazole and 2 ml of CH_3I in 60 ml of Me_2CO was refluxed for 4 hr. The inorganic precipitate formed during the reaction was filtered off and the solution was evaporated to dryness. The oily residue on tlc (silica gel, Et_2O–petroleum ether (bp 30–50°) 1:1) showed one spot (R_f 0.1) corresponding to 1-methyl-5-ethyl-2-nitroimidazole and a further spot having R_f 0.2. The two products were separated through a 2 × 20 cm silica gel column eluted with petroleum ether containing increasing quantities of Et_2O. The fractions were pooled according to the analysis. Those containing the product having R_f 0.2 gave 780 mg of 1-methyl-2-nitro-4-ethylimidazole after recrystallization from i-Pr_2O, mp 49–50°. From those containing the compound having R_f 0.1 was obtained 195 mg of 1-methyl-2-nitro-5-ethylimidazole, identical with a sample prepared from 1-methyl-2-amino-5-ethylimidazole according to method G.

1-(2-Hydroxyethyl)-2-nitro-4-methylimidazole (61). Method M. To a suspension of 1.17 g of silver 4(5)-methyl-2-nitroimidazole, in 90 ml of $CH_3C_6H_5$, 0.5 ml of bromoethanol was added and the mixture was refluxed 7 hr under stirring. The inorganic salt was filtered off and the organic phase was evaporated. The residue was extracted several times with boiling H_2O and, after purification with charcoal, the solution was evaporated to an oily syrup which solidified on standing. By recrystallization from EtOAc was obtained 496 mg of yellow crystals, mp 121–125°.

Acknowledgment. We are greatly indebted to Dr. M. Serralunga for the toxicity determinations.

Lincomycin. VIII. 4′-Alkyl-1′-demethyl-4′-depropylclindamycins. Potent Antibacterial and Antimalarial Agents[1]

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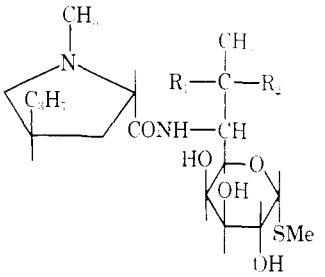
The preparation of methyl 7(*S*)-chloro-7-deoxythiolincosaminide (**4**) is described and evidence favoring the 7(*S*) configuration for the 7-chloro substituent is presented. This compound was used in the preparation of 4′-alkyl-1′-demethyl-4′-depropylclindamycins shown to be potent antibacterial and antimalarial agents.

Replacement of the 7(*R*)-hydroxyl group of lincomycin (**1**)[2] and of a number of its 4′-alkyl-4′-depropyl analogs[3] by chlorine afforded derived antibiotics which



1, R_1 = OH; R_2 = H
2, R_1 = H; R_2 = Cl

possessed enhanced antibacterial potency. As part of a program to delineate the potentiating effect of this substituent the synthesis of 1′-demethyllincomycin analogs containing a 7(*S*)-chloro-7-deoxy grouping was undertaken. The 7(*S*)-chloro substituent was introduced into lincomycin[2] and 4′-alkyl-4′-depropyllincomycin analogs by treatment of the parent antibiotic with $SOCl_2$.[3] This procedure was not applicable to the synthesis of certain types of chlorinated lincomycins, particularly those possessing reactive groups in the amino acid moiety. Maximum flexibility in analog synthesis appeared to be attainable by chlorination of methyl thiolincosaminide (MTL) (**3**), followed by condensation of the resulting chloro sugar (**4**) with an appropriately substituted proline derivative. To this end, our initial efforts were directed toward the synthesis of methyl 7(*S*)-chloro-7-deoxythiolincosaminide (**4**).

Although lincomycin can be cleaved with hydrazine hydrate to yield the sugar, methyl thiolincosaminide (**3**),[4] similar treatment of clindamycin[5] (**2**) did not afford the corresponding chloro sugar **4**. Therefore the direct introduction of Cl into methyl thiolincosaminide (**3**) was investigated. Treatment of **3** with excess triphenylphosphine dichloride in MeCN afforded a monochloro substituted product in 40% yield. Condensation of this product with *trans*-1-methyl-4-*n*-propyl-L-proline[6] yielded clindamycin (**2**) identical, both chemically and microbiologically, with that prepared from lincomycin (Chart I). This conversion indicated that the Cl in **4** was in the same position and configuration as the 7-Cl of clindamycin (**2**).

Since the configuration about the 7-carbon of clindamycin (**2**) was uncertain at the time that methyl 7-chloro-7-deoxythiolincosaminide (**4**) was first prepared, experiments were directed toward establishing the

(1) Presented in part at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 9–14, 1967, and at the Eleventh Medicinal Chemistry Symposium, Quebec, Canada, June 1968.

