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CHEMICAL MODIFICATION OF NEAMINE

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ABSTRACT

The aminocyclitol antibiotic neamine has been modified chemically by removing one or two hydroxyl groups from the 2-deoxystreptamine moiety to give 5- and 6-deoxyneamines (**5** and **10**), as well as 5,6-dideoxyneamine (**15**). Their antimicrobial activities were determined against several microorganisms, including kanamycin-resistant strains

INTRODUCTION

To establish the relationship between a variation in the structure of an aminocyclitol and the activity of the corresponding aminocyclitol antibiotic, three different approaches are feasible: (*1*) bioconversion of an aminocyclitol into an antibiotic; (*2*) chemical synthesis of an antibiotic that contains an aminocyclitol of known structure; and (*3*) chemical modification of the aminocyclitol moiety in a naturally occurring antibiotic.

RESULTS AND DISCUSSION

The first approach has been initiated by Rinehart and his coworkers[1] and antibiotics named hybrimycins have been prepared in which the 2-deoxystreptamine of the neomycins has been replaced by streptamine (*scyllo*-inosadiamine-1,3) or 2-epistreptamine (*myo*-inosadiamine-1,3).

The second approach is now under way in our laboratory using 2,5- and 2,4-dideoxystreptamines[2], which are converted into 5- (ref. 3) and 6-deoxyparomamines, respectively.

In the present article, we report experiments employing the third approach, in which neamine[4] has been modified chemically by removing a hydroxyl group from its 2-deoxystreptamine moiety, giving 5- (**5**) and 6-deoxyneamine (**10**), and also 5,6-dideoxyneamine (**15**).

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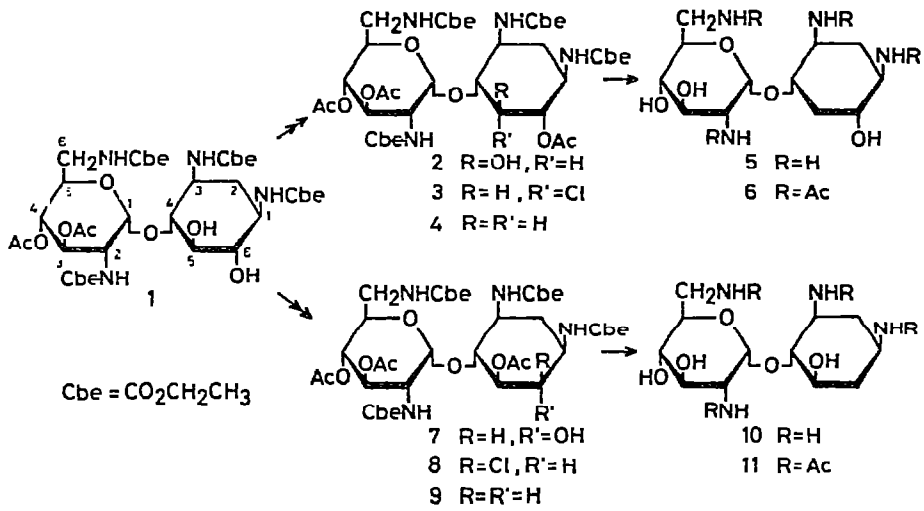
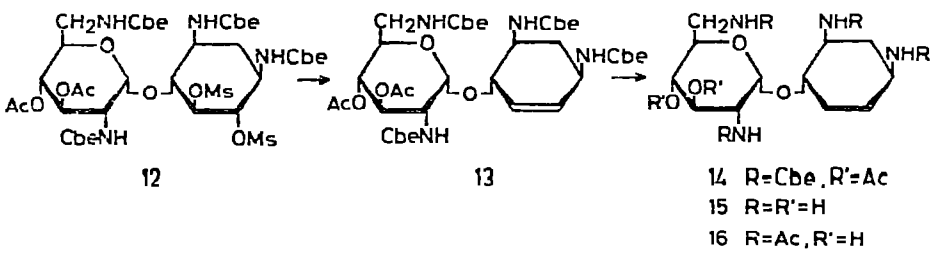
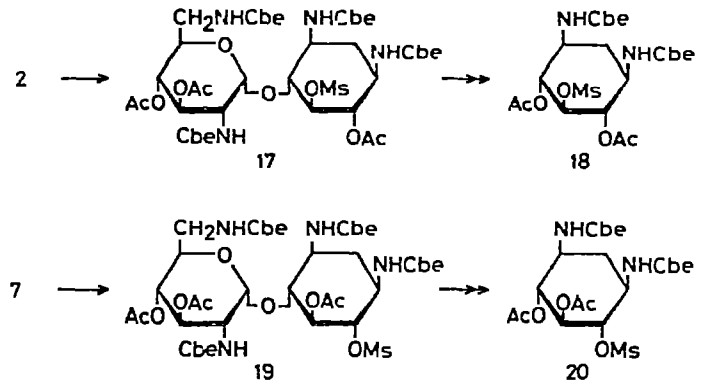


