Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.6; H, 8.2.

Conversion of the Dienone Ester 3 to the Enedione Ester 6.—A solution of 1.02 g of dienone ester **3** in 20 ml of DME and 10 ml of water was stirred at room temperature with 0.83 g of 97% *m*-chloroperoxybenzoic acid for 5 hr. The product was isolated with ether[10b] (10% KOH wash to remove acidic material) affording 1.02 g of crude epoxide **4**, a mixture of stereoisomers. This material was dissolved in 50 ml of benzene and 1.0 ml of boron trifluoride etherate was added *via* hypodermic syringe.[8,10a] After 1.5 min aqueous sodium bicarbonate was added, and the product was isolated with benzene[10a] to give 0.88 g (88%) of a colorless semisolid mixture of acetyl epimers **5** and **6** (2:1 according to the integrated nmr spectrum). The major isomer **5** was purified by recrystallization from hexane–ether to give a white solid: mp 148–148.5°; λ_{max}^{KBr} 5.80, 5.88, and 6.00 μ; $\delta_{TMS}^{CCl_4}$ 5.96 (vinylic CH), 3.62 (OCH_3), and 2.30 ppm (CH_3CO).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.15; H, 7.63. Found: C, 68.0; H, 7.5.

A 0.44-g sample of the aforementioned 2:1 mixture of enediones **5** and **6** was stirred at room temperature with 25 ml of MeOH, 1 ml of water, and 0.03 g of sodium carbonate for 5 hr.[10a] Isolation with benzene[10b] afforded 0.44 g (99%) of oily enedione **6**: λ_{max}^{film} 5.78, 5.85, and 6.01 μ; $\delta_{TMS}^{CCl_4}$ 5.93 (vinylic CH), 3.73 (CH_3O), 2.17 (CH_3CO), and 0.98 ppm (CH_3 doublet, J = 6 Hz).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.15; H, 7.63. Found: C, 68.4; H, 7.8.

Conversion of the Enedione Ester 6 to the Bis-Ketal Aldehyde 9.—A solution of 0.44 g of enedione ester **6** in 40 ml of benzene containing 6 ml of ethylene glycol and 0.13 g of *p*-toluenesulfonic acid was stirred at reflux with a Dean–Stark trap for 12 hr.[10a] Solid sodium bicarbonate was added and the product was isolated with benzene[10b] affording 0.58 g (95%) of bis-ketal ester **7**: λ_{max}^{film} 5.78 μ; $\delta_{TMS}^{CCl_4}$ 5.58 (vinylic CH), 3.82 ($-OCH_2CH_2O-$), 3.63 (CH_3O), 1.20 (CH_3), and 0.95 ppm (CH_3, unresolved doublet).

The above material in 50 ml of ether was treated with 0.50 g of lithium aluminum hydride and the mixture was stirred at reflux for 24 hr. Water (0.5 ml), 15% aqueous NaOH (0.5 ml), and water (1.5 ml) were added in turn, stirring was continued for 0.5 hr, and the mixture was filtered. Removal of ether under reduced pressure left 0.50 g (95%) of bis-ketal alcohol **8**: λ_{max}^{film} 3.0 and 9.51 μ; $\delta_{TMS}^{CDCl_3}$ 5.60 (vinyl H, unresolved triplet), 3.87 ($-OCH_2-CH_2O-$), 1.24 (CH_3), and 0.98 ppm (CH_3, unresolved doublet).

The above alcohol in 3 ml of DMSO was treated with 0.12 ml of pyridine, 0.06 ml of trifluoroacetic acid, and 0.94 g of dicyclohexylcarbodiimide in 3 ml of benzene.[9,10a] After stirring for 18 hr at room temperature, the mixture was poured into 25 ml of ethyl acetate, and a solution of 0.42 g of oxalic acid in 4 ml of MeOH was added. After 0.5 hr, the mixture was filtered and the filtrate was washed with water, aqueous sodium bicarbonate, and saturated brine and dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure left 0.46 g (93%) of bis-ketal aldehyde **9**: λ_{max}^{film} 3.7 and 5.81 μ; $\delta_{TMS}^{CCl_4}$ 9.75 (CHO), 5.68 (vinyl H, unresolved triplet), 3.91 ($-OCH_2CH_2O-$), 1.27 (CH_3), and 1.10 ppm (CH_3, unresolved doublet).

