tions, except that the sublimtation of the crude product required a longer time (2 days, 60° oil bath) and the sublimate was recrystallized from Et_2O–low boiling petr ether; 25% yield; mp 87.5–89°. *Anal.* ($C_{16}H_7NBrF$) C, H, N.

General Procedure for Preparation of Urea and Thiourea Derivatives of 3-Aminoisoquinolines 22, 23, 24.—The urea derivatives were prepared by condensation of the 3-aminoisoquinolines with the corresponding isocyanates and isothiocyanates in warm C_6H_6 solutions (several days). The yields (purified) were 85% for **22**, 61% for **23**, and 30% for **24**. Recrystallization solvents and elements analyzed are given in Table I.

General Procedure for Preparation of Sulfonamides of 3-Aminoisoquinolines.—The sulfonamides **18**, **20**, and **21** were obtained by heating at *ca.* 90° the aminoisoquinolines with the corresponding sulfonyl chlorides in pyridine. The yields of purified materials were 59% for **18**, 90% for **20**, and 55% for **21**. The acetamide **20** was deacetylated in a refluxing (30 min) mixture of EtOH-conc HCl (5:1) for 30 min and the sulfanilamide **19** was isolated in *ca.* 60% yield as the free base.

***N*-(3-Isoquinolyl)crotonamide (15).**—In an attempt to aminate *N*-(3-isoquinolyl)-3-chlorobutyramide[4] with excess of *N*,*N*-dimethyl-*N'*-ethylethylenediamine in refluxing $CHCl_3$ only the elimination product *N*-(3-isoquinolyl)crotonamide was isolated (48%), mp 150–152° (Table I).

***N*-(3-Isoquinolyl)acrylamide (14).**—This compound was isolated as the elimination product of *N*-(3-isoquinolyl)-3-chloropropionamide[4] with PhNHMe in refluxing $CHCl_3$ in the presence of Na_2CO_3 (Table I).

3-Benzamidoisoquinolines.—*N*-(3-Isoquinolyl)benzamide (**16**) and *N*-(3-isoquinolyl)-3-nitrobenzamide (**17**) were obtained in fair yields by the reactions of 3-aminoquinoline with the appropriate benzoyl chlorides in refluxing C_6H_6 (Table I).

Lincomycin. XI. Synthesis and Structure of Clindamycin.[1] a Potent Antibacterial Agent[2]

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Several processes for preparing clindamycin·HCl (**4a**) are described and evidence is presented indicating that the chloro substituent is in the 7(*S*) configuration. This compound and its 7-Br and 7-I analogs (**4c**, **4d**) are potent antibacterial agents.

The structure of the antibiotic lincomycin·HCl (**1a**) and the spectrum of its antibacterial activity were described in previous communications from this laboratory.[3,4] As part of a continuing program on the chemical modification of lincomycin directed toward the examination of structure–activity relationships,[5] the preparation of a halogen-containing analog was initiated.

Treatment of lincomycin·HCl (**1a**) with $SOCl_2$ in CCl_4 at room temperature afforded a product which was assigned the 3,4-cyclic sulfite structure (**2a**) on the basis of its elemental and spectral analyses and its facile regeneration of lincomycin on alcoholysis. Both the *in vitro* and *in vivo* assays of antibacterial activity of **2a** were equivalent to those of **1a**. Formation of the cyclic sulfite is not unexpected in view of the *cis* relationship of the C-3 and C-4 OH groups and the ease of formation of other similar cyclic derivatives such as the isopropylidene ketal **2b** and the cyclic carbonate **2c**.[6]

Further treatment of **2a** with $SOCl_2$ in boiling CCl_4 yielded chlorinated products **3** and **5**. Structure assignments were made on the basis of elemental and spectral analyses and quantitative conversion by alcoholysis to clindamycin (**4a**).[1] Evidence for the structure **4a** was provided by its elemental and spectral analyses, the ir spectrum clearly showing the presence of amide I and amide II absorptions similar to those observed in lincomycin.[3] The position of the Cl atom is **4a** was inferred from the downfield shift in the 60-MHz nmr spectrum of the doublet attributable to the hydrogens of the terminal Me (C-8). In lincomycin (**1a**) these C-8 hydrogens are recognizable by the doublet they produce at 66 and 73 Hz. In the chlorinated product **4a** these absorptions are shifted downfield to 84 and 91 Hz, as expected if the C-7 OH group were replaced by Cl.[7] When a Br or I atom was substituted for OH, the downfield shift of the C-8 Me doublet was greater, appearing at 94 and 101 Hz for **4c** and 108–115 Hz for **4d**. With the exception of the C-8 Me shift, the nmr spectra of the monohalolincomycins were essentially the same as that of lincomycin.