When 6,3′,4′-tri-*O*-acetyl-1,3,2′,6′-tetra-*N*-ethoxycarbonylneamine[5] (**2**) was treated with sulfuryl chloride in pyridine, the corresponding chloro derivative (**3**) was obtained as crystals. Dehalogenation of **3** by hydrogenolysis in the presence of Raney nickel did not give a satisfactory result. However, tributylstannane[6] removed the halogen atom expeditiously to give the corresponding deoxyneamine derivative (**4**). Compound **4** was further converted into **5** by removing the protecting groups on the amino and the hydroxyl groups with boiling barium hydroxide solution.

In the case of 5,3′,4′-tri-*O*-acetyl-1,3,2′,6′-tetra-*N*-ethoxycarbonylneamine[5] (**7**), halogenation with sulfuryl chloride in pyridine yielded another chloro derivative (**8**). The chlorine atom in **8** was readily removed by hydrogenolysis with Raney nickel[10] T-4 in a hydrogen atmosphere to give another deoxyneamine derivative (**9**). Compound **9** was converted into **10** by the same procedure employed in the preparation of **5**.



Finally, 3′,4′-di-*O*-acetyl-1,3,2′,6′-tetra-*N*-ethoxycarbonylneamine[5] (**1**) was treated with methanesulfonyl chloride in pyridine to give the 5,6-di-*O*-mesyl derivative (**12**), which was converted into the 5,6-ene derivative (**13**) by reaction with sodium iodide and zinc powder[7]. Catalytic hydrogenation of **13**, followed by hydrolysis in barium hydroxide solution afforded **15**.



In the preceding paper[5], the structures of **2** and **7** were deduced from their ^{1}H n.m r. spectra by the deuterioacetylation technique[8,9]. In the present article, their structures are unambiguously established by chemical evidence. That is, **2** and **7** were treated with methanesulfonyl chloride in pyridine, and the products were then hydrolyzed in methanolic hydrogen chloride. The hydrolyzates were acetylated, and subsequently purified by column chromatography. By this procedure, compound **2** gave optically inactive 4,6-di-*O*-acetyl-1,3-di-*N*-ethoxycarbonyl-5-*O*-mesyl-2-deoxystreptamine (**18**), whereas **7** gave optically active (+)-4,5-di-*O*-acetyl-1,3-di-*N*-ethoxycarbonyl-6-*O*-mesyl-2-deoxystreptamine (**20**).

No direct proof was obtained for the configurations of the chloro groups in **3** and **8**, but, considering the proposed reaction mechanism of the chlorination described by Jones *et al.*[11], the following structures were proposed tentatively: 1D-4-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-2,6-diethoxycarbonylamido-α-D-glucopyranosyl)-6-*O*-acetyl-5-chloro-1,2,3,5-tetradeoxy-1,3-diethoxycarbonylamido-*neo*-inositol for **3**, and 1D-6-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-2,6-diethoxycarbonylamido-α-D-glucopyranosyl)-1-*O*-acetyl-2-chloro-2,3,4,5-tetradeoxy-3,5-diethoxycarbonylamido-*myo*-inositol for **8**.