(2) (a) R. D. Birkenmeyer, Abstracts of Papers, Fifth Interscience Conference on Antimicrobial Agents and Chemotherapy and IVth International Congress of Chemotherapy, Washington, D. C., Oct 17–21, 1965, p 17; (b) R. D. Birkenmeyer and F. Kagan, to be published; (c) B. J. Magerlein, R. D. Birkenmeyer, and F. Kagan, *Antibacterial Agents Chemotherapy*, 727 (1966).

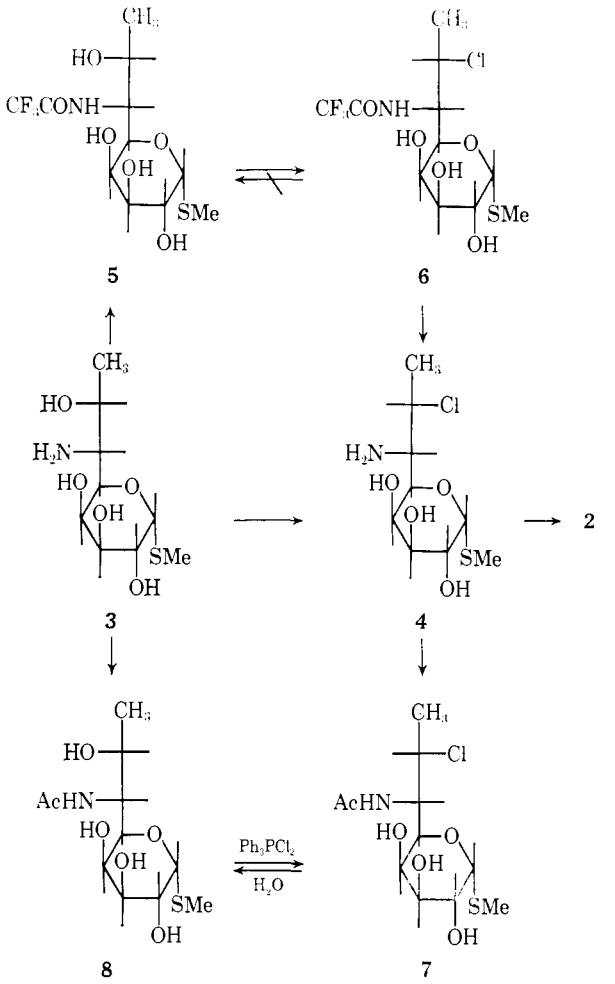
(3) B. J. Magerlein, R. D. Birkenmeyer, and F. Kagan, *J. Med. Chem.*, **10**, 355 (1967).

(4) W. Schroeder, B. Banister, and H. Hoeksema, *J. Am. Chem. Soc.*, **89**, 2448 (1967).

(5) Clindamycin is the generic name for 7(*S*)-chloro-7-deoxylincomycin.

(6) B. J. Magerlein, R. D. Birkenmeyer, R. R. Herr, and F. Kagan, *J. Am. Chem. Soc.*, **89**, 2459 (1967).

CHART I

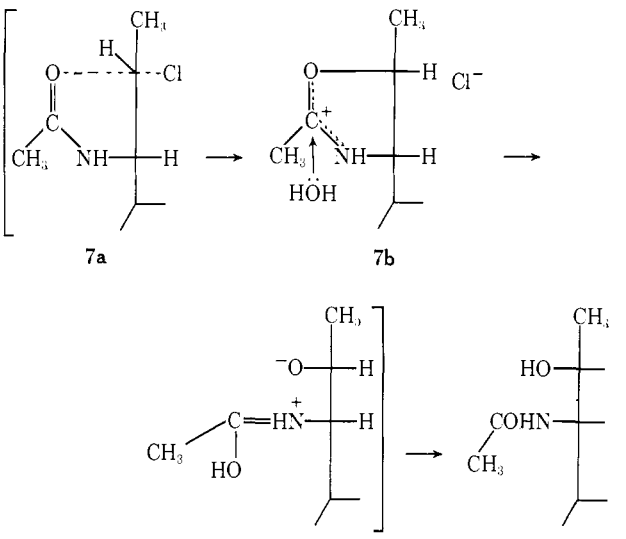


stereochemistry at C-7 for the chlorinated sugar. A consideration of the mechanism of chlorination of lincomycin must take into account the possibility of anchimeric assistance by the amide carbonyl group.[7] Although amide participation was not possible during the chlorination of methyl thiolincosaminide (**3**), participation of the amino N could not be ruled out. To obviate participation of the amino N during introduction of the 7-chloro group, MTL (**3**) was converted to the N-trifluoroacetate **5**. The trifluoroacetyl group is known to be a poor neighboring group in SN2 reactions[8] and, further, trihaloacetyl groups fail to play any role in "front-side participation" to form ortho acid derivatives.[9] The powerful electron-withdrawing property of the trifluoroacetyl group would make it highly unlikely that the N atom could act in a neighboring-group fashion.

