NITROGEN-CONTAINING CARBOHYDRATE DERIVATIVES

PART XXVI*. PERIODATE OXIDATION OF METHYLATED DERIVATIVES OF AMINO SUGARS

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ABSTRACT

Studies have been made of the periodate oxidation of carbohydrate derivatives containing the –CH(OH)–CH(NHMe)– and –CH(OH)–CH(NMe_2)– groupings, and having an *eq,eq* and *ax,ax* arrangement in each case. In the dimethylamino system, each compound gave the *N*-oxide, whereas the methylamino systems followed an oxidation pattern similar to that of the analogous –CH(OH)–CH(NH_2)– system studied in earlier work. Oxidation of compounds containing the –CH(OMe)–CH(NH_2)– grouping occurred very slowly in a non-Malapradian fashion.

INTRODUCTION

The reaction of periodate with vicinal amino-alcohols, where the amine group was di- or tri-substituted (with alkyl or aryl groups), has been reported to depend extensively on the structure of the compound oxidised and on the experimental conditions[1–5]. A study of the periodate oxidation of a series of methylated, amino sugars of known configuration was therefore thought to be useful, particularly since several *N*-methylated, amino sugars have been found as components of antibiotics[2,5–11].

The preferred conformations of the two series of compounds studied are shown in formulae **1** and **2** (*altro*) and **4** and **5** (*gluco*). Periodate oxidation of the corresponding diols[12] and amino-alcohols[13,14], as well as cuprammonium studies[15], have confirmed the conformational stability of these systems. The pK_a values for compounds **1**, **2**, **4**, and **5** have already been reported[16]. Compounds **3** and **6**, containing a vicinal, amino-methoxy system, were also prepared and studied.

EXPERIMENTAL

Methyl 3-amino-4,6-O-benzylidene-3-deoxy-2-O-methyl-α-D-glucoside (**6**). — Methyl 4,6-*O*-benzylidene-3-deoxy-2-*O*-methyl-3-phenylazo-α-D-glucoside[17] (3.6 g) in

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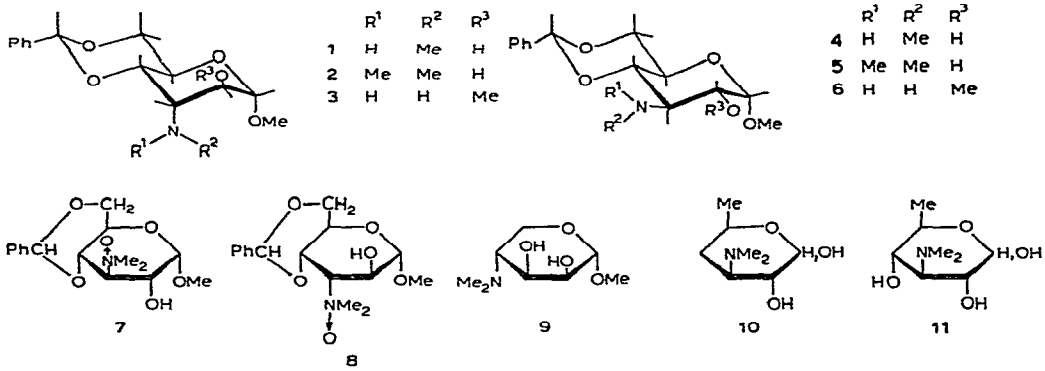

methanol (200 ml) was heated with hydrogen (60 atmos.) in the presence of Raney nickel[18] at 85° for 12 h. The pale-yellow, solid residue, obtained after removal of the nickel and the solvent, was extracted with boiling water. The extract was treated with charcoal and concentrated to give white crystals (2.3 g, 82%), m.p.146–147°, which were recrystallised from ethanol–light petroleum to give **6**, m.p. 146–147°, $[\alpha]_D^{19}$ +99° (*c* 0.48)* (Found: C, 61.2; H, 7.0; N, 4.9. $C_{15}H_{21}NO_5$ calc.: C, 61.0; H, 7.2; N, 4.7%).

Methyl 4,6-O-benzylidene-3-deoxy-3-ethoxycarbonylamino-α-D-glucoside. — Methyl 3-amino-4,6-*O*-benzylidene-3-deoxy-α-D-glucoside (3 g) in ice-cold dichloromethane (120 ml) containing triethylamine (3 ml) was stirred for 2 h with ethyl chloroformate[19] (3 ml). The solid formed was removed by filtration and combined with the residue from the acid-washed solvent. Recrystallisation from ethanol–light petroleum gave colourless crystals (2.4 g, 64%), m.p. 258–259°, which on further recrystallisation from the same solvent gave the title compound, m.p. 261–262°, $[\alpha]_D^{25}$ +73.2° (*c* 0.71) (Found: C, 57.8; H, 6.5; N, 4.1. $C_{17}H_{23}NO_7$ calc.: C, 57.8; H, 6.6; N, 4.0%).