Conversion of the Bis-Ketal Aldehyde 9 to the Enedione 10.—A solution of 0.46 g of bis-ketal aldehyde **9** in 25 ml of ethylene glycol and 3.5 ml of 85% hydrazine hydrate was heated at 120° with stirring for 1 hr.[10a] The solution was allowed to cool, 1.5 g of KOH was added, and the temperature was increased to 205° and maintained near that point for 2 hr. The solution was allowed to cool and the product isolated with ether.[10b] The resulting material in solution with 10 ml of acetone, 1 ml of water, and 3 drops of concentrated HCl was stirred at reflux for 1 hr.[10a] Extraction with benzene[10b] followed by short-path distillation at 130° (0.01 mm) afforded 0.24 g (78%) of pale yellow enedione. Further purification by preparative layer chromatography (silica gel) and short-path distillation yielded the analytical sample: λ_{max}^{film} 5.85 and 6.00 μ; $\delta_{TMS}^{CCl_4}$ 5.93 (vinylic CH), 2.07 (CH_3CO), 1.04 (angular CH_3), and 0.93 ppm (CH_3 doublet, J = 6 Hz).

Anal. Calcd for $C_{14}H_{20}O$: C, 76.33; H, 9.15. Found: C, 76.1; H, 9.3.

A solution of methylenetriphenylphosphorane was prepared as previously described from 0.48 g of NaH and 7.65 g of methyl triphenylphosphonium bromide in 40 ml of DMSO. A 2.60-ml sample was removed *via* syringe and added to 248 mg of enedione **10** in 2 ml of DMSO. The mixture was stirred at room temperature for 4 hr, and the product was isolated with pentane[10b] and chromatographed on silica gel to give 55 mg of (±)-nootkatone: mp 44–45°; λ_{max}^{film} 5.98 (CO), 6.16 (C=C), and 11.3 μ (C=CH_2); $\delta_{TMS}^{CCl_4}$ 5.60 (H-4), 4.66 (C=CH_2, doublet, J = 1 Hz), 1.66 (vinyl CH_3), 1.10 (angular CH_3), and 0.95 ppm (CH_3, doublet, J = 6 Hz). The spectral characteristics of the synthetic material were identical with those of the natural material.[3]

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.39; H, 10.16.

An early fraction amounting to 8 mg was obtained with hexane elution. This material exhibited spectral properties suggestive of the expected bis condensation product of dione **10**.

Registry No.—**1** dimethyl ketal, 27024-77-7; ketal keto ester [bp 112° (0.2 mm)], 27024-78-8; **2**, 27024-79-9; **3** (cis), 27024-80-2; **3** (trans), 27024-81-3; **5**, 27024-82-4; **6**, 27024-83-5; **7**, 27024-84-6; **8**, 27024-85-7; **9**, 27024-86-8; **10**, 27024-87-9; **11**, 20071-81-2; **12**, 27024-89-1.

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Lincomycin. XII.[1] The Preparation of Methyl *N*-Methyl-α-thiolincosaminide

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Cleavage of the antibiotic lincomycin in refluxing hydrazine hydrate led to the isolation of methyl 6-amino-6,8-dideoxy-1-thio-D-*erythro*-α-D-*galacto*-octopyranoside (methyl α-thiolincosaminide) (MTL) (**1**) in good yield.[2] Treatment of this sugar with triphenylphosphine dichloride afforded methyl 7(*S*)-chloro-7-deoxy-α-thiolincosaminide which when coupled with various 4-alkyl-L-prolines gave a series of potent antibacterial and antimalarial agents.[3] Further chemical transformations of methyl α-thiolincosaminide (**1**) to form methyl *N*-methyl-α-thiolincosaminide (**8**) and methyl *N*,*N*-dimethyl-α-thiolincosaminide (**2**) are now described.