TABLE I

ANTIMICROBIAL ACTIVITY OF 5-DEOXY- (**5**), 6-DEOXY- (**10**) AND 5,6-DIDEOXY-NEAMINE (**15**) AND NEAMINE

Compound (concn. I mg/ml)	*Diameter of the inhibition zone in mm, by the paper disk method*					
	Staphylococcus aureus *6538 P*	Bacillus subtilis *ATCC 6633*	Escherichia coli *K-12*	Mycobacterium smegmatis *ATCC 607*	Klebsiella* pneumoniae *7*	Escherichia* coli *ML-1629*
5	23.7	32.4	33.6	30.0	17.0	10.5
10	21.7	31.0	31.8	24.4	0	0
15	22.0	32.6	31.9	24.0	21.9	14.2
Neamine	22.4	30.1	31.8	30.0	0	0

*Kanamycin-resistant strains.

To establish the structures of **5** and **10**, each compound was degraded in conc. hydrobromic acid. An optically inactive, 2,5-dideoxystreptamine derivative was obtained from **5**, and an optically active (+)-2,6-dideoxystreptamine derivative was recovered from **10**.

Antimicrobial activities were determined by the paper-disk method and are listed in Table I.

Removal of the hydroxyl group at C-6 from the 2-deoxystreptamine moiety of neamine decreases the antimicrobial activity relative to the parent neamine, but removal of the hydroxyl group on C-5 enhances the activity, especially against kanamycin-resistant strains.

EXPERIMENTAL

General methods. — Melting points were determined in capillary tubes and are uncorrected. Solutions were evaporated under diminished pressure. Optical rotations were measured with a Japan Spectroscopic DIP-SL polarimeter. ^{1}H n.m.r. spectra were recorded at 60 MHz with a Varian A-60D spectrometer for solutions in chloroform-*d*, unless otherwise noted, with tetramethylsilane as the internal standard and the peak positions are given in δ values. I.r. spectra were recorded on potassium bromide disks with a Hitachi–Perkin–Elmer 225 spectrophotometer. Acetylation was performed conventionally with acetic anhydride in pyridine. T.l.c. was performed on Wakogel B-10 (Wako Pure Chemical Co. Ltd.) plates. Silica gel (Wakogel C-300) was employed for column chromatography. Elemental analyses were performed by Mr. Saburo Nakada.

3′,4′-Di-O-*acetyl-1,3,2′,6′-tetra*-N-*ethoxycarbonylneamine* (**1**). — The product was prepared by the method described in the preceding paper[5].

*1*D-*4*-O-(*3,4-Di*-O-*acetyl-2,6-dideoxy-2,6-diethoxycarbonylamido*-α-D-*glucopyranosyl*)-*6*-O-*acetyl-5-chloro-1,2,3,5-tetradeoxy-1,3-diethoxycarbonylamido*-neo-*inositol* (**3**). — 6,3′,4′-Tri-*O*-acetyl-1,3,2′,6′-tetra-*N*-ethoxycarbonylneamine[5] (**2**, 310 mg) was dissolved in dry pyridine (8 ml), and sulfuryl chloride (0.14 ml) was added to the solution at −15°. The mixture was agitated for 4 h with ice cooling, and then diluted with chloroform (20 ml). The chloroform solution was washed successively with sodium hydrogensulfate solution, sodium hydrogencarbonate solution, and cold water. After drying over anhydrous sodium sulfate, the solution was evaporated. The residue was recrystallized from ethanol–ether to give 210 mg (64%) of **3** as pale-yellow crystals: m.p. 130–132°, $[\alpha]_D^{23}$ +81.2° (*c* 0.83, chloroform); ^{1}H n.m.r. δ 1.1–1.4 (m, 12, $4CO_2CH_2CH_3$), 2.00 (s, 3, OAc), 2.03 (s, 3, OAc), and 2.12 (s, 3, OAc).

Anal. Calc. for $C_{30}H_{47}ClN_4O_{16}$: C, 47.71; H, 6.27; Cl, 4.69; N, 7.42. Found: C, 47.68; H, 6.16; Cl, 4.94; N, 7.14.

6,3′,4′-Tri-O-*acetyl-1,3,2′,6′-tetra*-N-*ethoxycarbonyl-5-deoxyneamine* (**4**). — Compound **3** (175 mg) was added to a solution of tributylstannane[6] (0.5 ml) in dry toluene (16 ml), and the mixture was heated for 2 h at 90° in the presence of di(α-cyanoisopropyl)diazene (6 mg) under nitrogen. The solution was evaporated, and the

residue was washed with ether. The residue was purified on a column of silica gel with 5:60:4 (v/v) acetone–chloroform–ethanol to give 138 mg (83%) of **4** as an amorphous powder; m.p. 118–122°, $[\alpha]_D^{27}$ +78° (*c* 1.02, chloroform); ^{1}H n.m.r. δ 1.06–1.47 (m, 12, $4CO_2CH_2CH_3$), 2.01 (s, 3, OAc), 2.03 (s, 3, OAc), and 2.05 (s, 3, OAc).