Methyl 4,6-O-benzylidene-3-deoxy-3-methylamino-α-D-glucoside. (**4**). — The urethane prepared above (2.9 g) was suspended in dry tetrahydrofuran (20 ml) and heated under reflux with lithium aluminium hydride (2 g) for 24 h[20]. After treatment of the mixture with water and extraction with acetone, a white solid was obtained by evaporation of the solvent. Recrystallisation from chloroform–light petroleum gave **4** (1.42 g, 59%), m.p. 119.5–120.5°, $[\alpha]_D^{25}$ +102° (*c* 1.27) (Found: C, 60.9; H, 7.1; N, 4.8. $C_{15}H_{21}NO_5$ calc.: C, 61.0; H, 7.2; N, 4.7%).

N-Methylation of methyl 3-amino-4,6-O-benzylidene-3-deoxy-α-D-glucoside. — (*a*) Methyl 3-amino-4,6-*O*-benzylidene-3-deoxy-α-D-glucoside (1 g) was heated under reflux for 15 min with formaldehyde (40% w/v, 2.5 ml) and formic acid (98%, 1 ml) in ethanol (25 ml). After partial evaporation, the mixture was made alkaline with aqueous sodium hydroxide, water was added, and the mixture was extracted continuously with chloroform for 20 h. Concentration of the chloroform extract gave a semi-crystallline solid, which was recrystallised from ethanol–light petroleum to

*Optical rotations are for solutions in chloroform.

give white crystals of methyl 4,6-*O*-benzylidene-3-deoxy-3-dimethylamino-α-D-glucoside (**5**), m.p. 137–139°, $[\alpha]_D^{20}$ +115° (*c* 0.56) (Found: C, 61.9; H, 7.5; N, 4.5. $C_{16}H_{23}NO_5$ calc.: C, 62.1; H, 7.5; N, 4.5%).

Repetition of the above experiment, but using formic acid (5.2 ml) and a reaction time of 2 h, gave methyl 3-deoxy-3-dimethylamino-α-D-glucopyranoside (from chloroform–light petroleum) (68%), m.p. 105–106.5° (lit.[21] m.p. 107–108°), which was characterised as the hydrochloride, m.p. 201–202°, $[\alpha]_D^{20}$ +115° (*c* 0.4, water); lit.[21] m.p. 194°, $[\alpha]_D$ +112° (water).

Treatment of methyl 3-deoxy-3-dimethylamino-α-D-glucopyranoside with benzaldehyde. — The title sugar was treated with freshly distilled benzaldehyde and freshly fused zinc chloride, the molar ratios of the reactants to 1 mole of sugar being variously 21–27 and 8–12 moles, respectively. The reactions were carried out by stirring or shaking the reaction mixtures at room temperature for 19–50 h; the processing of the reaction mixtures followed the usual procedure[22]. No pure benzylidene derivative was isolated from any of the preparations.

When the reaction was carried out in the presence of hydrogen chloride[23] instead of zinc chloride, unreacted sugar was isolated.

Methyl 3-azido-4,6-O-benzylidene-3-deoxy-2-O-methyl-α-D-altroside. — Methyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-altroside[24] (9.1 g) was dissolved in chloroform (20 ml), and methyl iodide (30 ml) was added. The mixture was heated until reflux started, and silver oxide (15 g) was then added in small portions, with vigorous stirring, during 90 min. Heating was then continued for 24 h. After removal of the silver oxide and the solvent, the residue was crystallised from chloroform–light petroleum to give white crystals (8.23 g, 87%), m.p. 94–96°; t.l.c. showed one main component plus an impurity. The mixture was chromatographed on alumina with 200 ml of benzene. Evaporation of the eluent gave a white solid (7.85 g, 83%), m.p. 110° (homogeneous by t.l.c.). Recrystallisation from chloroform–light petroleum gave white crystals of the title compound, m.p. 111–112°, $[\alpha]_D^{19}$ +38° (*c* 0.65) (Found: C, 56.2; H, 6.1; N, 12.9. $C_{15}H_{19}N_3O_5$ calc.: C, 56.1; H, 6.0; N, 13.1%).