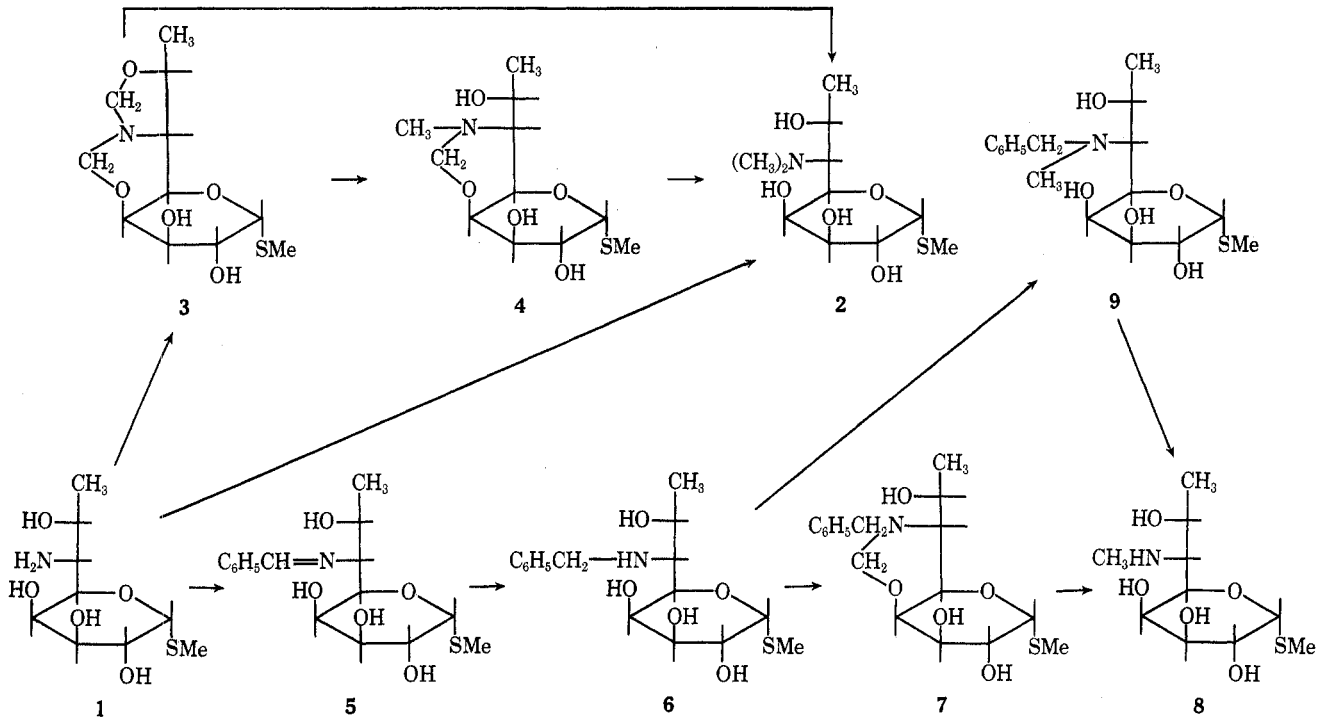
Reductive alkylation of methyl α-thiolincosaminide (**1**) with excess formaldehyde readily formed *N*,*N*-dimethyl sugar **2**. In the presence of but 1 molar equiv of formaldehyde, reductive alkylation gave no evidence of the mono-*N*-methyl sugar **8**, but only a lowered yield of **2** and unreacted amino sugar **1**.

Examination by tlc (thin layer chromatography) of partially completed reductive alkylations revealed the presence of two new compounds both less polar than starting sugar **1** as well as *N*,*N*-dimethyl sugar **2**. These compounds could not be detected after further reduction. After separation by chromatography, the least polar of these intermediates was shown to be the initial condensation product of **1** with 2 mol of formaldehyde. This compound was assigned structure **3** on

(1) Previous paper in this sequence: R. D. Birkenmeyer and F. Kagan, *J. Med. Chem.*, **13**, 616 (1970).

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

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



the basis of elemental and nmr data. The assignment of the bond to oxygen at C-4 was made after examination of models indicated that attachment to the axial hydroxyl at C-4 was favored over the equatorial hydroxyls at C-3 or C-2. The formation of the bicyclic structure **3** is analogous to the facile condensation of 2-amino-1,3-diols with carbonyl compounds to yield 1-aza-3,7-dioxabicyclo[3.3.0]octanes.[4] 1-Aza-3,7dioxabicyclo[3.3.0]octanes are reported to undergo hydrogenolysis to form dialkylamino alcohols[4] which is analogous to the hydrogenolysis of **3** to *N*,*N*-dimethyl sugar **2**.

The second compound isolated from the incomplete reduction was assigned structure **4**. Elemental analyses and nmr data were consistent with a *N*-methyl compound bearing a methylene bridge, such as **4**. The attachment of the methylene bridge is shown to the ring hydroxyl by analogy with *N*-benzyl compound **7**, whose structure is discussed below. Hydrogenolysis of either **3** or **4** afforded methyl *N*,*N*-dimethyl-α-thiolincosaminide (**2**).