Anal. Calc. for $C_{30}H_{48}N_4O_{16}$: C, 49.99; H, 6.71; N, 7.77. Found: C, 49.69; H, 6.61; N, 7.47.

5-Deoxyneamine (**5**). — A mixture of **4** (310 mg) and barium hydroxide (2.4 g) in water (8 ml) was heated for 6 h under reflux. Carbon dioxide was bubbled into the mixture, and the precipitate was filtered off. The filtrate was evaporated, and the residue was purified on a column of Amberlite CG-50 (NH_4^+). The column was washed with 0.05M aqueous ammonia and then eluted with 0.3M aqueous ammonia to give 88 mg (67%) of **5** as an amorphous solid; m.p. 160° (dec), $[\alpha]_D^{21}$ +128° (*c* 1.58, water); ν_{max}^{KBr} 1590 cm^{-1} (NH_2); ^{1}H n.m.r. (D_2O at pD 1): δ 1.2–3.1 (m, 4, 2 ring methylene) and 5.77 (d, 1, *J* 3.5 Hz, H-1′). The product showed a single spot having R_F 0.3 on t.l.c. in a 5:8:10:7 (v/v) 28% ammonia–butanol–ethanol–water solvent system.

*1,3,2′,6′-Tetra-*N*-acetyl-5-deoxyneamine* (**6**). — Compound **5** (80 mg) was acetylated with acetic anhydride (0.3 ml) in methanol (6 ml), overnight with ice cooling. The solution was evaporated, and the residue was washed with a small volume of methanol to give 94 mg (76%) of **6**; m.p. 250° (dec.), $[\alpha]_D^{21}$ +105° (*c* 1.05, water); ^{1}H n.m.r. (D_2O): δ 1.97 (s, 6, 2NAc), 2.01 (s, 6, 2NAc), and 4.93 (d, 1, *J* 3 Hz, H-1′).

Anal. Calc. for $C_{20}H_{34}N_4O_9$: C, 50.62; H, 7.22; N, 11.81. Found: C, 50.69; H, 7.45; N, 11.92.

1D-6-O-(3,4-Di-O-acetyl-2,6-dideoxy-2,6-diethoxycarbonylamido-α-D-glucopyranosyl)-1-O-acetyl-2-chloro-2,3,4,5-tetradeoxy-3,5-diethoxycarbonylamido-myo*-inositol* (**8**). — 5,3′,4′-Tri-*O*-acetyl-1,3,2′,6′-tetra-*N*-ethoxycarbonylneamine[5] (**7**, 250 mg) was treated with sulfuryl chloride (0.15 ml) in pyridine (7 ml) as described in the preparation of **3**, to give 240 mg (95%) of **8** as a glassy solid that did not crystallize despite repeated attempts: $[\alpha]_D^{26}$ +71.1° (*c* 0.85, chloroform); ^{1}H n.m.r. δ 1.1–1.4 (m, 12, $4CO_2CH_2CH_3$), 1.99 (s, 3, OAc), 2.02 (s, 3, OAc), and 2.07 (s, 3, OAc).

Anal. Calc. for $C_{30}H_{47}ClN_4O_{16}$: C, 47.71; H, 6.27; Cl, 4.69; N, 7.42. Found: C, 47.39; H, 6.09; Cl, 4.92; N, 7.25.

