and 25 g of phenol was heated and stirred on a steam bath for 4 hr. After cooling, the mixture was treated with 100 ml of Me_2CO containing 10 ml of concentrated HCl, and the resulting precipitate was collected by filtration. Two recrystallizations from *i*-PrOH gave 2.3 g (24%) of 6-chloro-2-methoxy-9-(piperidinoamino)acridine monohydrochloride (VIIIf) as a bright yellow powder, mp 204–206° dec.

4,4′-(1,4-Piperazinediyldiimino)bis(7-chloroquinoline) (VII).—A mixture of 19.8 g (0.10 mole) of 4,7-dichloroquinoline and 5.8 g (0.050 mole) of 1,4-diaminopiperazine[9] was heated in 50 g of phenol for 4 hr on a steam bath. Excess concentrated HCl was added, and the mixture was poured into 3 l. of Me_2CO. Trituration with fresh Me_2CO, then with Et_2O, gave 9.2 g of yellow solid, mp >300°. This was dissolved in H_2O, and the solution was made alkaline with NaOH. The resulting precipitate was collected by filtration, washed well with H_2O, and dried at 65° *in vacuo* to give 2.5 g (11%) of a pale yellow solid, mp >310°. *Anal.* ($C_{22}H_{20}Cl_2N_6$) C, H, N.

9,9′-(1,4-Piperazinediyldiimino)bis(6-chloro-2-methoxyacridine) (IX).—A mixture of 9.3 g (0.080 mole) of 1,4-diaminopiperazine,[9] 49.0 g (0.18 mole) of 6,9-dichloro-2-methoxyacridine, and 220 g of phenol was heated on a steam bath for 4 hr. Excess concentrated HCl was added, and the mixture was diluted with 1.5 l. of Me_2CO. The resulting precipitate was collected by filtration and washed with Me_2CO. The crude hydrochloride was suspended in H_2O, excess NaOH was added, and the resulting base was extracted into warm EtOAc. Upon standing, crystals were deposited. These were collected by filtration, washed successively with hot 75% EtOH and Me_2CO, and dried at 60° *in vacuo* to give 26.5 g (55%) of yellow-orange crystals, mp 251°. *Anal.* ($C_{32}H_{28}Cl_2N_6O_2$) H, N; C: calcd, 64.10; found, 63.68.

7-Chloro-4-{[2-(dimethylamino)ethoxy]amino}quinoline Dihydrochloride (XIIa).—A mixture of 9.9 g (0.05 mole) of 4,7-dichloroquinoline, 8.9 g (0.05 mole) of 2-(dimethylamino)-ethoxyamine dihydrochloride,[12] and 25 g of phenol was stirred and heated on a steam bath for 4 hr. The resulting brown solution was cooled and poured into Me_2CO. The gummy product which formed solidified on standing and was dried *in vacuo*. Crystallization from *i*-PrOH afforded 5.9 g (33%) of product, mp 213–216° dec. *Anal.* ($C_{13}H_{16}ClN_3O \cdot 2HCl \cdot 0.75H_2O$) C, H, N, H_2O.

7-Chloro-4-{[2-(diethylamino)ethoxy]amino}quinoline (XIIb).—A solution of 50.0 g (0.25 mole) of 4,7-dichloroquinoline and 37.0 g (0.28 mole) of 2-(diethylamino)ethoxyamine[13] in 500 ml of EtOH containing 65 ml (3 equiv) of concentrated HCl was heated under reflux for 8 hr. Volatile materials were removed *in vacuo*, and the residue was dissolved in H_2O, overlaid with $CHCl_3$, and made basic with aqueous NaOH. The $CHCl_3$ layer was separated, dried (K_2CO_3), and concentrated to dryness *in vacuo*. The residue was dissolved in EtOH and diluted with 2 l. of H_2O. The solid which formed was collected and crystallized from hexane to give 17.0 g, mp 69–76°. This material was recrystallized twice from a mixture of *i*-Pr_2O–heptane. The solid was then dissolved in dilute HCl and the pH was adjusted to 6.0 with NaOH. A small amount of solid which formed was removed and discarded. The filtrate was brought to pH 8.0, and the yellow solid was collected by filtration. Recrystallization from hexane gave 13.0 g (17%) of the product, mp 76–82°. *Anal.* ($C_{15}H_{20}ClN_3O \cdot H_2O$) C, H, N, H_2O; Cl: calcd, 11.37; found, 11.84.