The foregoing suggested that a successful synthesis of the desired mono-*N*-methyl compound **8** could be achieved provided the amino group of **1** could be suitably blocked to allow reaction with only 1 equiv of formaldehyde. Accordingly, **1** was converted to benzylidine derivative **5** which on careful hydrogenation over platinum formed methyl *N*-benzyl-α-thiolincosaminide (**6**) in high yield. Benzyl derivative **6** readily coupled with formaldehyde to form a less polar compound assigned structure **7**. Elemental analyses and nmr data indicated a cyclic structure containing a methylene group. The choice of attachment of the methylene bridge is shown to the ring hydroxyl rather than to the 7-hydroxyl since chlorination *with* triphenylphosphine–carbon tetrachloride[5] gave a monochloride in which the 8-methyl signal in the nmr was shifted downfield as noted with other 7-chloro compounds of this type.[1]

Hydrogenolysis of **7** over palladium yielded methyl *N*-methyl-α-thiolincosaminide (**8**) and varying amounts of dimethyl compound **2**. The presence of the latter compound probably is due to partial decomposition of **7** or debenzylated **7**, since the hydrogenolysis reaction required an acidic solution.

In an alternate, but less successful procedure to prepare **8** from **6**, compound **6** was formylated with ethyl formate and reduced with $LiAlH_4$ to give impure *N*-benzyl-*N*-methyl **9** in low yield. Hydrogenolysis of crude **9** gave methyl *N*-methyl-α-thiolincosaminide (**8**) identical with that prepared by the previous method.

Attempts to condense either methyl N-methyl-α-thiolincosaminide (**8**) or methyl *N*-benzyl-α-thiolincosaminide (**6**) with 4-*n*-propylhygric acid by the method previously described[3] were unsuccessful.

Experimental Section

Melting points were taken in Pyrex capillaries and are corrected. Infrared spectra, recorded on a Perkin-Elmer Model 21 spectrophotometer, and nuclear magnetic resonance spectra, recorded on a Varian high-resolution, 60-MHz instrument, were consistent with the structures shown. M^+ values were determined using a Varian MAT CH4 mass spectrometer equipped with a direct insertion probe. Optical rotations were taken in the solvent noted ($c \sim 1$). Silica gel used for chromatography was silica gel 0.05–0.20 mm for chromatography, E. Merck A. G. Distibutors, Brinkman Industries, Inc., Westbury, N. Y.

Methyl *N*-Benzylidene-α-thiolincosaminide (5).—With vigorous stirring 24.7 ml of benzaldehyde was added to a suspension of 50.0 g of methyl α-thiolincosaminide in 990 ml of water containing 5 ml of 5% sodium hydroxide solution. The solid rapidly dissolved and crystals precipitated in a few minutes. The solution was filtered and the residue washed with water and dried. There was thus obtained 46.7 g (69.1%) of **5**, mp 206–207°, λ_{max}^{EtOH} 248 nm (ε 16,000), $[\alpha]D$ +178° (MeOH).

Anal. Calcd for $C_{16}H_{23}NO_5S$: C, 56.28; H, 6.79; N, 4.10; S, 9.39. Found: C, 56.31; H, 6.61; N, 4.08; S, 9.36.

Methyl *N*-Benzyl-α-thiolincosaminide (6).—A solution of 46.7 g of **5** in 800 ml of methanol containing 8 g of PtO_2 in 100 ml of ethanol was shaken under hydrogen pressure (3 atm) for 4.5 hr. The catalyst was removed by filtration and the solvent distilled

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(5) J. B. Lee and T. J. Nolan, *Can. J. Chem.*, **44**, 1331 (1966).

under vacuum. The crystalline residue was dissolved in 100 ml of warm methanol and diluted with 400 ml of ethyl acetate. The crystals which formed were collected by filtration and dried. They weighed 30.7 g (65%) and melted at 155–157°. The analytical sample, prepared by two recrystallizatios from methanol, melted at 157–159° and gave $[\alpha]_D$ +235° (MeOH).

Anal. Calcd for $C_{16}H_{25}NO_5S$: C, 55.95; H, 7.34; N, 4.08; S, 9.34. Found: C, 55.73; H, 7.31; N, 4.20; S, 9.52.

