TABLE III.—R_f DIFFERENCES AND INTENSITY OF COMPOUNDS

	R_f	Intensity
3-Chloropropyldimethylamine	0.84	Light blue
Phosphine (III)	0.88	Deep blue
Oxide (IV)	0.26	Light blue
Sulfide (V)	0.83	Very deep blue

at reduced pressure, affording an oil which was taken up in 30 ml. of skellysolve B. On cooling, 800 mg. (49%) of light yellow crystals were obtained, m.p. 78.5°.

Anal.—Calcd. for $C_{17}H_{22}NPS$: C, 67.28; H, 7.32; N, 4.62. Found: C, 67.06; H, 7.24; N, 4.58.

Thin-Layer Chromatography.—All materials in this series could very conveniently be checked for homogeneity and identity by thin-layer chromatography, carried out as follows. A 0.25-mm. layer of aluminum oxide G (Merck) was deposited on glass plates, which were activated by heating at 125° for 30 min. and stored in a desiccator. Spots representing 5 μl. of 10% solutions in acetone were applied, and the chromatograms were developed with a 1:1 mixture of acetone–chloroform. The spots were visualized by spraying with bromthymol blue. Aside from R_f differences, characteristic gradations in the intensity of the spot produced by the bromthymol blue reaction were observed.

Infrared Spectra.—In addition to the expected fundamental bands, these substances exhibited what appear to be highly characteristic infrared absorptions, which aided greatly in their characterization. All three substances, III, IV, and V, show a strong, sharp peak near 1430 cm.$^{-1}$. Additionally, the oxide possesses a very intense, broad band near 1180 cm.$^{-1}$, probably the P=O stretching frequency, and the sulfide shows a characteristic complex of seven intense bands between 690 and 810 cm.$^{-1}$.

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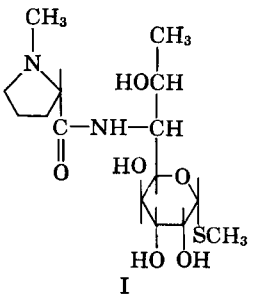
N-Alkylsulfamate Salts of Lincomycin

By BARNEY J. MAGERLEIN

A number of *N*-alkylsulfamic acids and the corresponding lincomycin *N*-alkylsulfamates were prepared. In contrast to most salts of the antibiotic, lincomycin, higher *N*-alkylsulfamate salts possessed low water solubility.

LINCOMYCIN[1] is an orally effective, water soluble antibiotic whose isolation (1), physical properties (2), and structure (3) were recently announced. This antibiotic possesses a medium antibacterial spectrum and is orally effective in the treatment of bacterial infections in experimental animals (4) and in humans (5).

Lincomycin (I) possesses one tertiary amine group which permits salt formation. Many of the common salts of lincomycin, such as the hydrochloride, though crystalline, are highly water soluble. Salts of lincomycin formed with the higher *N*-alkylsulfamic acids were found to be relatively water insoluble and therefore of interest for certain types of pharmaceutical formulation. This report describes the preparation and properties of certain *N*-alkylsulfamic acids and *N*-alkylsulfamate salts of lincomycin. One of these salts, namely, lincomycin *N*-*n*-hexadecylsulfamate (LHS), is reported to show slightly greater antibacterial properties than lincomycin hydrochloride in an experimental infected-mouse system (6).



I

N-Alkylsulfamic acids may be prepared by a variety of procedures which have been tabulated in two reviews (7, 8). *N*-Cyclohexylsulfamic acid (9), the most widely known member of this class of compounds, is commercially available.[2]

Initially, the preparation of the *N*-alkylsulfamic acids by the action of chlorosulfonic acid on an excess of amine was investigated (7–9). While this method was satisfactory for the preparation of lower *N*-alkylsulfamic acids, the isolation and purification of the higher homologs proved difficult due to the extreme insolubility of the alkylamine and alkali metal salts of the *N*-alkylsulfamic acids. To obviate these difficulties, the authors studied the cleavage of *N*-alkylsulfonamides with chlorosulfonic acid (10) as shown in the following equation. The *N*-alkylsulfamic acids prepared by this method are listed in Table I.

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[1] Marketed as Lincocin by The Upjohn Co., Kalamazoo, Mich.