*5,3′,4′-Tri-*O*-acetyl-1,3,2′,6′-tetra-*N*-ethoxycarbonyl-6-deoxyneamine* (**9**). — Compound **8** (240 mg) was hydrogenated in ethanol (15 ml) under a hydrogen atmosphere (3.4 $kg.cm^{-2}$) for 20 h in a Parr apparatus in the presence of Raney nickel[10] T-4 and Amberlite IR-45 (OH^-). After the catalyst had been removed by filtration, the filtrate was evaporated, and the residue was purified on a column of silica gel using 15:1 (v/v) benzene–isopropyl alcohol as eluant. Fractions showing a single spot at R_F 0.24 on t.l.c. in the same solvent were combined and evaporated to give 160 mg (71%) of **9**; m.p. 115–117°, $[\alpha]_D^{26}$ +58.3° (*c* 1.08, chloroform); ^{1}H n.m.r. δ 1.1–1.4 (m, 12, $4CO_2CH_2CH_3$), 1.98 (s, 3, OAc), 1.99 (s, 3, OAc), and 2.01 (s, 3 OAc).

Anal. Calc. for $C_{30}H_{48}N_4O_{16}$: C, 49.99; H, 6.71; N, 7.77. Found: C, 49.64; H, 6.54; N, 7.54.

6-Deoxyneamine (**10**). — Compound **9** (340 mg) was heated in barium hydroxide solution as described in the preparation of **5**, to give 65 mg (46%) of **10** as an amorphous powder; m.p. 135° (dec), $[\alpha]_D^{22}$ +98.8° (*c* 1.02, water); ν_{max}^{KBr} 1590 cm^{-1} (NH_2); ^1H n.m.r. (D_2O at pD 1): δ 1.5–2.9 (m, 4, 2 ring methylene), and 6.12 (d, 1, *J* 3.5 Hz, H-1'). The product showed a single spot at R_F 0.3 on t.l.c. in the same solvent as that described for **5**.

1,3,2',6'-Tetra-N-*acetyl-6-deoxyneamine* (**11**). — Compound **10** (48 mg) was *N*-acetylated as described in the preparation of **6**, to give 32 mg (43%) of **11**; m.p. >300°, $[\alpha]_D^{22}$ +85.1° (*c* 0.45, water); ^1H n.m.r. (D_2O): δ 1.97 (s, 3, NAc), 2.02 (s, 3, NAc), 2.04 (s, 3, NAc), 2.07 (s, 3, NAc), and 5.38 (d, 1, *J* 3 Hz, H-1').

Anal. Calc. for $C_{20}H_{34}N_4O_9$: C, 50.62; H, 7.22; N, 11.81. Found: C, 50.30; H, 7.02; N, 11.67.

3',4'-Di-O-*acetyl-1,3,2',6'-tetra*-N-*ethoxycarbonyl-5,6-di*-O-*mesylneamine* (**12**). — 3',4'-Di-*O*-acetyl-1,3,2',6'-tetra-*N*-ethoxycarbonylneamine[5] (**1**, 710 mg) was treated with methanesulfonyl chloride (0.8 ml) in pyridine (4 ml) for 20 h with agitation, and the mixture was poured into ice-cold water (40 ml) to give a crystalline product that was collected by filtration. The product was recrystallized from isopropyl alcohol to give 560 mg (64%) of **12** as needles; m.p. 188–189°, $[\alpha]_D^{21}$ +35.0° (*c* 0.92, chloroform); ^1H n.m.r. δ 1.1–1.4 (m, 12, $4CO_2CH_2CH_3$), 1.98 (s, 3, OAc), 2.03 (s, 3, OAc), 3.12 (s, 3, SO_2CH_3), and 3.25 (s, 3, SO_2CH_3).

Anal. Calc. for $C_{30}H_{50}N_4O_{20}S_2$: C, 42.34; H, 5.92; N, 6.58; S, 7.53. Found: C, 42.36; H, 5.85; N, 6.21; S, 7.48.

3',4'-Di-O-*acetyl-5,6-dideoxy-1,3,2',6'-tetra*-N-*ethoxycarbonylneamin-5-ene* (**13**). — A mixture of **12** (505 mg), sodium iodide (5.0 g), and zinc powder (2.5 g) in *N*,*N*-dimethylformamide (10 ml) was heated for 2.5 h at 100° with agitation. The mixture was diluted with chloroform (40 ml) and filtered. The filtrate was washed successively with saturated sodium chloride solution, sodium thiosulfate solution, and water. After drying over anhydrous sodium sulfate, the solution was evaporated. The residue was purified on a column of silica gel with 10:1 (v/v) benzene–isopropyl alcohol as eluant to give 169 mg (43%) of **13** as an amorphous powder, which showed a single spot at R_F 0.34 on t.l.c. in the same solvent; m.p. 120°, $[\alpha]_D^{22}$ +159° (*c* 1.8, chloroform); ^1H n.m.r. δ 1.23 (t, 12, $4CO_2CH_2CH_3$), 2.00 (s, 3, OAc), 2.02 (s, 3, OAc), and 5.65 (broad s, 2, H-5 and 6).