The configuration of the OH at C-7 in lincomycin was previously established as 7(*R*) and the sugar side chain (C-6 and C-7) as D-*erythro*.[3] When epilincomycin·HCl (**1b**) (OH at C-7 in the S configuration, side chain D-*threo*)[8] was treated with $SOCl_2$ under the conditions cited, a new monochlorolincomycin was formed. This compound was less mobile on tlc than **4a** and exhibited about 0.5 the antibacterial activity of **4a**. Since the elemental and spectral data were essentially the same as that obtained for clindamycin·HCl (**4a**), we

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

(2) A preliminary announcement of a portion of this work was presented earlier: R. D. Birkenmeyer, B. J. Magerlein, and F. Kagan, Fifth Interscience Conference on Antimicrobial Agents and Chemotherapy and Fourth International Congress of Chemotherapy, Oct 17–21, 1965, Washington, D. C.

(3) (a) H. Hoeksema, B. Bannister, R. D. Birkenmeyer, F. Kagan, B. J. Magerlein, F. A. MacKellar, W. S. Schroeder, G. Slomp, and R. R. Herr, *J. Amer. Chem. Soc.*, **86**, 4223 (1964); (b) R. R. Herr and G. Slomp, *ibid.*, **89**, 2444 (1967); (c) W. Schroeder, B. Bannister, and H. Hoeksema, *ibid.*, **89**, 2448; (d) G. Slomp and F. MacKellar, *ibid.*, **89**, 2454; (e) B. J. Magerlein, R. D. Birkenmeyer, R. R. Herr, and F. Kagan, *ibid.*, **89**, 2459.

(4) (a) D. J. Mason, A. Dietz, and C. DeBoer, *Antimicrob. Ag. Chemother.*, 554 (1962); (b) R. R. Herr and M. E. Bergy, *ibid.*, 560; (c) L. J. Hanka, D. J. Mason, M. R. Burch, and R. W. Treick, *ibid.*, 565; (d) C. N. Lewis, H. W. Clapp, and J. E. Grady, *ibid.*, 570.

(5) (a) B. J. Magerlein, R. D. Birkenmeyer, and F. Kagan, *J. Med. Chem.*, **10**, 355 (1967); (b) B. J. Magerlein, *ibid.*, **10**, 1161; (c) B. J. Magerlein and F. Kagan, *ibid.*, **12**, 780 (1969).

(6) (a) W. Schroeder, U. S. Patent 3,264,282 (1966); (b) R. D. Birkenmeyer, U. S. Patent 3,284,438 (1966).

(7) R. H. Bible, Interpretation of NMR Spectra, Plenum Publishing Co., New York, N. Y., 1965, p 16.

(8) H. Hoeksema, Abstracts of Papers, 149th National Meeting of the American Chemical Society, Detroit, Mich., 1965, p 9c.

concluded that this compound, **4b**, was the C-7 epimer of **4a**. Treatment of lincomycin·HCl (**1a**) or epilincomycin·HCl (**1b**) with $SOCl_2$ in CCl_4 resulted in a highly stereospecific reaction. If more than one 7-Cl product was formed during the reaction, the amount was too small to be detected by tlc in solvent systems which easily separate the epimers.