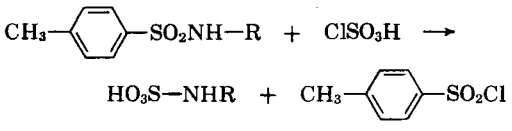
[2] Marketed as Hexamic Acid by Abbott Laboratories, North Chicago, Ill.

TABLE I.—*N*-ALKYLSULFAMIC ACIDS

Name	Formula	Anal. Calcd.	Anal. Found	M.p., °C.	Yield, %
N-*n*-Dodecylsulfamic acid	$C_{12}H_{27}NO_3S$	C, 54.30 H, 10.26 N, 5.28 S, 12.08	C, 54.17 H, 10.56 N, 5.09 S, 12.30	195–196	50
N-*n*-Tetradecylsulfamic acid	$C_{14}H_{31}NO_3S$	C, 57.29 H, 10.65 N, 4.77 S, 10.93	C, 57.13 H, 11.05 N, 5.28 S, 11.02	190–192	62
N-*n*-Hexadecylsulfamic acid	$C_{16}H_{35}NO_3S$	C, 59.77 H, 10.97 N, 4.36 S, 9.97	C, 59.77 H, 10.85 N, 4.30 S, 10.06	178–180	67
N-*n*-Octadecylsulfamic acid	$C_{18}H_{39}NO_3S$	C, 61.84 H, 11.25 N, 4.01 S, 9.17	C, 61.47 H, 11.22 N, 4.16 S, 9.52	191–193	74

TABLE II.—LINCOMYCIN *N*-ALKYLSULFAMATES

Name	Formula	Anal. Calcd.	Anal. Found	M.p., °C.	Yield, %
Lincomycin *N*-cyclohexylsulfamate (cyclamate)	$C_{24}H_{47}N_3O_9S_2$	C, 49.21 H, 8.09 N, 7.18 S, 10.95	C, 49.01 H, 8.15 N, 7.41 S, 10.96 H_2O, ...	167–170	93
Lincomycin *N*-*n*-dodecylsulfamate	$C_{30}H_{61}N_3O_9S_2$	C, 53.62 H, 9.15 N, 6.25 S, 9.54	C, 53.34 H, 9.02 N, 6.01 S, 9.52 H_2O, 2.49	170–173	85
Lincomycin *N*-*n*-tetradecylsulfamate	$C_{32}H_{65}N_3O_9S_2$	C, 54.90 H, 9.36 N, 6.00 S, 9.16	C, 54.73 H, 9.37 N, 6.17 S, 9.29 H_2O, 1.12	172–174	79
Lincomycin *N*-*n*-hexadecylsulfamate	$C_{34}H_{69}N_3O_9S_2$	C, 56.09 H, 9.55 N, 5.77 S, 9.81	C, 56.52 H, 9.72 N, 5.71 S, 8.95 H_2O, 0.37	168–171	78
Lincomycin *N*-*n*-octadecylsulfamate	$C_{36}H_{73}N_3O_9S_2$	C, 57.18 H, 9.73 N, 5.56 S, 8.48	C, 57.23 H, 9.93 N, 5.47 S, 8.10 H_2O, 0.38	182–185	74



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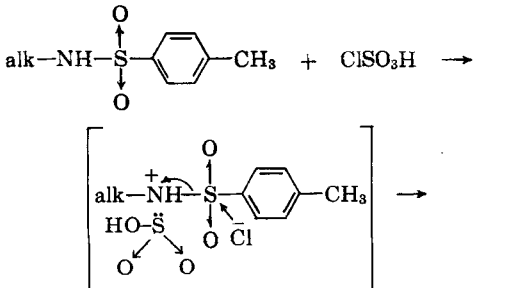
R = $-C_{14}H_{29}$
R = $-C_{16}H_{33}$
R = $-C_{18}H_{37}$



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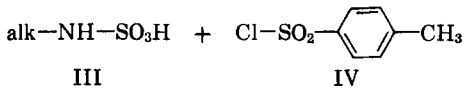

III IV

One possible mechanism for the formation of sulfamic acids by this route embodies as the first step the formation of the intermediate (II) which undergoes nucleophilic attack by chloride ion to form the *N*-alkylsulfamic acid (III) and *p*-toluenesulfonyl chloride (IV).