Anal. Calc. for $C_{28}H_{44}N_4O_{14}$: C, 50.90; H, 6.71; N, 8.48. Found: C, 51.05; H, 6.74; N, 8.33.

3',4'-Di-O-*acetyl-1,3,2',6'-tetra*-N-*ethoxycarbonyl-5,6-dideoxyneamine* (**14**). — Compound **13** (116 mg) was hydrogenated in methanol (8 ml) under a hydrogen atmosphere (3.4 $kg.cm^{-2}$) for 15 h in the presence of platinum oxide (10 mg). After the catalyst had been removed by filtration, the filtrate was evaporated to give 113 mg (97%) of **14** as an amorphous powder; m.p. 61–94°, $[\alpha]_D^{20}$ +78.1° (*c* 2.5, chloroform); ^1H n.m.r. data: δ 1.22 (t, 12, $4CO_2CH_2CH_3$), 1.98 (s, 3, OAc), and 2.01 (s, 3, OAc).

Anal. Calc. for $C_{28}H_{46}N_4O_{14}$: C, 50.75, H, 7.00; N, 8.45. Found: C, 50.84: H, 7.00; N, 8.15.

5,6-Dideoxyneamine (**15**). — Compound **14** (302 mg) was hydrolyzed in barium hydroxide solution, and the hydrolyzate was purified as described in the preparation of **5**, to give 74 mg (56%) of **15**: m.p. 128–142°, $[\alpha]_D^{20}$ +125° (*c* 2.0, water); ν_{max}^{KBr} 1580 cm^{-1} (NH_2); ^1H n.m.r. (D_2O at pD 1): δ 1.1–2.9 (m, 6, 3 ring methylene), and 5.65 (d, 1, *J* 3.5 Hz, H-1'). The product showed a single spot at R_F 0.14 on t.l.c. in the solvent described for **5**.

1,3,2',6'-Tetra-N-*acetyl-5,6-dideoxyneamine* (**16**) — Compound **15** (20 mg) was *N*-acetylated as described in the preparation of **6**, to give 23 mg (70%) of **16**: m.p. >280°, $[\alpha]_D^{20}$ +111° (*c* 1.0, water); ^1H n.m.r. (D_2O): δ 1.93 (s, 3, NAc), 1.98 (s, 3, NAc), 2.02 (s, 3, NAc), 2.03 (s, 3, NAc), and 4.98 (d, 1, *J* 3.5 Hz, H-1').

Anal. Calc. for $C_{20}H_{34}N_4O_8 \cdot H_2O$: C, 50.41; H, 7.62; N, 11.76 Found: C, 50.34; H, 7.42; N, 11.44.

6,3',4'-Tri-O-*acetyl-1,3,2',6'-tetra*-N-*ethoxycarbonyl-5*-O-*mesylneamine* (**17**). — Compound **2** (251 mg) was treated with methanesulfonyl chloride (0.2 ml) in pyridine (2 ml) for 3 h with occasional agitation. The solution was poured into ice-cold water (50 ml), and the aqueous phase was extracted repeatedly with chloroform. After it had been washed successively with sodium hydrogensulfate solution, sodium hydrogen carbonate solution and water, the chloroform layer was dried over anhydrous sodium sulfate and then evaporated. The residue was recrystallized from ethanol–ether to give 197 mg (71%) of **17**: m.p. 205–206° (dec.), $[\alpha]_D^{20}$ +43.7° (*c* 0.9, pyridine); ^1H n.m.r. δ 1.98 (s, 3, OAc), 2.03 (s, 3, OAc), 2.10 (s, 3, OAc), and 3.06 (s, 3, SO_2CH_3).

Anal. Calc. for $C_{31}H_{50}N_4O_{19}S$: C, 45.69; H, 6.19; N, 6.88, S, 4.11. Found: C, 45.61; H, 6.04; N, 6.97; S, 4.14.

