CHEMICAL TRANSFORMATION OF 3'-CHLORO-3'-DEOXYAMINOGLYCOSIDES INTO NEW CYCLIC PSEUDO-TRISACCHARIDES

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Cyclic pseudo-trisaccharides (2a,b) and 3'-epi-aminoglycosides (4a,b) were obtained from 3'-chloro-3'-deoxyaminoglycosides (1a,b) by treatment with a base.

In a previous paper[1], we reported a novel and efficient method for the selective dehydroxylation of aminoglycoside antibiotics via 3'-chloro-3'-deoxyaminoglycosides.

We now wish to describe[2] the synthesis of new cyclic pseudo-trisaccharides by an intramolecular cyclization of aminoglycosides.

Treatment of 3'-chloro-3'-deoxyxylostasin[1] (1a) with 5% aqueous sodium hydroxide at room temperature for 24 hr afforded two new compounds in 80% and 9% yields, respectively. The elemental analysis coupled with the mass spectrum of the major product [mp 240-245°C, $[\alpha]_D$ +26.5° (c=0.9, H_2O), Anal. Calcd. for $C_{17}H_{32}N_4O_9 \cdot H_2O$: C, 44.92; H,

7.54; N, 12.32. Found: C, 45.14; H, 7.33; N, 12.02, the tetra-N-acetyl-tetra-O-trimethylsilyl derivative[3]: m/e 892 (M^+)] indicated that, on this reaction, HCl was eliminated from the starting compound. Considerable changes of the chemical shifts of each carbons in 2,6-diaminoglucose moiety and C-5" were observed by comparison of the ^{13}C-nmr spectrum of the product with that of xylostasin[4], while the chemical shifts of the other carbons were almost identical in both compounds**. O-Alkylation at C-5" was, in particular, suggested by 8.1 ppm downfield shift in the C-5" signal[5]. According to the above results, cyclic pseudo-trisaccharide structure was assigned to this product (2a).

In order to confirm the assignment, 2a was treated with 2N-HCl methanolic solution at 70°C to give a mixture of methyl α- and β-glycosides [mp 105-114°C, Anal. Calcd. for $C_{18}H_{36}N_4O_{10}\cdot 1.5H_2O$: C, 43.62; H, 7.93; N, 11.30. Found: C, 43.69; H, 7.83; N, 11.08, the tetra-N-acetyl-penta-O-trimethylsilyl derivative: m/e 981 (M^+-15)]. The mass

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** ^{13}C-Chemical shifts of C-1' to C-6' and C-5" of xylostasin, cyclic pseudo-trisaccharide (2a), neamine and 3'-epi-neamine (6)[6].

	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'	C-5"
xylostasin	99.8	56.4	74.0‡	72.3	74.1‡	42.6(t)†	61.3(t)
2a	93.9	49.4	82.1‡	81.4‡	68.4	40.3(t)	69.4(t)
neamine	101.5	56.2	74.4	72.4	73.4	42.6(t)	-
6	102.4	47.7	71.3	70.1	67.8	42.1(t)	-

† (t) designates triplet in off resonance proton decoupling and the others are doublet.

‡ Assignments may be reversed.

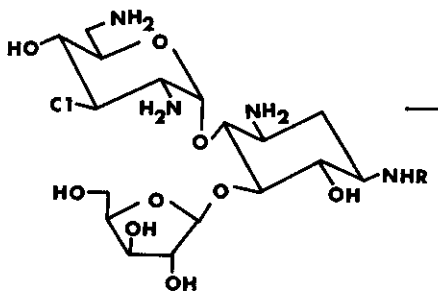
spectrum and the elemental analysis were consistent with those of the expected linear pseudo-trisaccharide (3).

The minor product was assumed to be 3'-epi-xylostasin (4a) on the basis of the mass spectrum and from the fact that, on methanolysis, it gave 3'-epi-neamine (6) mentioned below.

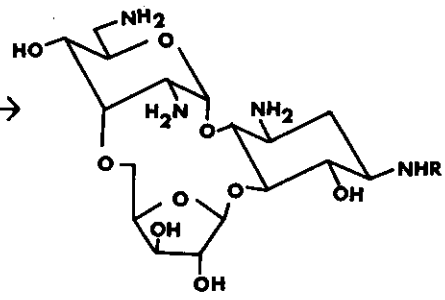
Isolation of 2a and 4a, both having the 3'-axial oxygen atom, suggested that this reaction proceeded by intra- or intermolecular substitution reaction of the chlorine atom at C-3' with C-5"-hydroxyl group of 1 or hydroxyl anion in the medium. Furthermore, the participation of the C-2'-amino group was ruled out in this reaction because 2',3'-epimino-2'-deamino-3'-deoxyxylostasin[1] was recovered unchanged under the present reaction conditions.