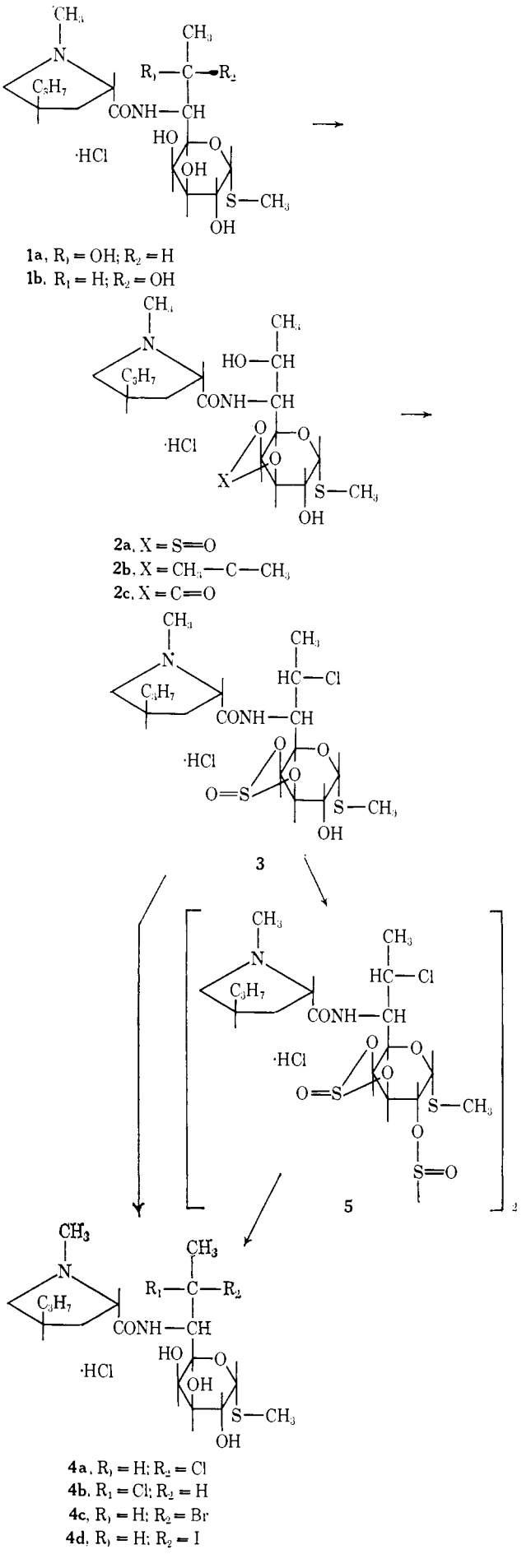
An alternate method for the preparation of **4a** involved the use of triphenylphosphine dichloride. The halogenation of alcohols with triphenylphosphite methiodide and related compounds[9] is known to proceed with inversion of configuration except when anchimerically assisted by a neighboring group.[10] Similar results were obtained when these reagents were used to halogenate various carbohydrates.[11] The related triphenylphosphine dihalides are also reported to halogenate optically active alcohols with net inversion of configuration.[12] When lincomycin·HCl (**1a**) was treated with triphenylphosphine dichloride, a monochlorinated product was isolated which was identical with **4a**. This result implied that chlorination of **1a** by $SOCl_2$ occurred with inversion of configuration.

A third route to the preparation of **4a** involved the use of triphenylphosphine and CCl_4, a procedure which is also known to chlorinate alcohols with inversion of configuration.[13] The product obtained when **1a** was chlorinated by this method was identical with **4a**. This result strengthened our belief that chlorination of lincomycin·HCl (**1a**), under the conditions described, occurred with inversion of configuration at C-7. Support for this hypothesis was obtained by chemical degradation.

Another paper in this series describes the cleavage of **1a** into two major components, 4′-*n*-propylhygric acid (**6**) and methyl α-thiolincosaminide (**7**) (MTL).[14] Magerlein and Kagan have chlorinated **7** *via* the triphenylphosphine–carbon tetrachloride procedure to yield 7-chloro-MTL (**8**) which upon coupling with **6** gave material identical with **4a**.[15]

These authors described chemical evidence which strongly suggested the 7(*S*)-Cl configuration for **4a** and **8**. Unequivocal evidence defining the configuration of the Cl substituent in **4a** and **8** was obtained by conversion of **8** into the dimethylmercaptal **9**, followed by oxidation of this material with periodate–permanganate.[16] An acidic fragment isolated from this reaction was identified as L-chloropropionic acid (**10**). A comparison of its optical rotation with those reported in the literature for D- and L-chloropropionic acid as well as with that of an authentic sample of L-chloropropionic acid prepared from L-alanine led to the assignment of the L configuration for **10**. Since the configuration of the OH at C-7 in **1a** is known to be D or 7(*R*), it follows that chlorination of **1a** by any of the three methods

SCHEME I



(9) (a) S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, 2224 (1953); (b) D. G. Coe, S. R. Landauer, and H. N. Rydon, *ibid.*, 2281 (1954); H. N. Rydon and B. L. Tonge, *ibid.*, 3043 (1956).