4,6-Di-O-*acetyl-1,3-di*-N-*ethoxycarbonyl-5*-O-*mesyl-2-deoxystreptamine* (**18**). — Compound **17** (190 mg) was heated for 10 h under reflux in 1.2M methanolic hydrogen chloride (14 ml). The solution was evaporated and the residue was fractionated on a column of silica gel with 9:1 (v/v) chloroform–methanol as eluant. Fractions that showed a single spot a R_F 0.4 on t.l.c. in the same solvent were combined and evaporated. The residue was acetylated to give 78 mg (71%) of **18** as crystals; m.p. 236–237° (dec.), ^1H n.m.r. (Me_2SO-d_6): δ 1.16 (t, 6, $2CO_2CH_2CH_3$), 2.00 (s, 6: 2 OAc), 3.09 (s, 3, SO_2CH_3), and 4.03 (q, 4, $2CO_2CH_2CH_3$)

Anal. Calc. for $C_{17}H_{28}N_2O_{11}S$: C, 43.59; H, 6.02; N, 5.98; S, 6.84. Found: C, 43.69; H, 5.90; N, 5.95; S, 6.95.

5,3',4'-Tri-O-*acetyl-1,3,2',6'-tetra*-N-*ethoxycarbonyl-6*-O-*mesylneamine* (**19**). — Compound **7** (280 mg) was treated with methanesulfonyl chloride as described in the preparation of **17**. The product was recrystallized from ethanol to give 284 mg (92%) of **19**: m.p. 192–193°, $[\alpha]_D^{20}$ +59.3° (*c* 1.05, pyridine); ^1H n.m.r. δ 1.26 (t, 12, $4CO_2CH_2CH_3$), 1.99 (s, 3, OAc), 2.03 (s, 3, OAc), 2.07 (s, 3, OAc), and 3.02 (s, 3, SO_2CH_3).

Anal. Calc. for $C_{31}H_{50}N_4O_{19}S$: C, 45.69, H, 6.19; N, 6.88; S, 4.11. Found: C, 45.36; H, 6.01; N, 6.60; S, 3.93.

(+)-4,5-Di-O-acetyl-1,3-di-N-ethoxycarbonyl-6-O-mesyl-2-deoxystreptamine (**20**). — Compound **19** (248 mg) was hydrolyzed in methanolic hydrogen chloride as described in the preparation of **18**, and the product was acetylated to give 61 mg (43%) of **20**; m.p. 220–221°, $[\alpha]_D^{22}$ +8.3° (*c* 1.6, acetone); ^{1}H n.m.r. (acetone-d_6): δ 1.17 (t, 3, *J* 7 Hz, $CO_2CH_2CH_3$), 1.20 (t, 3, *J* 7 Hz, $CO_2CH_2CH_3$), 1.95 (s, 3, OAc), 1.99 (s, 3, OAc), and 3.06 (s, 3, SO_2CH_3).

Anal. Calc. for $C_{17}H_{28}N_2O_{11}S$: C, 43.59; H, 6.02; N, 5.98; S, 6.84. Found: C, 43.38; H, 5.84; N, 6.20; S, 6.64.

Degradation of **5** *in 8.8*M *hydrobromic acid.* — Compound **5** (46 mg) was boiled in 8.8M hydrobromic acid (6 ml) for 20 h under reflux, and then evaporated. The residue was treated with ethyl chloroformate in M sodium hydroxide solution. The product was acetylated, and subsequently purified by column chromatography on silica gel to give 17 mg of a syrup that was identified as 4,6-di-*O*-acetyl-1,3-di-*N*-ethoxycarbonyl-2,5-dideoxystreptamine by comparing the i.r. and ^{1}H n.m.r. spectra with those of an authentic sample[5].

Degradation of **10** *in 8.8*M *hydrobromic acid.* — Compound **10** (65 mg) was hydrolyzed in 8.8M hydrobromic acid, and the hydrolyzate was processed as just described, to give 10 mg of (+)-4,5-di-*O*-acetyl-1,3-di-*N*-ethoxycarbonyl-2,6-dideoxystreptamine as a syrup; $[\alpha]_D^{22}$ +14.1° (*c* 0.78, chloroform). The product was identified by comparing its i.r. and ^{1}H n.m.r. spectra with those of an authentic sample of the racemic compound[5].

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