6-Chloro-9-{[2-(dimethylamino)ethoxy]amino}-2-methoxyacridine (XIII).—A mixture of 13.9 g (0.05 mole) of 6,9-dichloro-2-methoxyacridine and 8.9 g of 2-(dimethylamino)ethoxyamine dihydrochloride[12] in 50 g of phenol was heated on a steam bath for 5 hr. The cooled solution was poured into Me_2CO to give a brownish solid which was collected by filtration and dried. The crude material was crystallized twice from MeOH. This procedure did not provide a completely pure material. The solid was then dissolved in H_2O, filtered to remove a small amount of insoluble material, and made basic with NH_4OH. The resulting yellow solid was collected and recrystallized from MeCN to give 1.9 g (11%) of the product, mp 155–157°. *Anal.* ($C_{18}H_{20}ClN_3O_2$) C, H, N.

Acknowledgments.—The authors express their appreciation to Mr. Carl Youngstrom for chemical assistance, and to Dr. Paul E. Thompson and coworkers of these laboratories for the antimalarial and antischistosomal evaluation of these substances. We also thank Dr. J. M. Vandenbelt and coworkers for the spectral studies and Mr. Charles E. Childs and associates for the microanalyses.

Lincomycin. IX. 7-Thiol and Thioamido Analogs of Lincomycin[1]

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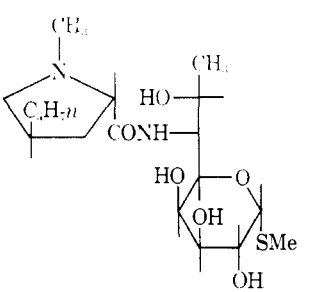
7-Deoxy-7(*R*)- and -7(*S*)-thiolincomycin (**10** and **15**) were prepared from methyl thiolincosaminide, a degradation product of lincomycin. Thioamido analogs (**18** and **20**) were prepared from lincomycin (**1**) and clindamycin (**16**), respectively. The 7-thiol analogs possessed slight antibacterial activity, while the thioamido analogs were about one-fourth as active as the antibiotic from which they were derived.

Potentiation of antibacterial activity of lincomycin (**1**) was achieved by a variety of chemical modifications.[2] Introduction of halogen at C-7, preferably in the 7(*S*) configuration, enhanced the *in vitro* and *in vivo* antibacterial activity in several series of analogs.[3] This substituent is also primarily responsible for the antimalarial activity encountered in 1′-demethylclindamycins.[3b,4] Introduction of other substituents at C-7 was therefore undertaken. The preparation and antibacterial activity of 7-thiol analogs of lincomycin are now described. In addition to the introduction of sulfur into the critical 7 position of lincomycin, replacement of the oxygen of the amide carbonyl by sulfur was also accomplished in both the lincomycin and clindamycin series.