Methyl *N*-Benzyl-4,6-*O*,*N*-methylene-α-thiolincosaminide (7).—A solution of 11.6 g of *N*-benzyl sugar **6** and 4 ml of formalin in 200 ml of methanol was maintained at 26° for 30 min. Evaporation of the solvent gave a residue of 11.8 g which was chromatographed over 1.2 kg of silica gel using chloroform–methanol (4:1) for elution. A fraction of 11.8 g of oil was recovered. A portion was dissolved in acetone, clarified, and evaporated to a glassy solid, $[\alpha]_D$ +175° (MeOH).

Anal. Calcd for $C_{17}H_{25}NO_5S$: C, 57.44; H, 7.09; N, 3.94; M^+, 355. Found: C, 57.33; H, 6.92; N, 3.93; M^+, 355.

Methyl *N*-Methyl-α-thiolincosaminide (8).—**7** (6 g) was dissolved in 160 ml of methanol and the solution was acidified with 6 *N* hydrochloric acid. Pd/C (10%) (6 g) suspended in 40 ml of 95% ethanol was added. The resulting mixture was shaken for 5 hr under 2 atm of hydrogen pressure. A few drops of acid were added to acidify the solution and hydrogenation continued for 12 hr. The catalyst was removed by filtration and the solvent distilled *in vacuo* after the mixture was made basic with triethylamine. The residue, 7.1 g, was chromatogaphed over 700 g of silica gel. Elution with methanol afforded 1.2 g of dimethyl compound **2**, which was recrystallized from methanol to give 700 mg of crystals, mp 174–176°. The more polar fraction was recrystallized from methanol to yield 900 mg of monomethyl compound **8**, mp 187–189°. Stripping the column with methanol–ammonium hydroxide (5%) followed by recrystallization gave an additional 330 mg of **8**, mp 186–188°. A portion of **8** was recrystallized from methanol. It now melted at 180–182° and gave $[\alpha]_D$ +267° (H_2O).

Anal. Calcd for $C_{10}H_{21}NO_5S$: C, 44.92; H, 7.92; N, 5.24; S, 12.00. Found: C, 45.20; H, 7.54; N, 5.34; S, 11.62.

Methyl *N*-Benzyl-*N*-methyl-α-thiolincosaminide (9).—A mixture of 3 g of **6** and 100 ml of ethyl formate was heated for 2.5 hr at 100° in a stirred autoclave. After cooling, the solution was removed and evaporated to yield an oil. Tlc showed no starting amine **6**, while infrared data indicated stong amide and ester bands. The oil was dissolved in 60 ml of tetrahydrofuran and added to a mixture of 3 g of $LiAlH_4$ in 50 ml of tetrahydrofuran. The mixture was heated at reflux for 20 hr. Water was added and the supernant was decanted from the precipitated salts and evaporated. The residue was crystallized from methanol–acetone to give 200 mg of crude crystals, mp 155–175°. Recrystallization from the same solvent gave 120 mg of **9**, mp 165–175. The nmr spectrum in DMSO was satisfactory. This material was not purified further but used as described below.

Methyl *N*,*N*-Dimethyl-α-thiolincosaminide (2) and Methyl *N*-Methyl-4,6-*O*,*N*-methylene-α-thiolincosaminide (4).—A solution of 10.8 g of methyl α-thiolincosaminide and 4.9 ml of formalin (37%) in 50 ml of water was maintained at room temperature for 30 min. The solution was lyophilized. The amorphous solid was dissolved in 150 ml of methanol and shaken under hydrogen over 1 g of 10% Pd/C for 18 hr. Two grams of catalyst was added and shaking continued for 18 hr. The catalyst was removed by filtration and the filtrate evaporated *in vacuo*. The residue was dissolved in water, the solution was clarified, and the filtrate was lyophilized. Chromatography over silica gel using chloroform–methanol, 4:1, for elution gave chiefly two oily fractions which crystallized on standing. These fractions were triturated with ethyl acetate to yield the following crops of crystals. The less polar fraction afforded 2.6 g (18.9%) of crystalline **2**, mp 173–179°; the more polar fraction, 1.15 g (82%) of **4**, mp 166–176°. Each fraction showed only one spot on tlc.

The dimethyl compound (**2**) was recrystallized twice from methanol to afford an analytical sample, mp 177–179°, $[\alpha]_D$ +270° (MeOH).