Treatment of N-trifluoroacetate **5** with triphenylphosphine dichloride yielded the substituted chloro sugar **6**. When **6** was dissolved in dilute alkali the trifluoroacetyl group was removed affording methyl 7(*S*)-chloro-7-deoxythiolincosaminide (**4**) identical with that prepared by direct introduction of Cl into **3**. The configuration of the 7-Cl in **4**, prepared directly from **3** or by way of its trifluoroacetyl derivative, is the same as that in **2** prepared from lincomycin. Therefore we conclude that neither the amide carbonyl in lincomycin nor the amino N in methyl thiolincosaminide participated during the introduction of halogen. Since the replacement of OH by Cl using Rydon reagents[10] is known to proceed with inversion, except when anchimerically assisted by a neighboring group,[11] the 7-Cl substituent seemed likely to be introduced with inversion resulting in the 7(*S*) configuration.

Further chemical evidence in favor of the 7(*S*) configuration for **4** was obtained by solvolysis studies. After heating an aqueous solution of methyl N-acetyl-7(*S*)-chloro-7-deoxythiolincosaminide (**7**) under reflux for 5 hr, only 5% of **7** remained and methyl N-acetylthiolincosaminide (**8**) was isolated in about 50% yield. An unidentified product, possibly epimeric with **8** at C-7, was isolated in 7% yield. In contrast methyl N-trifluoroacetyl-7(*S*)-chloro-7-deoxythiolincosaminide (**6**) was recovered in 44% yield after refluxing in aqueous solution for 18 hr. No evidence of 7-OH compound **5** was noted by tlc. Since the solvolysis of **7** was much faster than that of **6** which contains the nonparticipating trifluoroacetyl group, we concluded that hydrolysis of N-acetyl-7(*S*)-chloro compound **7** was anchimerically assisted by the neighboring CO. The reaction very likely involves transition state **7a** and acetoxonium ion **7b**. The attack of this intermediate by water would be favored at the carbonyl carbon[12] to yield **8** as indicated.

These solvolysis studies therefore suggested that replacement of 7-Cl by OH was accompanied by inversion. Since the 7-OH of **8** has the same configuration



as does the 7-OH of lincomycin [*i.e.*, 7(*R*)] the Cl in **7** and accordingly in **4** and **2** must be in the 7(*S*) configuration.

While the chemical evidence presented above strongly suggested that the 7-Cl was introduced with inversion, subsequent degradation of clindamycin (**2**) showed unequivocally that inversion has occurred and the absolute configuration at C-7 was indeed (*S*).[2b]

We previously reported that 4′-alkyl-1′-demethyl-4′-depropyllincomycins possessed significant antibacterial

(7) For a detailed discussion of the mechanism of the chlorination of lincomycin see ref 2b.

(8) R. G. Strachan, W. V. Ruyle, T. Y. Shen, and R. Hirschmann, *J. Org. Chem.*, **31**, 507 (1966).

(9) R. Boschan and S. Winstein, *J. Am. Chem. Soc.*, **78**, 4921 (1956).

(10) S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, 2224 (1953).

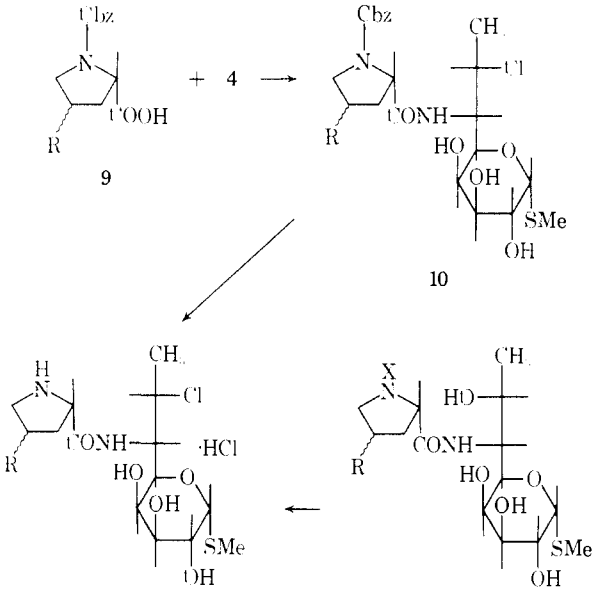
(11) (a) G. A. Wiley, B. M. Rein, and R. H. Hershkowitz, *Tetrahedron Letters*, 2509 (1964); (b) J. P. Schaefer and D. S. Weinberg, *J. Org. Chem.*, **30**, 2639 (1965).

