## Synthesis of 3-Amino-2,3-dideoxy-a-D-arabino-hexopyranosyl Gentamine C1

By PETER J. L. DANIELS, ALAN K. MALLAMS, and JOHN J. WRIGHT\* (Research Division, Schering Corporation, Bloomfield, New Jersey 07003)

Summary Acid catalysed addition of 3-acetamido-3-deoxy-4,6-di-O-acetyl-D-glucal (2) to the relatively complex pseudodisaccharide (4) resulted in regio- and stereoselective formation of the 2-deoxy- $\alpha$ -glycoside (5).

IMPORTANT recent trends in aminoglycoside chemistry have focused on a synthetic modification, or elimination of sites within the antibiotic molecule which have been shown to be targets for inactivation by enzymes present in resistant organisms. A number of such modifications have recently been remarkably successful.<sup>1</sup> The discovery that antibiotics of the kanamycin-gentamicin class, *e.g.* 3',4'-dideoxykanamycin B (1), can be inactivated by adenylylation at the 2''-position by certain resistant bacteria<sup>2</sup> has made the efficient synthesis of 3-amino-2,3-dideoxy- $\alpha$ -glycopyranosides of particular importance. The acid catalysed condensation of an alcohol with the glucal<sup>3</sup> (2) provides such a method.

The acid catalysed addition of alcohols to glycals to afford 2-deoxyglycosides is well known. This reaction, however, has usually required a large excess of the alcohol to be condensed and has suffered from the further limitation that accompanying allylic rearrangements occur when the substituent at C-3 is an acetoxy-group as, for example, in the case of tri-O-acetyl-D-glucal<sup>4</sup> (3). Yields from such reactions have consequently been typically low. It was reasoned, however, that compound (2), having a poorer leaving group at the 3-position should undergo addition of alcohols without rearrangement and this was proved to be the case. Condensation of tetra-N-benzyloxycarbonylgentamine  $C_1$  (4) (2.2 equiv.), prepared by standard methods from the free amine,<sup>5</sup> with the glucal (2) (4.0 equiv.) in the presence of toluene-p-sulphonic acid hydrate (0.27 equiv.) in dry benzene at  $45-50^{\circ}$  for 36 h gave (5) (88%) together with some unchanged glycal. Removal of the benzyloxycarbonyl and acetate groups was effected with sodium in liquid ammonia, followed by dilute aqueous alkali, to give, after chromatography, 3-amino-2,3-dideoxy-a-D-arabino-hexopyranoside (6),  $[\alpha]_{D} + 101.5^{\circ}$  (c 0.4, H<sub>2</sub>O), in 48% overall yield from (4). Although two hydroxy-groups are in principal available for condensation in compound (4), reaction takes place only at the least hindered site. This was



demonstrated by an N-acetylation, permethylation, and hydrolysis sequence<sup>6</sup> which gave symmetrical N,N'-diacetyl-2-deoxy-N,N'-5-O-trimethylstreptamine (7), m.p. 221-223°, identical with authentic material, as the sole product. The <sup>1</sup>H n.m.r. spectrum of (6) showed two doublets, a somewhat broadened signal at  $\delta$  5.11 (J 3.5 Hz), and a sharper absorption at  $\delta$  5.05 (J 3.5 Hz), which could be assigned to the anomeric  $H_1''$  and  $H_1'$  protons, respectively, of the two  $\alpha$ -glycosides. All other <sup>1</sup>H n.m.r. signals could be assigned in accordance with structure (6). Irradiation of the 2"-methylene protons at  $\delta$  1.6 resulted in collapse of the doublet at  $\delta$  5.11 into a singlet. The fragmentation pattern in the mass spectrum of (6) was consistent with the assigned structure and fitted well into the pattern observed for related compounds.<sup>7</sup> The <sup>13</sup>C n.m.r. spectrum of (6) was also consistent with the assigned structure.

Compound (5) was the only product of the condensation reaction. The reaction was therefore cleanly regio- and stereo-selective. Such high yielding, stereoselective, a-glycoside syntheses from alcohols as complex as (4) are relatively rare. The exclusive formation of the  $\alpha$ -anomer may reflect simply the stereoelectronic requirements in addition of the alcohol to a cationic intermediate such as (8). Alternatively the reaction may proceed via the protonated bicyclic intermediate (9) in which participation of the 3-acetamidogroup would dictate exclusive  $\alpha$ -glycoside formation. A similar bicyclic intermediate has recently been proposed to account for reactions of another 3-acetamido sugar.8 Experiments are in progress to clarify the mechanism of this reaction.

The 2"-deoxyaminoglycoside (6) was essentially inactive as an antibacterial which was surprising in view of the interesting antibacterial activity found for the related 2"-deoxygentamicin C2.9

During the progress of this work a report appeared describing the acid catalysed addition of heterocyclic bases to the related glycal (2;  $R = NHCOOC_2H_5$ ),<sup>10</sup> which afforded nucleoside analogues in high yields without rearrangement.

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