(10) J. P. Schaefer and D. S. Weinberg, *J. Org. Chem.*, **30**, 2635, 2639 (1965).

(11) N. K. Kochetkov and A. I. Usov, *Tetrahedron*, **19**, 973 (1963).

(12) (a) G. A. Wiley, R. I. Hershkowitz, R. B. Rein, and B. C. Chung, *J. Amer. Chem. Soc.*, **86**, 964 (1964); G. A. Wiley, B. J. Rein, and R. L. Hershkowitz, *Tetrahedron Lett.*, **36**, 2509 (1964).

(13) (a) J. B. Lee and I. M. Downie, *Tetrahedron*, **23**, 359 (1967); (b) D. Brett, I. M. Downie, and J. B. Lee, *J. Org. Chem.*, **32**, 855 (1967).

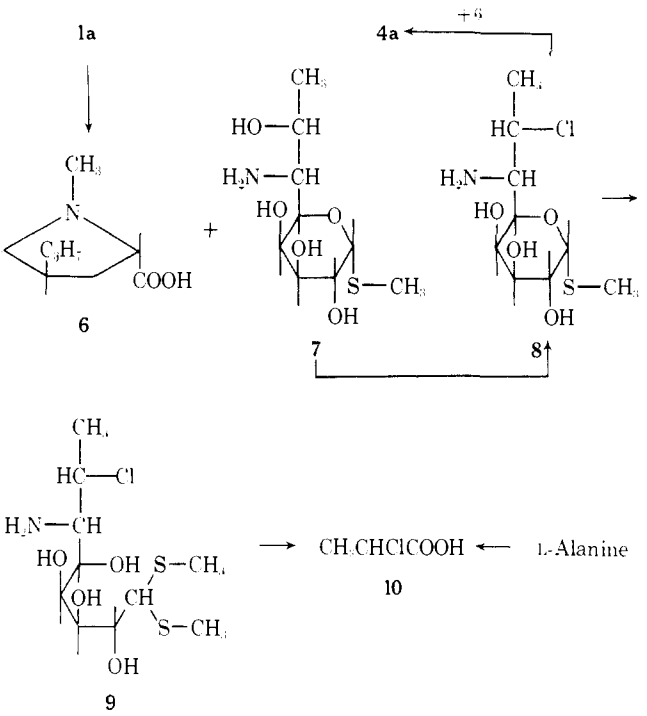
(14) W. Schroeder, B. Bannister, and H. Hoeksema, *J. Amer. Chem. Soc.*, **89**, 2448 (1967).

(15) B. J. Magerlein and F. Kagan, *J. Med. Chem.*, **12**, 780 (1969).

(16) R. V. Lemieux and E. vonRudloff, *Can. J. Chem.*, **33**, 1711 (1955).

described proceeds with inversion of configuration to produce 7(*S*)-chloro-7-deoxylincomycin hydrochloride (**4a**). Subsequent to this work, confirmation of the structure of **4a** was obtained by X-ray crystallography.[17]

The 7-Br and 7-I analogs, **4c** and **4d**, were prepared *via* the triphenylphosphine-CX_4 procedure using MeCN as a solvent. The 7-Br analog **4c** was also prepared by the triphenylphosphine dihalide route.



Lit. α^{25}D −18.2° (neat)[18]

found: α^{25}D −18 (neat)

Biological Activities.—Replacement of the C-7 OH of lincomycin (**1a**) by a halogen has a profound influence on the *in vitro* antibacterial activity of the molecule. A summary of the effect of this substitution is presented in Table I. Note that while in the C-7 OH series the 7(*R*) configuration **1a** is more potent than the 7(*S*) **1b,** this relationship is reversed when the OH is replaced by Cl. In the latter case, the 7(*S*)-Cl compound **4a** is significantly more potent *in vitro* and *in vivo* than its 7(*R*) epimer **4b.** The toxicity of the 7(*S*) epimer **4a** is of low order, the oral LD_{50} in rats being >5000 mg/kg of body weight.[19] The 7-Br and 7-I analogs, **4c** and **4d**, also exhibit enhanced antibacterial activity of the same order of magnitude as **4a**. Of special interest is the marked increase in inhibitory activity for Gram-negative organisms apparent in the 7-Cl analog **4a**. This compound, when tested against *Escherichia coli*, has inhibitory activity 16 times greater than that of the parent antibiotic and in the case of the 7-iodo analog **4d** this activity is increased by a factor of 32. Further testing of clindamycin (**4a**) revealed that the lipid solubility of the molecule also was greatly increased.[20] When administered orally to human subjects, clindamycin (**4a**) was absorbed much more rapidly than the parent compound, giving peak blood levels in about 30 min. In contrast to many antibiotics, this extremely fast absorption is not affected to a significant degree by the presence of food in the gastrointestinal tract.