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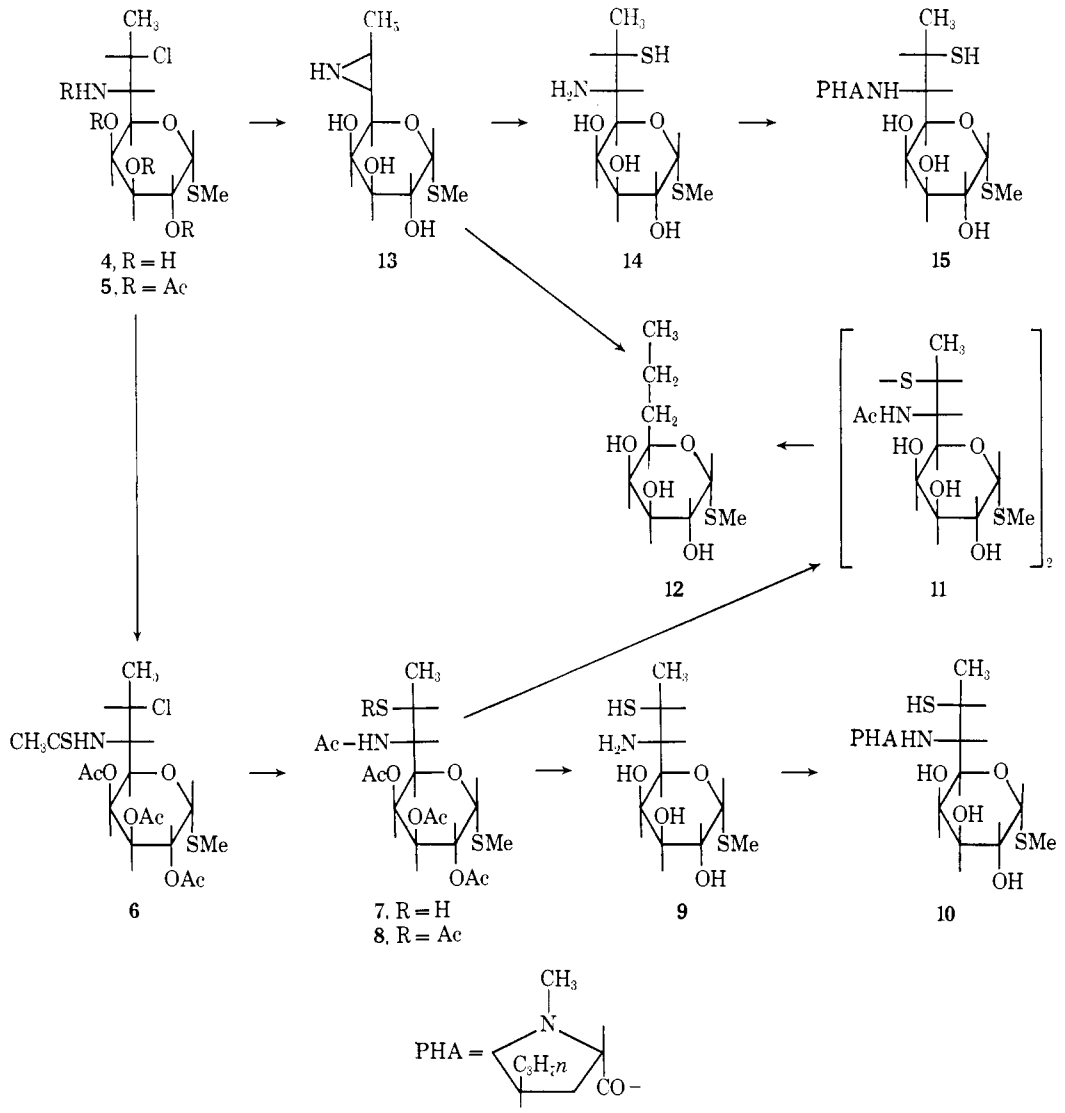
(1) Presented in part at the 11th Medicinal Chemistry Symposium, Quebec, Canada, June 1968.

(2) B. J. Magerlein, R. D. Birkenmeyer, and F. Kagan, *Antimicrobial Agents Chemotherapy—1966*, 727 (1967).

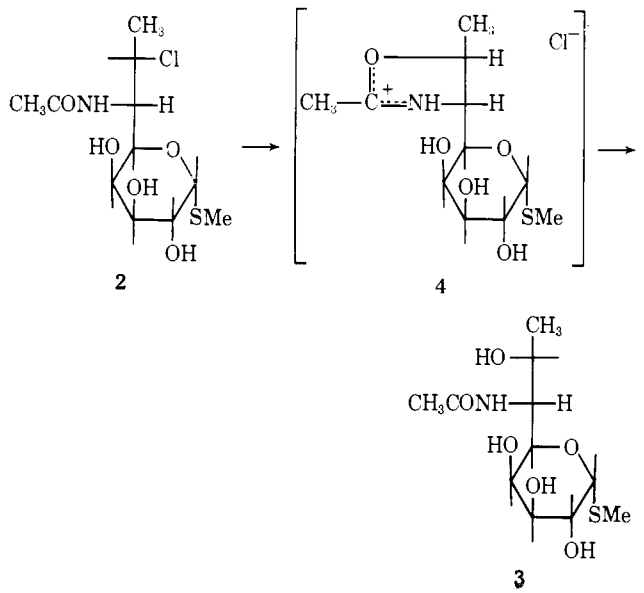
(3) (a) B. J. Magerlein, R. D. Birkenmeyer, and F. Kagan, *J. Med. Chem.*, **10**, 355 (1967); (b) B. J. Magerlein and F. Kagan, *ibid.*, **12**, 780 (1969).