(12) S. Winstein and R. Boschan, *J. Am. Chem. Soc.*, **72**, 4669 (1950).

activity.[3] These analogs were particularly interesting because they showed greater activity against streptococci than would be predicted on the basis of the standard curve assay. To assess the antibacterial activity of 1′-demethyllincomycin analogs in the clindamycin series, **4** was condensed with a variety of 4-substituted prolines. The preparation of 1′-demethylclindamycin (**11b**) was further stimulated by the isolation of a polar metabolite from the urine of humans treated orally with clindamycin.[13] Preparation of **11b** afforded material which could not be separated from the urinary metabolite by tlc.[13]

In the initial step of the synthesis of 4′-alkyl-1′-demethyl-4′-depropylclindamycin (Chart II), **4** was

CHART II



11a. R = C_2H_5
b. R = *n*-C_3H_7 (*cis-trans*)
c. R = *n*-C_3H_7 (*trans*)
d. R = *n*-C_4H_9 (*cis-trans*)
e. R = *n*-C_5H_{11} (*cis-trans*)
f. R = *n*-C_6H_{13} (*cis-trans*)
g. R = *n*-C_7H_{15} (*cis-trans*)

12. R = C_3H_{11} (*cis-trans*): X = H; HCl salt
13. R = C_3H_7 (*trans*): X = H; HCl salt
14. R = C_3H_7 (*trans*): X = Cbz

condensed with the appropriate 1-carbobenzoxy-4-alkyl-L-proline (**9**)[3] to form **10** (see Table I). Hydrogenolysis of the carbobenzoxy group led to the isolation of 1′-demethylclindamycin analog **11** as a mixture of isomers at 4′. The compounds thus prepared are given in Table II. Since separation of the isomers was difficult, the mixture of approximately 70% *cis* and 30% *trans* isomers was used for microbiological testing. An alternate method was also investigated in which Cl was introduced into 1′-demethyllincomycins **12** and **13**[3] at the final step. In this manner the *trans* isomer **11c** was prepared from 1′-demethyllincomycin **13**.[14] The preparation of **11c** from **13** by way of the 1′-carbobenzoxy derivative **14** did not improve the over-all yield.

Antimicrobial Activities.—The antibacterial activity of lincomycin analogs is markedly lowered when Me on the amino acid N atom is replaced by H, *e.g.*, 1′-demethyllincomycin shows only 2% of the antimicrobial activity of lincomycin. In sharp contrast, clindamycin analogs containing H on the amino acid N atom showed unexpectedly high antibacterial activities compared to their 1′-Me congenors. A summary of the antibacterial activities of the 1′-demethylclindamycins (**11**) is presented in Table III. The compounds were tested against *Sarcina lutea*, *Staphylococcus aureus* OSU284, *S. aureus* UC552, *Streptococcus faecalis* UC3235, *Escherichia coli* ATCC28, *Proteus vulgaris* ATCC8427, *Salmonella schottmuelleri*, and *Diplococcus pneumoniae* I. These data show that antimicrobial potency increases with the chain length of the 4′-alkyl substituent, reaching a maximum when the 4′-alkyl group is pentyl. This behavior is similar to that observed in the 4′-alkyl-4′-depropyllincomycins;[3] however, the *in vitro* data for the 1′-demethylclindamycins (Table III) more closely parallel *in vitro* potencies than in the lincomycin series.

Evaluation of the chlorinated lincomycin analogs against *Plasmodium berghei* infected mice produced surprising results[15] (*cf.* Table IV). Whereas lincomycin was essentially inactive, 1′-demethyl-7(*S*)-chloro analogs demonstrated potent antimalarial activity, several having CD_{50}'s comparable to chloroquine and dimethyldiphenyl sulfone (DDS) and in this assay. Antimalarial potency appeared to closely follow *in vitro* antibacterial potency. 1′-Demethyl-4′-depropyl-4′-pentylclindamycin (**11e**) also showed good activity against chloroquine-resistant and DDS-resistant strains of mouse malaria.[15] Antimalarial activities of 1′-demethyl-4′-depropyl-4′-pentylclindamycin and clindamycin *vs. Plasmodium cynomolgi* in monkeys will be published shortly.[16]