Clindamycin (**4a**) and derivatives thereof may be useful as antiplasmodial agents. When tested *in vivo* against the rodent malaria parasite *Plasmodium berghei* and the simian parasite *P. cynomolgi* these compounds demonstrated significant activity.[21] This therapeutic activity persisted even when strains of *P. berghei* were used which were resistant to the maximum tolerated doses of antimalarial agents such as chloroquine, pyrimethamine, primaquine, and quinine.

Extensive testing in animals and humans indicated that C-7 halosubstitution of lincomycin significantly alters the parameters of biological activity of the parent compound. In the case of clindamycin (**4a**) the potency is enhanced, the spectrum of antibacterial activity is broadened, the efficiency of absorption increased and an entirely new type of biological action, antiplasmodial activity, is generated.

Experimental Section[22]

Lincomycin 3,4-*O*-Cyclic Sulfite (2a).—To a suspension of 221 g of lincomycin·HCl (**1a**) in 5 l. of CCl_4 was added 900 ml of $SOCl_2$. After stirring at 25° for 2 hr, a 25-ml portion of the reaction was poured into 200 ml of Et_2O. The solid precipitate was collected by filtration and after drying weighed 1.0 g. *Anal.* ($C_{18}H_{32}N_2O_5S_2$·HCl) C, H, N, S; Cl: calcd 7.25; found 7.71.

Bis[clindamycin 3,4-*O*-cyclic sulfite] Sulfite (5) and Clindamycin 3,4-*O*-Cyclic Sulfite (3).—The reaction mixture present in the preparation of **2a** was heated at reflux for 2 hr and then concd under vacuum at a temp of about 35° to 2 l. The yellow solid ppt was collected and dried. A portion of this material was chromatographed over silica gel using $CHCl_3$–MeOH (9:1) for elution. An early fraction contained material which crystallized upon evaporation of the solvent. Recrystallization from EtOH gave a few milligrams of the free base of **5**, mp 184–186°. *Anal.* ($C_{36}H_{60}Cl_2N_4O_{13}S_3$) C, H, Cl, S; N: calcd 5.67; found, 5.25. Later fractions of the chromatogram contained a second material which was the free base of **3**, [α]D +171° ($CHCl_3$). *Anal.* ($C_{18}H_{31}ClN_2O_6S_2$) C, H, Cl, N; S: calcd 13.61; found, 13.20.

Clindamycin (4a) *via* $SOCl_2$ Route. First Procedure.—The yellow solid obtained in the preparation of **3** and **5** was dissolved in 300 ml of MeOH, adjusted to pH 11 with 2 *N* NaOH solution and 1.5 l. of H_2O was added. Extraction with Et_2O and evaporation of the extracts yielded an amorphous solid. Conversion into the HCl salt followed by crystallization from EtOH–EtOAc gave 74 g (32%) of **4a**; mp 141–143°, [α]D +144° (H_2O). *Anal.* ($C_{18}H_{34}Cl_2N_2O_5S$) C, H, Cl, N, S. A portion of the amorphous solid was crystallized from EtOH–H_2O to give the free base of

(17) D. J. Duchamp, Abstracts of the American Crystallography Association Meeting, Summer Meeting, Aug 20–25, 1967, Minneapolis, Minn., Paper D5.

(18) S. J. Fox, S. M. Birnbaum, and J. P. Greenstein, *J. Amer. Chem. Soc.*, **76**, 6051 (1954).

(19) B. J. Magerlein, R. D. Birkenmeyer, and F. Kagan, *Antimicrob. Ag. Chemother.*, 727 (1967).