Anal. Calcd for $C_{11}H_{23}NO_5S$: C, 46.95; H, 8.34; N, 4.98. Found: C, 46.96; H, 8.37; N, 5.02.

The more polar fraction after recrystallization from methanol melted at 184–186° and gave $[\alpha]_D$ +254° (MeOH).

Anal. Calcd for $C_{11}H_{21}NO_5S$: C, 47.29; H, 7.58; N, 5.01. Found: C, 47.46; H, 7.91; N, 4.93.

Methyl *N*-Methyl-α-thiolincosaminide (8) by Hydrogenolysis of 9.—The crude crystals of **9** from above were dissolved in 25 ml of methanol and shaken under hydrogen over 200 mg of 10% Pd/C for 7 hr. The catalyst was removed by filtration and the filtrate evaporated. The residue was crystallized from methanol–acetone to give 40 mg of **8**, mp 179–184°, whose infrared spectrum was identical with that of a known sample of **8**.

Methyl 4,6:6,7-Di-*O*,*N*-methylene-α-thiolincosaminide (3).—A solution of 10 g of methyl α-thiolincosaminide in 50 ml of water and 5 ml of formalin was stirred for 10 min. The solution was lyophilized. Chromatography over silica gel (chloroform–methanol, 4:1) gave a 5-g fraction of glassy solid, $[\alpha]_D$ +239° (H_2O).

Anal. Calcd for $C_{11}H_{19}NO_5S$: C, 47.63; H, 6.90; N, 5.05. Found: C, 47.58; H, 6.98; N, 5.21.

Methyl *N*,*N*-Dimethyl-α-thiolincosaminide (2). A. From Methyl 4,6:6,7-Di-*O*,*N*-methylene-α-thiolincosaminide (3).—Methyl 4,6:6,7-di-*O*,*N*-methylene-α-thiolincosaminide (**3**) (500 mg) was shaken over 200 mg of 10% Pd/C for 17 hr under hydrogen pressure. Tlc indicated about equal amounts of dimethyl compound **2** and monomethyl compound **4**. Fresh Pd/C (200 mg) was added and the mixture again shaken for 20 hr. A final addition of 150 mg of PtO_2 was made and shaking continued for 4 hr longer. The catalyst was removed by filtration and the solvent distilled *in vacuo*. The residue was crystallized from methanol to yield 145 mg of **2**, mp 169–172°, identical by infrared absorption with a known sample of **2**.

B. From Methyl *N*-Methyl-4,6-*O*,*N*-methylene-α-thiolincosaminide (4).—**4** (200 mg) was hydrogenolyzed over 100 mg of 10% Pd/C in the manner described above. Evaporation of the solvent after filtration afforded a crystalline residue which when recrystallized from methanol yielded 50 mg of **4**, mp 170–173°. This product was identical by infrared data with known **4**.

Chlorination of Methyl *N*-Methyl-4,6-*O*,*N*-methylene-α-thiolincosaminide (4).—A solution of 0.75 g of **4** and 2.2 g of triphenylphosphine in 10 ml of acetonitrile and 9 ml of carbon tetrachloride was stirred at ambient temperature for 17 hr. Methanol (2 ml) was added and the solvents were evaporated. Chromatography over silica gel afforded 400 mg of oily chlorination product showing only one spot on tlc ($CHCl_3$–MeOH, 6:1). The nmr spectrum in $CDCl_3$ showed a three-proton doublet centered at δ 1.5 (3 H-8). The nmr spectrum of **4** possessed a three-proton doublet centered at δ 1.2 (3 H-8).

Registry No.—**2**, 22939-47-5; **3**, 27093-10-3; **4**, 27093-11-4; **5**, 22939-44-2; **6**, 22939-45-3; **7**, 27141-08-8; **8**, 22939-46-4; **9**, 27093-15-8.

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The Photochemical Acid Type II Reaction of Organic Esters[1a]

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The recent report by Nicholls and Leermakers[2] which established the occurrence of a type II photochemical elimination reaction in butyric and valeric acids, and the absence of such a reaction for butyramide, valeramide, and *N*,*N*-dimethylbutyramide prompts us to communicate our results concerning a closely related reaction. The reaction to which we refer is a type II elimination in the alkyl group of the acid portion of organic esters (acid type II reaction). The

(1) (a) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. (b) National Science Foundation Undergraduate Research Participant, 1969.

(2) C. H. Nicholls and P. A. Leermakers, *J. Org. Chem.*, **35**, 2754 (1970).