Experimental Section[17]

Methyl 7(*S*)-Chloro-7-deoxylincosaminide (4).—To a solution of 393 g of $(C_6H_5)_3P$ in 3 l. of anhydrous MeCN was added 105 g of Cl_2 keeping the temperature at less than 40° by cooling. Methyl thiolincosaminide (101 g) was added. After stirring at 26° for 24 hr, 200 ml of MeOH was added. The solution was concentrated under vacuum. The residue was partitioned between $CHCl_3$ and H_2O. The aqueous solution was adjusted to pH 5.2 by the addition of $KHCO_3$ and extracted with $CHCl_3$. The addition of KOH to pH 9 precipitated crude **4**. The crystals were collected by filtration and dried. Recrystallized from 95% EtOH yielded 31.6 g (29.2%) of **4**, mp 171–178°. A second crop of 11.7 g (10.8%) of **4**, mp 164–173°, was obtained by concentrating the mother liquors. Recrystallization of a portion of first crop crystals afforded an analytical sample, mp 177–180°, $[\alpha]D$ +348° (DMSO). *Anal.* ($C_9H_{18}ClNO_4S$) C, H, Cl, N, S.

Methyl N-Trifluoroacetylthiolincosaminide (5).—To a suspension of 25.3 g of methyl thiolincosaminide (**3**) in 250 ml of MeCN, 16.5 ml of Et_3N, and 25.25 ml of trifluoroacetic anhydride were added simultaneously with stirring and cooling. After 24 hr at 26° the solvent was removed under vacuum. The residue was dissolved in EtOAc, washed successively with dilute acid and 5% $NaHCO_3$ solution, and dried. A red oil (20 g) was obtained on concentration. This oil was dissolved in 100 ml of MeOH and a few drops of Et_3N was added. After 18 hr at 26° the solvent was

(13) T. F. Brodasky, A. D. Argoudelis, and T. E. Eble, *J. Antibiot.* (Tokyo), **21**, 327 (1968).

(14) A. D. Argoudelis, J. A. Fox, and D. J. Mason, *Biochemistry*, **4**, 710 (1965).

(15) C. Lewis, *J. Parasitol.*, **54**, 169 (1968).

(16) L. H. Schmidt, J. Harrison, E. Ellison, and P. Worcester, *Am. J. Trop. Med. Hyg.*, in press.

(17) Melting points were taken in a Thomas–Hoover Unimelt apparatus and are corrected for stem exposure. Tlc was carried out on microslides coated with Brinkman silica gel GF_{254}. Column chromatography employed silica gel 0.05–0.20 mm for chromatography, Brinkman Instruments, Inc., Westbury, L. I., N. Y. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements are within ±0.4% of the theoretical values. Absorption bands of spectra (ir, nmr) were as expected for all compounds.

TABLE I
4′-ALKYL-1′-CARBOBENZOXY-4′-DEPROPYLCLINDAMYCINS (10)

R	Yield, %	Mp, °C	Formula	Analyses
C_2H_5			$C_{24}H_{35}ClN_2O_7S$	C, H, N
n-C_3H_7		189–192	$C_{25}H_{37}ClN_2O_7S$	C, H, N, Cl
n-C_4H_9	55	185–187	$C_{26}H_{39}ClN_2O_7S$	C, H, N
n-C_6H_{13}	72	185–187	$C_{28}H_{43}ClN_2O_7S$	C, H, N
n-C_8H_{17}	31	175–177	$C_{30}H_{47}ClN_2O_7S$	*a*

[a] Tlc data on two systems showed one spot moving as expected. No elemental analyses were obtained.

TABLE II
4′-ALKYL-1′-DEMETHYL-4′-DEPROPYLCLINDAMYCINS (11)

R	Yield, %	Mp, °C	$[\alpha]_D$, deg (H_2O)	Formula	Analyses
C_2H_5 (*cis-trans*)		240–242	+159	$C_{16}H_{30}Cl_2N_2O_5S$	C, H
C_3H_7 (*cis-trans*)	82	228–234	+159	$C_{17}H_{32}Cl_2N_2O_5S$	C, H, N
n-C_3H_7 (*trans*)[a]	41	217–221	+155	$C_{17}H_{32}Cl_2N_2O_5S$	C, H, N, S
n-C_4H_9 (*cis-trans*)	58	207–209	+134[b]	$C_{18}H_{34}ClN_2O_5S$	N, S, mol wt
n-C_5H_{11} (*cis-trans*)[a]	28	222–223	+139	$C_{19}H_{36}Cl_2N_2O_5S$	C, H, N, S
n-C_6H_{13} (*cis-trans*)	62	219-221	+142	$C_{20}H_{38}Cl_2N_2O_5S$	C, H, Cl, N, S
n-C_8H_{17} (*cis-trans*)	62	201-203		$C_{22}H_{42}Cl_2N_2O_5S$	*c*

[a] Prepared by chlorination of the corresponding lincomycin analog. [b] MeOH. [c] See footnote *a*, Table I.