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

CHART I



In a previous paper in this series[3b] solvolysis of methyl N-acetyl-7-deoxy-7(*S*)-chlorothiolincosaminide (**2**) to methyl N-acetylthiolincosaminide (**3**) was shown to be anchimerically assisted by the amide carbonyl and we suggested that the reaction proceeded through oxazolonium (**4**). Since the oxygen of the amide carbonyl is postulated to transfer to C-7 with inversion during this reaction, solvolysis of a 7-deoxy-(*S*)-chlorothioamide should result in the introduction of a 7(*R*)-thio substituent at C-7. To test this hypothesis (*cf.* Chart I) methyl 7-deoxy-7(*S*)-chlorothiolincosaminide tetraacetate (**5**) was converted to thioamide **6** in good yield by treatment with P_4S_{10}. Solvolysis in aqueous DMF afforded the predicted product, methyl 7-deoxy-7(*R*)-thiolthiolincosaminide tetraacetate (**7**). Structural assignment of **7** was made on the basis of elemental analysis and nmr and mass spectral data.



Deacylation of **7** to the amino sugar **9** with hydrazine hydrate required milder conditions than employed in the cleavage of lincomycin;[5] however, greater difficulty was encountered in the purification of the product **9**. More vigorous hydrazinolysis conditions led to the formation of a mixture of products accompanied in part by loss of hydrogen sulfide. In one attempt to circumvent this problem, thio sugar **7** was oxidized to disulfide **11** which was then treated with hydrazine hydrate. From the resulting mixture a reduction product, whose structure is formulated as **12**, was isolated in low yield.

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

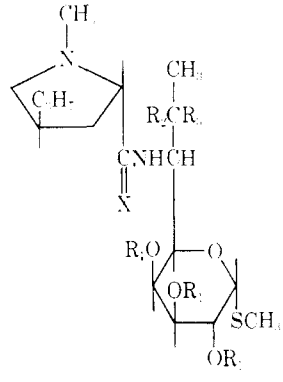
This compound was identical with a sample prepared by an independent synthesis, *vide infra*.

Methyl 7-deoxy-7(*R*)-thiothiolincosaminide (**9**) was condensed with *trans*-4-*n*-propylhygric acid[6] to afford 7-deoxy-7(*R*)-thiolincomycin which possessed spectral and elemental analyses in accord with the assigned structure.

When treated with base under anhydrous conditions, methyl 7-deoxy-7(*S*)-chlorothiolincosaminide (**4**) was readily dehydrohalogenated. On the basis of nmr data and acylation to a tetracetate, the 7(*R*)-aziridine structure (**13**) was assigned to the product. The addition of H_2S to 7(*R*)-aziridine (**13**) led to the formation of 7-(*S*)-thio sugar **14** in good yield. The conversion of this sugar to 7-deoxy-7(*S*)-thiolincomycin (**15**) was accomplished in the same manner as described for the 7(*R*) isomer.

Deamination of aziridine **13** with nitrous acid[7] followed by catalytic hydrogenation gave **12** which was identical with **12** isolated from the hydrazinolysis of disulfide **11** as described above.

Thioamido analogs of lincomycin (**1**) and clindamycin (**16**) were prepared by treating the fully acylated antibiotic with P_4S_{10}. Alkaline saponification of **17** readily afforded thioamidolincomycin (**18**). However, in the case of the 7(*S*)-chloro analog, acylated thioamide **19** was obtained in low yield so that isolation of a deacylated product was not attempted. The utilization of **19** for introduction of the thiol group into position **7** by the solvolytic method described above (**6** → **7**) was tried on a small scale. Tlc of the solvolytic product of **19** after alkaline hydrolysis indicated the presence of **10**, identified by tlc using chemical visualization and bioautograph *vs. Sarcina lutea*.



16, $R_1 = R_2 = H$; $R_3 = Cl$; X = O
17, $R_1 = Ac$; $R_2 = OAc$; $R_3 = H$; X = S
18, $R_1 = R_3 = H$; $R_2 = OH$; X = S
19, $R_1 = Ac$; $R_2 = H$; $R_3 = Cl$; X = S
20, $R_1 = R_2 = H$; $R_3 = Cl$; X = S

Antibacterial Activities.—Antibacterial testing data for the 7-thio and thioamido analogs of lincomycin described in this paper are summarized in Table I. The thioamido analogs **18** and **20** possess about 20–25% of the antibacterial potency of the parent antibiotics. The 7(*R*)- and 7(*S*)-thio analogs **10** and **15** are about 10% as active as lincomycin in the standard curve *S. lutea* assay, but surprisingly possessed considerably greater potency *vs. Staphylococcus* when administered subcutaneously in the mouse protection assay. Broth dilution assays against a variety of gram-positive and gram-negative organisms indicated that these analogs possess about the same antibacterial spectrum as lincomycin.

