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(18) For another example where gas-phase reactivity is strongly affected by charge solvation, see C. Minot and Nguyen Trong Anh, *Tetrahedron Lett.*, 3905 (1975).
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(21) S. D. Peyerimhoff and R. D. Buenker [*Chem. Phys. Lett.*, **65**, 434 (1979)] in their recent calculations on $FCCl_3^-$, find a low-lying $^2A'$ root (with a diffuse electron and a rising energy surface similar to that of the neutral) intersected by a rapidly descending valence-like $^2A'$ root. The intersection occurs so early that there should be no barrier to dissociation of $FCCl_3^-$. The difference with our own results can be ascribed to the lower initial energy of σ^*_{CCl} in $FCCl_3$ (where it is largely localized on the external, highly electronegative FCl_2 side) than in CH_3Cl.

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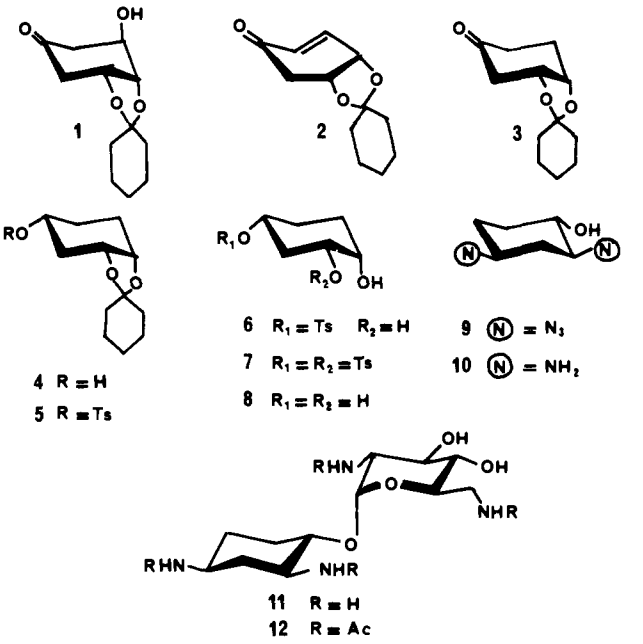

Synthesis of 2,5,6-Trideoxystreptamine and Its Transformation into Bioactive Pseudodisaccharides by Microbial and Chemical Methods

Sir:

The intrinsic toxicity and enzymatic inactivation of known aminocyclitol glycoside antibiotics makes the discovery of new drugs a goal of prime importance. Until the present time, most of the research efforts in this field were directed toward soil screening, chemical modifications of naturally occurring antibiotics, and mutasynthesis utilizing idiotrophs.[1-3] An alternative approach to the development of new amino glycosides would be total chemical synthesis. However, owing to the complex molecular architecture of the natural amino glycosides, this route has not been greatly utilized.

It is noteworthy that recently discovered amino glycosides such as Fortimicins[4] and Sporaricins[5] are composed of only two cyclic nuclei (aminocyclitol-*epi*-purpurosamine). Furthermore 4-O-substituted 2-deoxystreptamines are the antibacterial determinants of a variety of microbial products.[6] Therefore, it was envisaged that the preparation of relatively "simple" analogues of naturally occuring amino glycoside antibiotics could afford novel bioactive substances.

In this respect, it appeared to us that the chiral 2,5,6-trideoxystreptamine[7] **10** would be an interesting aglycon. Accordingly, we report here its synthesis from quinic acid and its microbial and chemical transformation into two bioactive pseudodisaccharides, **11** and **18**.