TABLE III
ANTIBACTERIAL ACTIVITIES OF 4′-ALKYL-1′-DEMETHYL-4′-DEPROPYLCLINDAMYCIN HYDROCHLORIDES (11)

Compd	Std curve assay with *S. lutea*[a]	Serial dilution minimal inhibitory concentration[b] *S. aureus* OSU284	*S. aureus* UC552[c]	*S. faecalis* UC3235	*E. coli* ATCC28	*P. vulgaris* ATCC8427	*S. schottmuelleri* ATCC9149	Mouse protection assay[d] *S. aureus* Sc	*S. aureus* Oral	*D. pneumoniae I* Sc	*D. pneumoniae I* Oral
Lincomycin	1	0.4	0.8	12.5	400	800	4000	1	1	1	1
11a	0.9	0.2	0.2	3.2	200	200	>200	2.8	1.0		
11b	3–5	0.05	0.1	1.6	50	100	50	5.8	3.5	15.1	13.9
11c	4–7	0.05	0.1	3.2	25	50	50	4.0	2.3	11.4	7.5
11d	5	0.05	0.05	1.6	12.5	12.5	12.5	4.0	2.3		
11e	4	0.025	0.025	0.05	12.5	50	12.5	4.0	3.0	19.6	18.8
11f	1.8	0.025	0.025	0.05	25	200	50	3.7	2.5		
11g	0.1	0.05	0.025	3.2	12.5	>200	25		0.2		

[a] L. J. Hanka, D. J. Mason, M. R. Burch, and R. W. Treick, *Antimicrobial Agents Chemotherapy*, 565 (1962). [b] Determinations made in Brain Heart Infusion medium (Difco). Inocula consisted of about 10^5 organisms/ml of medium. Twofold dilutions of the antibiotic were used in each sensitivity determination. End points were read at 20 hr and are expressed in minimal inhibitory concentration of compound in μg/ml. [c] Organism resistant to penicillin, streptomycin, tetracycline, and erythromycin. [d] Method of C. Lewis, H. W. Clapp, and J. E. Grady, *Antimicrobial Agents Chemotherapy*, 570 (1962).

TABLE IV
ANTIMALARIAL ACTIVITY OF 4′-ALKYL-1′-DEMETHYL-4′-DEPROPYLCLINDAMYCIN HYDROCHLORIDES (11) IN *Plasmodium berghei* INFECTED MICE[a]

Compd	CD_{50},[b] mg/kg Sc	Oral
Lincomycin	>160	>400
11a	47	
11b	19	37
11c	16	28
11d	3.7	
11e	4.7	12
11f	6.6	14
11g	36	
Chloroquine	8.1	14
DDS	25	58

[a] The authors are indebted to C. E. Lewis of these laboratories for the use of the data. [b] CD_{50} is median protective dose (95% limits).

distilled *in vacuo* and the residue was chromatographed over silica gel. A fraction of 12.7 g, which was eluted with $CHCl_3$–MeOH (4:1), was crystallized from MeCN–Et_2O. The yield of **5**, mp 144–146°, was 7.0 g (20.0%). A portion, recrystallized twice from MeCN, melted at 146–147°, $[\alpha]_D$ +240° (DMSO). *Anal.* ($C_{11}H_{18}F_3NO_6S$) C, H, F, N.

Methyl N-Trifluoroacetyl-7(*S*)-chloro-7-deoxythiolincosaminide (6).—Six grams of **5** was halogenated with $(C_6H_5)_3PCl_2$ prepared from 10.6 g of Cl_2 and 40.8 g of $(C_6H_5)_3P$ in 375 ml of MeCN. The crude product was chromatographed twice over silica gel using $CHCl_3$–MeOH (6:1) for elution to give 4.8 g of oily **6** which was crystallized from *i*-C_3H_7OH. The yield of **6**, mp 78–85° (solvated), was 2.18 g (34.5%). A portion was recrystallized from *i*-PrOH. It melted at 66–72° (solvated) and showed $[\alpha]_D$ +239° (DMSO). *Anal.* ($C_{11}H_{17}ClF_3NO_5S$) C, H, F, N.