TABLE I

Compd	Standard curve assay *vs. S. lutea*[a]	Mouse protection assay *vs. S. aureus*[b]
Lincomycin	1	1
7-Deoxy-7(*R*)-thiolincomycin hydrochloride (**10**)	0.1	1.5
7-Deoxy-7(*S*)-thiolincomycin hydrochloride (**15**)	0.1–0.3	0.8
Thioamidolincomycin (**18**)	0.25	0.2
7-Deoxy-7(*S*)-chlorothioamidolincomycin (**20**)	0.9	

[a] L. J. Hanka, D. J. Mason, M. R. Burch, and R. W. Treick, *Antimicrobial Agents Chemotherapy—1962*, 565 (1963). [b] C. Lewis, H. W. Clapp, and J. E. Grady, *ibid.*, 570 (1963).

Experimental Section

Melting points were determined on a Thomas–Hoover capillary melting point apparatus using a thermometer calibrated for stem exposure. Optical rotations were measured in the solvent noted (*c* ~1). Tlc was run on 2.5 × 7.5 cm microslides coated with Brinkman silica gel GF 254 using the solvent mixture given. Detection was effected by spraying with Lemieux reagent.[8] Brinkman silica gel (0.05–0.20 mm) for chromatography[9] was used for column chromatography. Where analyses are indicated only by symbols of the elements results obtained for these elements were within ±0.4% of the theoretical values. Ir and nmr spectra were obtained on all compounds; major bands were as expected. Mass spectral data were obtained for lincomycin analogs and most other compounds; M^+ agreed with the calculated values.

Methyl 7-Deoxy-7(*S*)-chlorothiolincosaminide Tetraacetate (5).—Acylation of methyl 7-deoxy-7(*S*)-chlorothiolincosaminide with C_5H_5N–Ac_2O afforded **5** (aqueous $AcCH_3$), mp 249–252°, $[\alpha]D$ +235° ($CHCl_3$). *Anal.* ($C_{17}H_{26}ClNSO_8$) C, H, Cl, N.

Methyl N-Thioacetyl-7-deoxy-7(*S*)-chlorothiolincosaminide Triacetate (6).—Methyl 7-deoxy-7(*S*)-chlorothiolincosaminide tetraacetate (**5**) (5 g) was treated with P_4S_{10} in dioxane[10] to yield 2.27 g (45.5%) of **6**, mp 199–200° dec, and 2.06 g (41.1%), mp 192–194° dec. The analytical sample (EtOAc–Skellysolve B[11]), $[\alpha]D$ +212° ($CHCl_3$), melted at 198–200°. *Anal.* ($C_{17}H_{26}ClNO_7S_2$) C, H, Cl, S.

Methyl 7-Deoxy-7(*R*)-thiolincosaminide Tetraacetate (7).—A solution of 870 mg of thioamide (**6**) in 20 ml of DMF and 10 ml of H_2O was heated at reflux for 1.5 hr. The solvent was distilled *in vacuo*. The residue was chromatographed over silica gel C_6H_{12}–$AcCH_3$ (2:1) for elution. The product fraction of 619 mg was recrystallized from EtOAc to afford 300 mg of **7**, mp 245–247°, $[\alpha]D$ +212° ($CHCl_3$). A positive test for –SH was obtained using the NaN_3–I_2 reagent.[12] *Anal.* ($C_{17}H_{27}NO_8S_2$) C, H, N, S.

Acylation with Ac_2O–C_5H_5N gave pentaacetate **8**, mp 251–253° (EtOAc–Skellysolve B). *Anal.* ($C_{19}H_{29}NO_9S_2$) C, H, N, S.

Disulfide (11) from Oxidation of Methyl 7-Deoxy-7(*R*)-thiolincosaminide Tetraacetate (7).—Oxidation of 434 mg of **7** with 0.1 *N* I_2 solution in MeOH yielded 300 mg of disulfide **7** (EtOAc), mp >320°. *Anal.* ($C_{34}H_{52}N_2O_{16}S_4$) C, H, S.

Methyl 7-Deoxy-7(*R*)-thiothiolincosaminide (9).—Tetraacetate (8 g) was heated at reflux for 2 hr with hydrazine hydrate. Evaporation of the hydrazine hydrate *in vacuo* gave a gray residue which on addition of *i*-PrOH deposited 5.2 g of crystals of indefinite melting point. Attempts to purify by chromatography or recrystallization gave darker colored decomposition products.