The crucial intermediate for the synthesis of **10** was the hydroxy ketone **1** which was readily available from quinic acid.[8] Treatment of **1** with *p*-toluenesulfonyl chloride in pyridine (5 days, room temperature) gave the crystalline conjugated enone **2**, in 95% yield: mp 56-58 °C; $[\alpha_D]$ +135° (*c* 1.0, $CHCl_3$); UV max (95% C_2H_5OH) 217 nm (ϵ 8.8 × 10^3); IR (film) 1670 (C=O) cm^{-1}; ^{13}C NMR ($CDCl_3$) $\delta(C_1 \rightarrow C_6)$ 195.6, 38.6, 70.7, 73.0, 146.2, 128.8. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.21; H, 7.73. Catalytic hydrogenation (10% Pd/C) of **2** in ethyl acetate produced the saturated ketone **3** (85%), mp 86-87 °C, $[\alpha]_D$ +136° (*c* 1.11, $CHCl_3$), as a white solid. Lithium borohydride reduction of **3** in diglyme furnished exclusively the syrupy alcohol **4**, which was converted into its crystalline tosylate **5** (90% from **3**), mp 88-89 °C, $[\alpha]_D$ +42° (*c* 1.08, $CHCl_3$). The cyclohexylidene group in **5** was hydrolyzed in methanol using Amberlite IR 120 (H^+) resin to give the amorphous diol **6** which was selectively tosylated to produce the desired ditosyloxycyclohexanol **7** (80% from **5**), mp 134 °C, $[\alpha]_D$ +19° (*c* 1.25, $CHCl_3$). Alternatively, **7** was also obtained by acidic removal of the ketal group in **4**, followed by selective *p*-toluenesulfonylation of the cyclohexanetriol **8**, mp 137-138 °C, $[\alpha]_D$ +18° (*c* 1.0, EtOH). The overall yield was 55% based on **1**. Azidolysis of **7** in dimethylformamide (120 °C, 30 min) produced the oily diazide **9**, $[\alpha]_D$ +81° (*c* 1.0, $CHCl_3$), which was hydrogenated using Adams' catalyst in methanol to yield the 2,5,6-trideoxystreptamine **10**, isolated as its dihydrochloride salt, mp 305-310 °C dec, $[\alpha]_D$ +17° (*c* 1.15, H_2O). Anal. Calcd for $C_6H_{16}Cl_2N_2O$: C, 35.48; H, 7.94; Cl, 34.91; N, 13.79. Found: 35.32; H, 7.91; Cl, 35.04; N, 13.55.

Using the method of Rinehart and co-workers[3] for producing mutasynthetic amino glycoside antibiotics, exogenously added, 2,5,6-trideoxystreptamine **10** was converted by the idiotroph of *Streptomyces fradiae* (ATCC 21401) into bioactive 5,6-dideoxyneamine **11**, isolated as its disulfate salt, mp 280-283 °C dec, $[\alpha]_D$ +40° (*c* 1.0, H_2O). Anal. Calcd for $C_{12}H_{26}N_4O_4 + 2H_2SO_4$: C, 29.62; H, 6.2; N, 11.5; S, 13.18. Found: C, 29.40; H, 6.35; N, 11.32; S, 13.04. The culture medium was supplemented with **10** (250 μg/mL) and 10% inoculum of the mutant was added. The culture was further incubated at 30 °C for 5-6 days, until antibacterial potency reached a maximum. 5,6-Dideoxyneamine **11** and unchanged 2,5,6-trideoxystreptamine **10** were absorbed on Amberlite IRC 50 (NH_4^+ form) from which they were eluted with 1 N ammonium hydroxide. Further purification was accomplished by ion exchange chromatography on Amberlite CG50 (NH_4^+ form) or CM-Sephadex C-25 (NH_4^+ form) using an increasing concentration of ammonium hydroxide as eluant.

The structure of the bioactive pseudodisaccharide isolated was confirmed on the basis of the data obtained from its *N*-acetate derivative **12**: mp >270 °C dec; $[\alpha]_D$ +96° (*c* 1, H_2O); ^1H NMR [4-N-Ac(S)] δ 1.98, 1.96, 1.93 and 1.89; chemical ionization mass spectrometry[9] *m/e* 459 (MH^+), fragments 245, 227, 215, and 197. Anal. Calcd for $C_{20}H_{34}N_4O_8$: C, 52.39; H, 7.47; N, 12.22. Found: C, 52.31; H, 7.35; N, 12.02. This derivative was found to be identical with the tetra-*N*-acetyl-5,6 dideoxyneamine reported recently by Suami and co-workers.[10]

Biotransformation of **10** into **11** is consistent with our previous postulation[11] that neomycin biosynthesis proceeds via an intermediate of the neamine type rather than 5-O-substituted 2-deoxystreptamine. This hypothesis is consistent with

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Table I. Comparative in Vitro Activity of Neamine 5,6-Dideoxyneamine and 3′,5,6-Trideoxykanamine A against *Bacillus subtilis* and *E. coli*

compd	MIC, μg/mL	
	Bacillus subtilis	*E. coli*
neamine	0.25	3
5,6-dideoxyneamine	0.25	4
3′,5,6-trideoxykanamine A	0.5	20

Table II. Antimicrobial Activity of Kanamine, Neamine, and 3′,5,6-Trideoxykanamine A against *Pseudomonas aeruginosa* (ATCC 10145)

