Synthesis of Ethyl 2,6-Diacetamido-2,3,6-trideoxy-α-D-*ribo*-hexopyranoside, a derivative of the Diamino-sugar Component of the Antibiotic Nebramycin Factor 6

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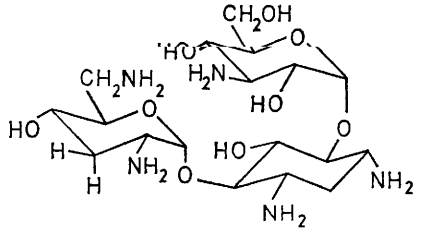
Summary Derivatives of a new diaminotrideoxy-D-hexose, a carbohydrate component of the pseudotrisaccharide antibiotic nebramycin factor 6 have been prepared; the synthesis is based on a conjugate 1,4-addition of azide ion on the α,β-unsaturated ketone (**2**).

THE recently isolated nebramycin factor 6 is a chemotherapeutically important aminoglycoside antibiotic.[1] *In vitro* studies[2] have shown that nebramycin is more active than gentamycin against *Pseudomonas* species, but slightly less active against other gram-negative bacteria. Structure (**1**) was proposed[1] for the pseudotrisaccharide on the basis of its physical properties and n.m.r. spectroscopic data. The antibiotic is composed of units of 2-deoxystreptamine, 3-amino-3-deoxy-D-glucose, and nebrosamine, a new diaminotrideoxy-D-hexose.

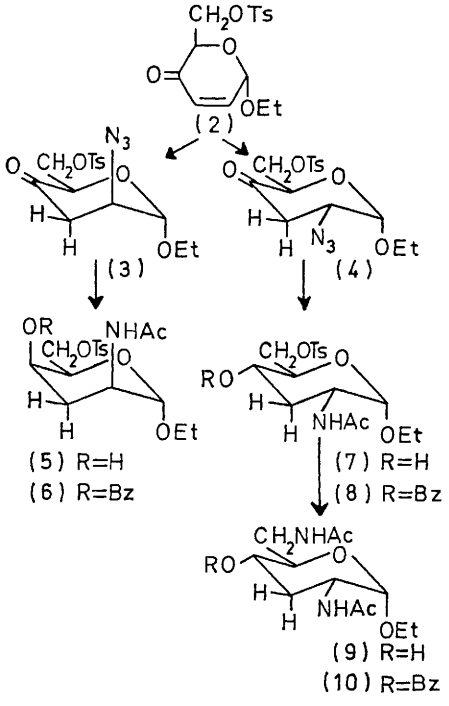
We report the synthesis of ethyl 2,6-diacetamido-2,3,6-trideoxy-α-D-*ribo*-hexopyranoside (**9**), by conjugate 1,4-



(1)

addition[3] of azide ion to the readily available α,β-unsaturated ketone (**2**)[4]. The ketone (**2**) was treated with sodium azide in aqueous acetic acid at room temperature,

and the progress of the reaction monitored by n.m.r. spectroscopy. After five minutes, the formation of compound (**3**) was observed. The structure of (**3**) was assigned on the basis of its ^{13}C n.m.r. spectrum. Compound (**3**) was



unstable, but afforded, on treatment with sodium borohydride followed by hydrogenation over Pd–C (5%) in acetic anhydride–methanol, compound (**5**), m.p. 172—173 °C, $[\alpha]_D^{25}$ + 6·5° (*c* 1·7, $CHCl_3$); the n.m.r. spectrum of its *O*-benzoate (**6**) clearly established its structure: $J_{1,2} < 2$, $J_{2,3a}$ 4, $J_{4,3a}$ 3 Hz. After five hours the main product (65%) was compound (**4**). The assignment of the D-*erythro*-configuration of (**4**) was confirmed by ^{13}C n.m.r. spectroscopy. Compound (**4**) was also unstable but was readily converted by an analogous series of reactions into (**7**), m.p. 170·5—173 °C, $[\alpha]_D^{25}$ + 99° (*c* 1·24, pyridine). The D-*ribo* configuration of (**7**) was unequivocally established by the n.m.r. spectrum of its *O*-benzoate (**8**); $J_{1,2}$ 3·5, $J_{2,3a}$ 12, $J_{2,3e}$ 4, $J_{4,5}$ 11 Hz.

Treatment of (**7**) with sodium azide in *NN*-dimethylformamide at 100° for 1·5 h, followed by hydrogenation of the resultant 6-azido derivative in acetic anhydride–methanol, afforded compound (**9**), m.p. 181—183 °C, $[\alpha]_D^{25}$ + 129° (*c* 1·55, MeOH). Benzoylation of compound (**9**) furnished compound (**10**) $J_{1,2}$ 4, $J_{2,3a}$ 12·5, $J_{2,3e}$ 4, $J_{4,5}$ 10 Hz.

The n.m.r. spectral data obtained for (**9**) and (**10**) are in agreement with those reported[1] for the methyl α-D-glycoside of *NN*-diacetylnebrosamine.

Compounds (**5**) and (**7**) are also of interest[5] as potential intermediates for the preparation of purpurosamine, epipurpurosamine, and the diamino-carbohydrate component of sisomicin.[5]

All new compounds gave satisfactory elemental analyses.

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Added in proof: Since submitting this manuscript, Professor R. D. Guthrie has informed us that a synthesis of derivatives of 2,6-diamino-2,3,6-trideoxy-α-D-*ribo*-hexopyranoside using an entirely different approach, has been accomplished in his laboratory.

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