(20) (a) H. P. Fletcher, 134th Meeting, American Association for the Advancement of Science, New York, N. Y., Dec. 1967; (b) J. G. Wagner, E. Novak, N. C. Patel, C. G. Chidester, and W. L. Lummis, *Amer. J. Med. Sci.*, **256**, 25 (1968).

(21) (a) C. Lewis, *J. Parasitol.*, **54**, 1875 (1968); (b) C. Lewis, *Antimicrob. Ag. Chemother.*, 537 (1967); (c) K. G. Powers, *Amer. J. Trop. Med. Hyg.*, **18**, 485 (1969).

(22) Tlc was carried out on microslides coated with Brinkman silica gel GF. Column chromatography employed silica gel 0.05–0.20 mm for chromatography, Brinkman Instruments, Inc., Westbury, Long Island, 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. Since lincomycin and its analogs and derivatives are prone to hydration, the water content of all the described compounds was determined by Karl Fischer titration and the appropriate correction applied to the found elemental analyses. The corrected values are reported. Nmr spectra were obtained on a Varian A-60A spectrometer using D_2O as the solvent for the HCl salts and $CDCl_3$ for the free bases. Absorption bands of spectra (ir, nmr) were as expected for all compounds.

TABLE I

ANTIBACTERIAL ACTIVITIES OF 7-HALO-7-DEOXYLINCOMYCIN HYDROCHLORIDES

	Standard curve assay	Serial dilution minimal inhibitory concentration[b]						Mouse protection assay[d]	
		Staphylococcus aureus	*Staphylococcus aureus*	*Streptococcus faecalis*	*Escherichia coli*	*Proteus vulgaris*	*Salmonella schottmeulleri*	*Staphylococcus aureus*	
Compd	*Sarcina lutea* ATCC 9341[a]	OSU 284	UC 552[c]	UC 3235	ATCC 26	ATCC 8427	ATCC 9149	Subcutaneous	Oral
1a	1	0.4	0.8	12.5	400	800	4000	1.0	1.0
1b	0.5	0.8	1.6	25.0	>200	>200	>200	0.4	0.8
4a	4	0.1	0.1	6.2	25	250	64	1.0	1.3
4b	2	0.4	0.8	12.5	>200	>200	>200	0.4	0.5
4c	4	0.05	0.05	6.2	100	100	50	0.9	1.5
4d	4–5	0.05	0.05	3.2	12.5	50	50		

[a] L. J. Hanka, D. J. Mason, M. R. Burch, and R. W. Treick, *Antimicrob. Ag. Chemother.*, 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. Endpoints were read at 20 hr and are expressed in minimal inhibitory concentration of compound in micrograms per milliliter. [c] Organism resistant to penicillin, streptomycin, tetracycline, and erythromycin. [d] Method of C. Lewis, H. W. Clapp, and J. E. Grady, *Antimicrob. Ag. Chemother.*, 570 (1962).

4a; $[\alpha]_D$ +214° ($CHCl_3$). *Anal.* ($C_{18}H_{33}ClN_2O_5S$) C, H, Cl, N, S.

Clindamycin (4a) *via* $(C_6H_5)_3PCl_2$ Route. Second Procedure.—To a solution of 26.3 g of $(C_6H_5)_3P$ in 400 ml of MeCN was added 7.09 g of Cl_2 keeping the temp at about 30° by cooling. Lincomycin (4.06 g) was added. After stirring at 25° for 3 hr, 100 ml of MeOH was added and the solution concd to dryness under vacuum. The residue was partitioned between Et_2O and H_2O. The H_2O phase was made basic with 2 *N* NaOH solution and extracted with $CHCl_3$ and the extract concd to dryness under vacuum. The residue was chromatographed over silica gel using $CHCl_3$–MeOH (9:1) for elution. The major fraction contained 3.1 g of the free base (73% yield) which was converted into the HCl salt and crystallized from EtOH–EtOAc to give material identical with **4a** prepared by the $SOCl_2$ procedure.