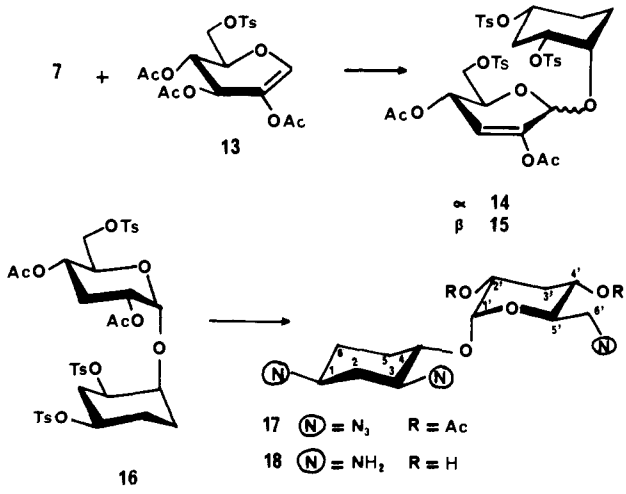
concn, mg/mL	diameter of inhibition zone in mm, by the paper disk method		
	kanamine	neamine	3′,5,6-trideoxy-kanamine A
0.5	0	0	6
1	0	0	8
2	0	0	10

the recently reported subunit assembly for the butirosins.[12]

In general, mutasynthesis provides vital information concerning the structural modification allowed for the aglycone moiety of amino glycosides.[1-3,13] **11** exhibits broad-spectrum antibacterial activity (Table I) comparable with that of neamine.[10] Consequently, the chemical synthesis of other pseudodisaccharides having 2,5,6-trideoxystreptamine as an aglycone, with altered amino sugar subunit, was considered.

A recently described[14] extension of Ferrier's reaction, leading to cyclitol α-glycoside, was used as glycosylation procedure. This method gives stereoselectively the α-glycosidic bond in high yield (70-80%) and simultaneously provides 3′-deoxyaminocyclitol glycosides, an important feature regarding enzymatic inactivation.

Addition of the glycal **13** (1.5 equiv) to a dichloroethane solution of **7** containing a catalytic amount of boron trifluoride etherate as described previously[14] furnished in 95% yield an anomeric mixture of unsaturated derivatives **14** and **15** in a ratio of 7:3, respectively, as shown by ^{13}C NMR: $\delta(C_{1'\beta})$ 94.9,



$\delta(C_{1'\alpha})$ 91.6 ppm. From the mixture the β-glycoside **15** could be isolated by crystallization, mp 156-157 °C, $[\alpha]_D$ +58° (*c* 1.6, $CHCl_3$). The reduction of the syrupy α-glycoside **14**, as noted previously,[14] proceeded regiospecifically giving the required compound **16** (65% overall yield based on **7**), mp 179-180 °C, $[\alpha]_D$ +79° (*c* 1.34, $CHCl_3$), with the D-ribo configuration as confirmed by ^1H and ^{13}C NMR [$J_{1',2'}$ = 3.5, $J_{2',3'a}$ = 12, $J_{2',3'e}$ = 5 Hz; δ 92.9 ($C_{1'}$) and 67.9 ($C_{5'}$)].

Azidolysis of **16** yielded the unstable oily triazide **17**. Sequential deacetylation and catalytic reduction gave the 3′,5,6-trideoxykanamine A **18** characterized as its trihydrochloride salt, mp 214-220 °C, $[\alpha]_D$ +67° (*c* 0.83, H_2O). Anal. Calcd for $C_{12}H_{28}Cl_3N_3O_4$: C, 37.46; H, 7.34; Cl, 27.65; N, 10.92. Found: C, 37.17; H, 7.47; Cl, 27.41; N, 10.72.

The structure of **18** was assigned[16] on the basis of its ^{13}C NMR spectrum [$\delta(C_1 \rightarrow C_6)$ 48.2, 33.3, 52.5, 74.7, 26.5, 28.2; $\delta(C_{1'} \rightarrow C_{6'})$ 93.7, 66.6, 34.8, 66.6, 69.9, 41.3] and chemical ionization mass spectrometry[9] [*m/e* 276 (MH^+), fragments 146 and 131].

The antibacterial activity of 3′,5,6-trideoxykanamine A is comparable with that of kanamine A against a variety of strains.[15] Surprisingly 3′,5,6-trideoxykanamine A exhibited activity against *Pseudomonas aeruginosa* (ATCC 10145), a great advantage over the parent kanamine A and also neamine (Table II).

Extension of this work is continuing in our laboratories.

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Synthesis and Structure of a Bis[terpyridineplatinum(II)] Complex and Its Evaluation as a Metallointercalator

Sir:

Intercalation is a mode of binding of flat molecules to nucleic acids.[1] Numerous organic dyes and drugs[2] as well as platinum complexes[3] such as **1** intercalate into DNA and RNA. X-ray crystallographic investigations have elucidated the geometry

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