TABLE III.—LINCOMYCIN *N*-ALKYLSULFAMATES

Name	Solubility in H_2O, mg./L.	*In Vitro* Assay % of Lincomycin · HCl $^1/_2$ H_2O Calcd.	Found
Lincomycin *N*-cyclohexylsulfamate (cyclamate)	10.5×10^4	76.9	75
Lincomycin *N*-*n*-dodecylsulfamate	900	67.2	67
Lincomycin *N*-*n*-tetradecylsulfamate	190	64.5	66
Lincomycin *N*-*n*-hexadecylsulfamate	4.9	62.1	60
Lincomycin *N*-*n*-octadecylsulfamate	2.6	59.8	58

Lincomycin salts were prepared by two methods. The first and most satisfactory was simple acid–base reaction in hot ethanol. The second was treatment of lincomycin hydrochloride with the given sodium *N*-alkylsulfamate. Due to the low aqueous solubility of sodium *N*-alkylsulfamates, the latter method was less reliable, frequently giving salts containing more ash than desirable. The lincomycin *N*-alkylsulfamates prepared are summarized in Table II.

These salts gave full antibacterial activity, as recorded in Table III, when assayed against the test organism *S. lutea* (11). The solubilities of the salts in water decreased with increasing length of the alkyl chain, as indicated in Table III.

Clinical evaluation of these salts will be reported elsewhere.

EXPERIMENTAL

N-Alkyl-p-toluenesulfonamides.—These amides were prepared by the standard procedure of treating the amine with *p*-toluenesulfonyl chloride in pyridine solution. The *N*-alkyl-*p*-toluenesulfonamides were obtained crystalline by dilution with dilute acid. The crude crystals were collected by filtration, washed well with water, and dried to constant weight at 50° under vacuum. The yields were 96–98%. The sulfonamides were used without recrystallization in the preparation of *N*-alkylsulfamic acids.

N-Alkylsulfamic Acids (General Procedure).—To a solution of 0.7 mole of *N*-alkyl-*p*-toluenesulfonamide in 750 ml. of chloroform there was added 300 Gm. of chlorosulfonic acid. The temperature of the reaction mixture rose to the boiling point of the solvent during this addition which required about 50 min. The reaction mixture was heated under reflux for 1 hr., during which time crystals of *N*-alkylsulfamic acid began to form. The reaction mixture was cooled to ambient temperature. The crystals were collected by filtration on a sintered-glass funnel and washed successively with chloroform, ethyl acetate, methanol, and again with ethyl acetate. The crystals were dried under vacuum at 50°. They were almost white in color. See Table I for yield, melting point, and elemental analyses.

Lincomycin N-Alkylsulfamate.—*Method A.*—A solution of 0.3 mole of alkylsulfamic acid was prepared in 2 L. of boiling 95% ethanol. An equimolar quantity of lincomycin was added. The solution was maintained at the boiling point for a few minutes until solution was completed. Crystalline lincomycin *N*-alkylsulfamate precipitated as the solution cooled to room temperature. The crystals were collected by filtration and recrystallized from about 4 L. of 95% ethanol. The yield, melting point, and elemental analyses are shown in Table II.

Lincomycin N-Octadecylsulfamate.—*Method B.*—With vigorous stirring 100 ml. of *N* sodium hydroxide was added to a solution of 34.96 Gm. of *N*-octadecylsulfamic acid in 750 ml. of boiling 95% ethanol. The reaction mixture was cooled in an ice-water bath and filtered. The sodium *N*-octadecylsulfamate thus obtained weighed 36.4 Gm. (98% yield). A 15.0-Gm. portion of this salt and 18.86 Gm. of lincomycin hydrochloride was dissolved in a boiling mixture of 546 ml. of water and 63 ml. of 95% ethanol. The hot solution was clarified by filtration and refrigerated overnight. The microcrystalline salt was collected by filtration, washed twice with water by resuspension, and dried at 55° under vacuum. The yield of lincomycin *N*-octadecylsulfamate was 26.2 Gm. (85.9%), m.p. 179–181°.

Anal.—Found: C, 57.69; H, 9.74; N, 5.04; S, 8.18; ash, 0.53.

Solubility of Lincomycin N-Alkylsulfamates in Water.—A suspension of 100 mg. of *N*-alkylsulfamic acid (4.00 Gm. in the case of *N*-cyclohexylsulfamic acid) in 50 ml. of deionized water was shaken at 25° for 24 hr. The mixture was filtered through a sintered-glass filter. The filtrate was assayed for lincomycin activity *versus* the test organism, *S. lutea* (11). The results are recorded in Table III.

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