Similarly, cyclic pseudo-trisaccharide (2b) [mp 185-193°C, $[\alpha]_D$ +20° (c=0.6, H_2O), the tetra-N-acetyl-penta-O-trimethylsilyl derivative: (m/e) 1050 (M^+)] and 3'-epi-butirosin A (4b) were obtained from 3'-chloro-3'-deoxybutirosin A (1b) in 35% and 11% yields, respectively. However, 3'-chloro-3'-deoxyneamine (5)[1] and 3'-chloro-3'-deoxykanamycin B[1] were both recovered unchanged under the present reaction conditions.

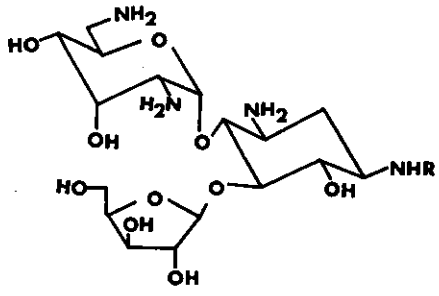
Although 5 was recovered at room temperature, treatment of 5 with 5% aqueous sodium hydroxide at 100°C gave two new products in addition to neamine. The elemental analyses and the mass spectra of these new products were quite similar to those of neamine. The major product [mp 205-210°C, $[\alpha]_D$ +62° (c=0.46, H_2O)] was determined to be 3'-epi-neamine (6) on the basis of its ^{13}C-nmr spectrum**. The introduction of axial hydroxyl group at C-3' was accounted for by the fact that the chemical shifts of C-2', 3', 4', and 5' were observed at higher field than those of neamine by 2.3 - 8.5 ppm[7]. The minor



(1)



(2)



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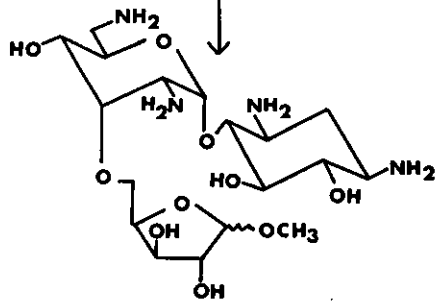
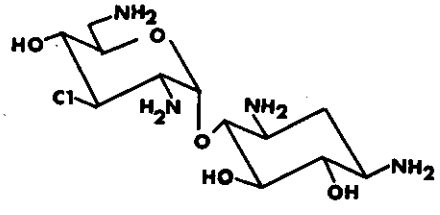


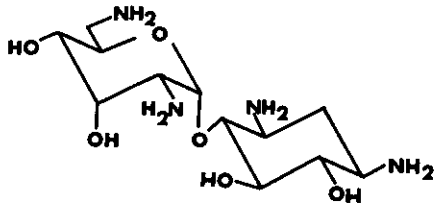
(3)

a ; R = H

b ; R = $COCHCH_2CH_2NH_2$ (OH)



(5)



(6)

product, which was fairly unstable, was tentatively assigned the 3'-epi-4'-epi-neamine with the 3',4'-diaxial orientation[8].

The facile chemical transformation of 1a, b into the cyclic pseudotrisaccharides (2a, b) shows that the C-5" hydroxyl group of xylose moiety are located very close to the C-3' position of the 2,6-diaminoglucose moiety, as Umezawa et al. proposed in enzymatic phosphorylation of aminoglycosides from the consideration of the molecular model[9].

All of the compounds obtained herein failed to show the antimicrobial activity.

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REFERENCES AND FOOTNOTES

1 T. Okutani, T. Asako, K. Yoshioka, K. Hiraga and M. Kida, J. Amer. Chem. Soc., 1977, 99, 1278.

2 All compounds described herein were separated by column chromatography on ion exchange resin Amberlite CG-50 (NH_4 form) and crystallized.

3 The samples for the mass spectra were prepared by acetylation of the aminoglycosides with acetic anhydride in methanol followed by silylation with bis-trimethylsilylacetamide in pyridine.

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6 The spectra were recorded for D_2O solution with an internal dioxane reference and the expression δ_C (TMS) = δ_C (dioxane) + 67.4 ppm was employed to express the chemical shifts downfield from TMS.

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8 It can be presumed that 3',4'-epoxy-3',4'-dideoxyneamine is the intermediate in the formation of neamine. Hydrolysis of the epoxide at C-4' should afford 3'-epi-4'-epi-neamine.

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