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

(7) R. D. Guthrie and D. King, *Carbohydrate Res.*, **3**, 128 (1967).

(8) R. U. Lemieux and H. F. Bauer, *Anal. Chem.*, **26**, 920 (1945).

(9) Brinkman Instruments, Inc., Westbury, L. I., N. Y.

(10) W. Walter and K. D. Bode, *Angew. Chem. Intern. Ed. Engl.*, **5**, 447 (1966).

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

(12) F. Feigl, "Spot Tests in Organic Analysis," 7th ed, Elsevier Publishing Co., Amsterdam, 1966, p 219.

apparently accompanied by loss of H_2S. Mass spectrographic examination of the crystals showed the expected M^+. This product was used in the next step where separation of a pure product proved less complicated.

7-Deoxy-7(*R*)-thiolincomycin (10).—Methyl 7-deoxy-7(*R*)-thiolincosaminide (**9**) (5.2 g) was treated with 4.14 g of *trans*-4-*n*-propyl-L-proline[3a] to give 6.26 g of crude product. Chromatography ($CHCl_3$–MeOH, 4:1) gave 5.96 g of **10**, $[\alpha]D$ +125° (H_2O), as an amorphous solid. The hydrochloride salt also was not crystalline. *Anal.* ($C_{18}H_{34}N_2O_5S_2$) C, H, N.

Methyl 7-Deoxy-6-deamino-6,7-aziridinothiolincosaminide (13).—Amino sugar **4** (1 g) was treated with K_2CO_3 in boiling DMF. Crystallization of the residue from MeOH after distillation of the DMF afforded 370 mg of **13**, mp 192–198°, and 160 mg, mp 182–189°. Two recrystallizations (MeOH–$AcCH_3$) gave crystals, mp 203–220° dec, $[\alpha]D$ +320° (DMSO). Only one spot was noted on tlc and the melting point was unchanged for further recrystallizations. *Anal.* ($C_9H_{15}NO_4S$) C, H, N.

Methyl 7-Deoxy-7(*S*)-thiolincosaminide (14).—A suspension of 1.5 g of aziridine **13** in 30 ml of *i*-PrOH saturated with H_2S at 0° was heated in a glass bomb on a steam bath for 5 hr. Filtration of the cooled reaction mixture yielded 1.6 g of **14**, mp 190–197°, which when recrystallized (EtOH) melted at 195–198°. *Anal.* ($C_9H_{19}NO_4S_2$) C, H, N, S.

The pentaacetate (**14a**), mp 266–268°, was prepared by acylation of **14** with Ac_2O–C_5H_5N in the usual manner. *Anal.* ($C_{19}H_{29}NO_9S_2$) C, H, N, S.

7-Deoxy-7(*S*)-thiolincomycin Hydrochloride (15).—In the manner previously described,[3b] 6.8 g of **14** was condensed with 5.2 g of *trans*-4-*n*-propyl-L-proline to yield 10.2 g of crude product. Chromatography ($CHCl_3$–MeOH, 4:1), followed by conversion to the hydrochloride, afforded 4.35 g of amorphous solid, $[\alpha]D$ −161° (H_2O). *Anal.* ($C_{18}H_{35}ClN_2O_5S_2$) C, H, N. Rechromatography of the free base gave an analytical sample. *Anal.* ($C_{18}H_{34}N_2O_5S_2$) C, H, N, S.

Methyl 6-Deamino-7-deoxythiolincosaminide (12). Method A.—Aziridine **13** (235 mg) was treated with HONO[7] followed by catalytic hydrogenation over 10% Pd–C in MeOH to give 60 mg of **12** ($AcCH_3$), mp 189–190°. *Anal.* ($C_9H_{18}O_4S$) C, H, S.

Method B.—Disulfide **11** (4.4 g) was heated at reflux for 18 hr with hydrazine hydrate. Chromatography ($CHCl_3$–MeOH, 4:1) followed by crystallization (H_2O) yielded 100 mg of **12**, mp 178–182°. Ir, mass spectra, and nmr data indicated identity with **12** prepared by method A.