Methyl 7(*S*)-Chloro-7-deoxythiolincosaminide (4) from Methyl N-Trifluoroacetyl-7(*S*)-chloro-7-deoxythiolincosaminide (6).—One gram of **6** was dissolved in 5 ml of 1 *N* NaOH. After 1 hr at room temperature crystals formed which were collected and dried. These crystals, mp 170–173°, weighed 670 mg (90.4%). One recrystallization raised the melting point to 173–179°. The optical rotation was $[\alpha]_D$ +361° (DMSO). Ir and nmr data confirmed this compound as **4**.

Clindamycin Hydrochloride (2) from Methyl 7(*S*)-Chloro-7-deoxythiolincosaminide (4).—4-*n*-Propylhygric acid (915 mg) was condensed with 1.09 g of **4**.[6] Tlc on silica gel using $CHCl_3$–MeOH (4:1) and EtOAc–$AcCH_3$–H_2O (8:5:1) showed that the major component of the reaction mixture moved with clindamycin (**2**), both when run separately or mixed with known **2**. Bioautograph *vs. S. lutea* was also identical with **2**.

Chromatography over silica gel using $CHCl_3$–MeOH (7:1) for elution gave a major fraction, 380 mg, of clindamycin (**2**) identified by tlc. Conversion to the HCl salt followed by recrystallization gave 180 mg of **2**, mp 158–160°, whose infrared curve was identical with that of a known sample of clindamycin hydrochloride (**2**).

Methyl N-Acetyl-7(*S*)-chloro-7-deoxylincosaminide (7).—Acylation of 1 g of methyl 7(*S*)-chloro-7-deoxylincosaminide (**4**) with Ac_2O in MeOH gave after recrystallization from EtOAc–Skellysolve B[18] 930 mg of **7**, mp 174–176°. The rotation was +290° (MeOH). *Anal.* ($C_{21}H_{39}ClO_8NS$) C, H, Cl, N.

Solvolysis of Methyl N-Acetyl-7(*S*)-chloro-7-deoxythiolincosaminide (7).—A solution of 2.0 g of **7** in 80 ml of H_2O was heated at reflux for 5.5 hr. Tlc ($CHCl_3$–MeOH, 4:1) showed the gradual disappearance of **7**, with two slower spots gradually increasing in concentration. The solution was lyophilized. The residue was chromatographed over silica gel using $CHCl_3$–MeOH (4:1) for elution. A fraction of 110 mg, identified by tlc as **7**, was eluted in the early fractions. This was followed by a 155-mg and a 1.06-g fraction, respectively. Crystallization of the major fraction from MeOH gave 470 mg of crude **8**, mp 222–226°. Recrystallization afforded 360 mg of crystals, mp 235–238°, whose infrared spectrum was identical with a known sample of **8**.[4] In another experiment, a fraction similar to the 155-mg fraction from above gave a product, mp 178–182°, whose infrared spectrum was very similar to that of **8** suggesting the 7(*S*) isomer.

Attempted Solvolysis of Methyl N-Trifluoroacetyl-7(*S*)-chloro-7-deoxythiolincosaminide (6).—A solution of 500 mg of **6** in 30 ml of H_2O was heated under reflux for 18 hr. Tlc ($CHCl_3$–MeOH, 6:1) indicated chiefly unreacted **6**, and also a small amount of a slower moving spot, but no 7-hydroxy compound **5**. When worked up as above 220 mg of recovered **6** and 55 mg of a more polar oil which resisted crystallization were obtained. Crystallization from *i*-PrOH afforded 110 mg of **6**, mp 72–81°. Ir data confirmed the identity of **6**.

1′-Carbobenzoxy-1′-demethylclindamycin (*cis-trans*) (10, R = *n*-C_3H_7).—1-Carbobenzoxy-4-(*cis* and *trans*)-*n*-propyl-L-proline[6] (2.33 g) was dissolved in 150 ml of MeCN containing 1.12 ml of Et_3N. The solution was cooled to 0° and 1.18 ml of isobutyl chloroformate added. After 10 min at 0°, a solution of 2.17 g of **4** in 40 ml of MeCN and 40 ml of H_2O was added. The mixture was stirred for 2 hr at ambient temperature and the MeCN distilled *in vacuo* to yield crystals which were collected by filtration. The yield of **10**, mp 180–183°, was 3.36 g. Recrystallization (EtOH) raised the melting point to 189–192°. *Anal.* ($C_{25}H_{37}ClN_2O_7S$) C, H, Cl, N.