Clindamycin (4a) *via* $(C_6H_5)_3PCCl_4$ Route. Third Procedure.—A solution of 50 g of lincomycin·HCl (**1a**), 120 g of $(C_6H_5)_3P$, and 500 ml of MeCN was cooled at 20° and 500 ml of CCl_4 was added. After stirring at 25° for 18 hr the reaction was concd to dryness under vacuum. The residue was shaken with 200 ml of H_2O for 2 hr and filtered and the solid, $(C_6H_5)_3PO$, was discarded. The filtrate was adjusted to pH 11 with 6 *N* NaOH solution and extracted with $CHCl_3$. The extracts were concd to dryness under vacuum, the residue dissolved in 200 ml of MeOH and heated at reflux for 1 hr. The MeOH was distd under vacuum and 100 ml of H_2O and 10 ml of 37% HCl were added to the residue. After shaking for 1 hr the mixture was filtered and the solid material discarded [more $(C_6H_5)_3PO$]. The filtrate was extracted with CCl_4 and the extracts discarded. The H_2O phase was adjusted to pH 11 with 6 *N* NaOH solution and extracted with $CHCl_3$. The extract was concd to dryness under vacuum, the residue converted into the HCl salt and crystallized from EtOH–EtOAc to give 35 g, (67%), of material identical with **4a** prepared by the $SOCl_2$ and $(C_6H_5)_3PCl$ procedures.

7(*R*)-Chloro-7-deoxylincomycin Hydrochloride (4b).—Epilincomycin·HCl (**1b**) was chlorinated *via* the $SOCl_2$ procedure to give a 29% yield of **4b**; $[\alpha]_D$ +122° (H_2O), mp 164–166°. *Anal.* ($C_{18}H_{34}Cl_2N_2O_5S$) C, H, Cl, N, S.

7-Bromo-7-deoxylincomycin Hydrochloride (4c).—Lincomycin·HCl was brominated by substituting $(C_6H_5)_3PBr_2$ for $(C_6H_5)_3PCl_2$ in the second procedure described for the preparation of **4a**. A 30% yield of **4c** $[\alpha]_D$ +130° (H_2O), mp 137–139° was obtained. *Anal.* ($C_{18}H_{34}ClBrN_2O_5S$) C, H, Cl, Br, N, S. By substituting CBr_4 for CCl_4 in the third procedure described for the preparation of **4a**, a 36% yield of product was obtained. This material was identical with **4c** obtained *via* the $(C_6H_5)_3PBr_2$ procedure.

7-Iodo-7-deoxylincomycin Hydrochloride (4d).—By substituting CI_4 for CCl_4 in the third procedure described for the preparation of **4a**, a 0.5% yield of **4d** was obtained. Although no elemental analytical data were obtained for this compound, its behavior upon tlc and the nmr spectrum and mass spectrum fragmentation patterns were consistent with the proposed structure.

Dimethyl Mercaptal of 7(*S*)-Chloro-7-deoxy-α-methylthiolincosaminide (9).—A mixture of 71 g of 7-chloro-MTL (**7**), 750 ml of 37% HCl, and 350 g of MeSH was stirred at 0° for 6 hr. H_2O (2 l.) was added and the reaction extracted well with Skellysolve B. The H_2O phase was adjusted to pH 11 by the addition of KOH pellets. A ppt formed which was collected, dried, and recrystd from MeOH to give 62 g (73%) of **9**; mp 122–124°, $[\alpha]_D$ +2° (DMF). *Anal.* ($C_{10}H_{22}ClNO_4S$) C, H, Cl, N; S: calcd 20.05; found, 19.53.

L-α-Chloropropionic Acid (10).—To a solution of 300 g of $NaIO_4$, 32 g of $KMnO_4$, and 21 g of K_2CO_3 dissolved in 1 l. of H_2O and stirred at 25° was added 16.8 g of **9**. Additional K_2CO_3 was added as necessary to keep the reaction at pH 7 to 7.5. After 18 hr the reaction was adjusted to pH 3 by the addition of concd H_2SO_4 and then extracted with Et_2O. The extracts were concd under vacuum and the residue distd through a 15-cm Vigreux column. Two grams (35%) of product **10** [bp 90–91° (15 mm), $[\alpha]_D$ −18° (neat); reported −18.2° (neat)[18]] was obtained. *Anal.* (C_3H_5CClO) C, H, Cl.

Alcoholysis of 2a, 3, and 5.—Treatment of **2a**, **3**, and **5** with aq base or hot MeOH resulted in the quantitative removal of the sulfite functions and regeneration of the alcohol.

Acknowledgments.—The authors are indebted to D. J. Mason and C. Lewis for the antibacterial assays.