Thioamidolincomycin Tetraacetate Hydrochloride (17·HCl).—Lincomycin tetraacetate (19.5 g), prepared by acylation of lincomycin with Ac_2O–C_5H_5N, was treated with 7 g of P_4S_{10} in aqueous dioxane as previously described. Conversion of the crude product to the hydrochloride yielded 24.6 g of **17**·HCl which gave 9.0 g of **17**·HCl, mp 207–214°, from $AcCH_3$–H_2O. Recrystallization gave **17**·HCl, mp 221–225° (hygroscopic). *Anal.* ($C_{26}H_{43}ClN_2O_9S_2$) C, H, N, S, Cl.

Thioamidolincomycin (18).—Five grams of **17**·HCl was treated with 0.5 *N* 50% aqueous methanolic NaOH at 26° for 1 hr. The crude product (3.5 g) was obtained by extraction with $MeCl_2$. Crystallization (aqueous MeOH) afforded 300 mg of **18**, mp 221–226°, and a second crop of 530 mg of **18**, mp 195–205°. The analytical sample was further purified by chromatography (Et-OAc–AcMe–H_2O, 8:5:1). *Anal.* ($C_{18}H_{34}N_2O_5S_2$) C, H, N, S.

Thioamidoclindamycin Triacetate (19).—In the manner described above, clindamycin was converted to the triacetate and treated with P_4S_{10}. After twice chromatographing (C_6H_{12}–AcMe, 2:1) 120 mg of **19**, mp 178–181°, was obtained from 4 g of triacetate. *Anal.* ($C_{24}H_{39}ClN_2O_7S_2$) C, H, N, S.

7-Deoxy-7(*S*)-chlorothiamidolincomycin (20).—Triacetate **19** (12.9 mg) was treated with dilute alkali in aqueous AcMe for 25 min. Only one spot was noted on tlc moving about where expected. The solution was acidified and lyophilized. Purification was not attempted.

Solvolysis of 19.—A solution of 10 mg of **19** in 50% aqueous DMF was heated at reflux for 17 hr. A more polar product which reacted very rapidly with Lemieux reagent (characteristic of thiols) was noted on tlc. The pH was adjusted to 10.5 and after 1 hr evaporated *in vacuo*. The major spot on tlc (C_6H_{12}–AcMe, 2:1) ($CHCl_3$–MeOH, 10:1) moved with and was not separated from **10** on 8-in. tlc plates. For visualization Lemieux reagent, I_2, and bioautograph *vs. S. lutea* were employed.

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The Relationship between Structure, Stereochemistry, and Diuretic Activity in the 2-Amino-α-phenylcyclohexanemethanol Series, a New Class of Diuretic Agents. II[1]

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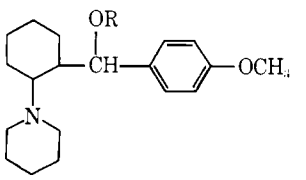
A series of 1,3-amino alcohols and 1,3-amino ethers were made for diuretic testing. The four diastereoisomers of both the alcohols and methyl ethers (I, R = H and CH_3, respectively) were synthesized and the relationship of stereochemistry to diuretic activity is discussed. 1-[2-(*p*,α-Dimethoxybenzyl)cyclohexyl]-piperidine (**2**) was resolved and the *d* enantiomorph (**3**) was chosen for further pharmacologic evaluation.

In this paper, a new class of diuretic agents[2] illustrated by structure I is reported. Compounds of structure type I have three asymmetric centers and, in the case of both the alcohols and methyl ethers (I, R = H and CH_3, respectively), the four possible diastereoisomers or racemates have been synthesized. Stereochemistry is a prime factor in the correlation of structure with biological activity and in the study of receptor surfaces.[3] We therefore undertook a detailed study of the relationship between stereochemistry and diuretic activity in this class of compounds.



I

(1) Paper I: J. Szmuszkovicz and L. L. Skaletzky, *J. Org. Chem.*, **32**, 3300 (1967).

(2) For a review of diuretic agents: (a) H.-J. Hess in "Annual Reports in Medicinal Chemistry, 1967," C. K. Cain, Ed., Academic Press Inc., New York, N. Y., 1968, p 62, and previous Annual Reports; (b) G. de Stevens, "Diuretics," Academic Press, Inc., New York, N. Y., 1963.

(3) (a) E. J. Ariëns, *Mol. Pharmacol.*, **1**, 232 (1964); (b) P. S. Portoghese, A. A. Mikhail, and H. J. Kupferberg, *J. Med. Chem.*, **11**, 219 (1968), and references noted therein.