1-Carbobenzoxy-1′-demethylclindamycin (14).—1′-Demethyllincomycin hydrochloride (428 mg) was treated with carbobenzyloxy chloride[19] to yield 500 mg of **14**, mp 152–163°. Recrystallization (EtOAc–H_2O) gave 350 mg of **14**, mp 173–177°. Two recrystallizations from the same solvent afforded crystals, mp 176–178°, $[\alpha]D$ +109°. *Anal.* ($C_{33}H_{38}N_2O_9S$) C, H, N.

1′-Demethylclindamycin (*cis* and *trans*) Hydrochloride (11b).—A solution of 22.9 g of **10** was dissolved in 500 ml of MeOH and 6 g of 10% Pd–C was added. Hydrogenolysis and crystallization was as previously described.[2] The yield of **11b**, mp 218–223° dec, was 15.8 g (80.2%). Recrystallization (AcMe–H_2O) afforded 10.7 g of **11b**, mp 228–234° dec, $[\alpha]D$ +159° (H_2O). Further dilution with AcMe gave 2.96 g of second crop crystals, mp 226–230° dec.

1′-Demethyl-4′-depropyl-4′-pentylclindamycin (11e).—Triphenylphosphine (22 g) in 400 ml of MeCN was treated with 5.68 g of Cl_2 to produce a colorless solution of $(C_6H_5)_3PCl_2$. To this solution 4 g of 1′-demethyl-4′-depropyl-4′-pentyllincomycin hydrochloride (**12**)[6] was added. After stirring at 26° for 18 hr, 15 ml of MeOH was added and the solvent distilled *in vacuo*. The residue was shaken with 250 ml of EtOAc–Et_2O (1:1) and filtered. The residue (13.7 g) was partitioned between H_2O and EtOAc and the product was recovered from the aqueous solution by lyophilizing. This residue of 8.5 g was further purified by chromatography over silica gel using $CHCl_3$–MeOH (4:1) for elution. The major fraction of 2.09 g was dissolved in AcMe and acidified with HCl to give analytically pure **11e**, mp 222–223°. *Anal.* ($C_{19}H_{36}Cl_2N_2O_5S$) C, H, N, S.

1′-Demethylclindamycin Hydrochloride (11c). Method A.—1′-Demethyllincomycin hydrochloride (**3**) (1.72 g) was chlorinated as above to give hydrochloride **11c**, mp 212–216°, weighing 0.73 g (40.8%). Recrystallization (AcMe–H_2O) gave 550 mg of hydrochloride, mp 217–221° dec, $[\alpha]D$ +155° (H_2O). *Anal.* ($C_{17}H_{32}Cl_2N_2O_5S$) C, H, N, S.

Method B.—One gram of **14** was chlorinated and subjected to hydrogenolysis; after chromatography it gave 103 mg of **11c**. This product was converted to its crystalline hydrochloride and identified on the basis of tlc data. It melted at 227–229° and weighed 95 mg.

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(18) A saturated hydrocarbon fraction, bp 60–71°, Skelly Oil Co., Kansas City, Mo.

(19) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 2, John Wiley and Sons, Inc., N. Y., 1961, p 891.

The Preparation and Antimycotic Properties of Derivatives of 1-Phenethylimidazole

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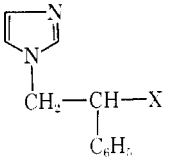
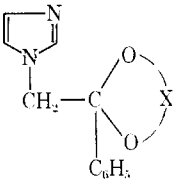
The synthesis of a large number of β-substituted 1-phenethylimidazoles is described. Many appropriately N-substituted 1-(β-aminophenethyl)imidazoles and cyclic ketals derived from 2-(1-imidazolyl)acetophenones were quite active against dermatophytes. However, 1-(β-benzyloxyphenethyl)imidazoles displayed potent, broad-spectrum activity, not only against dermatophytes but also against yeast cells (*Candida albicans*) and gram-positive bacteria.

For some years interest in our laboratories has been directed toward the synthesis and biological evaluation of imidazole derivatives.[1,2] As part of this program we prepared a series of 1-phenethylimidazoles, when it became apparent that certain O- and N-substituted derivatives of α-phenylimidazole-1-ethanol (A, X = OH) and 1-(β-aminophenethyl)imidazole (A, X = NH_2), respectively, displayed outstanding and broad-spectrum antimycotic activity. This observation



A, X = OH, NH_2



B, X = alkylene

(1) E. F. Godefroi, P. A. J. Janssen, C. A. M. Van der Eycken, A. H. M. T. Van Heertum, and C. J. E. Niemegeers, *J. Med. Chem.*, **8**, 220 (1965).

(2) E. F. Godefroi, J. van Cutsem, C. A. M. Van der Eycken, and P. A. J. Janssen, *ibid.*, **10**, 1160 (1967).