Methyl 3-amino-4,6-O-benzylidene-3-deoxy-2-O-methyl-α-D-altroside (**3**). — The foregoing azide (5 g) was heated under reflux with hydrazine hydrate (5 ml) in the presence of Raney nickel[18] for 6 h. After filtration and evaporation, a syrup was obtained which crystallised to give a pale-green solid (4.58 g), m.p. 77°. Recrystallisation from ethanol–light petroleum gave colourless crystals of **3** (3 g, 65%), m.p. 78.5–80°. Further recrystallisation gave material having m.p. 81–82°, $[\alpha]_D^{24}$ +100° (*c* 2.7) (Found: C, 61.0; H, 7.0; N, 4.8. $C_{15}H_{21}NO_5$ calc.: C, 61.0; H, 7.2; N, 4.7%).

Methyl 4,6-O-benzylidene-3-deoxy-3-methyl-amino-α-D-altroside (**1**) *and its dimethylamino analogue* **2**[25]. — The 3-methylamino derivative **1** had m.p. 181–182°, $[\alpha]_D^{19}$ +117° (*c* 0.47); lit.[25] m.p. 178–179°, $[\alpha]_D^{22}$ +119°. The 3-dimethylamino derivative **2** had m.p. 112–114°, $[\alpha]_D^{19}$ +94° (*c* 0.54); lit.[25] m.p. 110–111°, $[\alpha]_D^{20}$ +99°.

Reaction of methyl 4,6-O-benzylidene-3-deoxy-3-dimethylamino-α-D-altroside (**2**) *with hydrogen peroxide.* — Compound **2** (50 mg) was dissolved in methanol (2 ml), and a solution of hydrogen peroxide (0.6 ml, 30%) in water (1 ml) was added[2]. After

48 h at room temperature, the solvents were removed, and the residue was extracted with chloroform (70 ml). The dried ($MgSO_4$) extract was concentrated to give a semi-crystalline product (60 mg) which was crystallised from chloroform–light petroleum (40–60°) to give the *N*-oxide **8** as white crystals (35 mg, 68%), m.p. 144–145°, which showed one component (t.l.c.). The i.r. spectrum of this compound was identical to that obtained from the product of the reaction of sodium metaperiodate with the dimethylamino-altroside **2** (see below). A further recrystallisation raised the m.p. to 149°.

Kinetic studies. — The experimental conditions were as described in a previous paper[13]. Measurements were made over the whole of the reaction period and for some time after its "completion", in order to determine the rate of over-oxidation (if any). Periodate analysis was carried out spectrophotometetrically[26] and titrimetrically[27–29]. The Fleury–Lange method[29] was found to be the least satisfactory of the latter methods and was not used in the kinetic experiments.

Isolation of products. — (*a*) *From methyl 4,6-O-benzylidene-3-deoxy-3-methylamino-α-D-glucoside* (**4**). The i.r. spectrum of the solid that precipitated out during the oxidation was identical to that of the "dialdehyde dihydrate" (**7**) obtained from the oxidation of methyl 4,6-*O*-benzylidene-α-D-glucoside[30], m.p. 135–136° (lit.[30] m.p. 143°).

(*b*) *From methyl 4,6-O-benzylidene-3-deoxy-3-dimethylamino-α-D-glucoside* (**5**). The weight of product isolated after oxidation for two weeks (molar uptake of periodate, 1.2) was very slightly less than the weight of the starting material. T.l.c. of the white, solid product showed a single component that was different from the starting material; the i.r. spectrum of the product was appreciably different from that of the unoxidised sugar. The compound became syrupy on standing in air, but readily solidified on drying over phosphorus pentaoxide *in vacuo*; the *N*-oxide **7** decomposed at 160–163° (Found: C, 58.7; H, 7.7; N, 4.1. $C_{16}H_{23}NO_6$ calc.: C, 59.1; H, 7.1; N, 4.3%).

(*c*) *From methyl 4,6-O-benzylidene-3-deoxy-3-dimethylamino-α-D-altroside* (**2**). The weight of product (55 mg), isolated after oxidation for three weeks, was in excess of the weight initially added (50 mg). T.l.c. indicated that two compounds, neither of which was starting material, were present; the slower-moving spot was the largest and most intense. After recrystallisation three times from chloroform–light petroleum (40–60°), the *N*-oxide **8** had m.p. (decomp.) 149–150°, $[\alpha]_D$ +77.3° (*c* 0.056); another sample had m.p. 153–154° (Found: C, 58.6; H, 7.1. $C_{16}H_{23}NO_6$ calc.: C, 59.1; H, 7.1%).

RESULTS AND DISCUSSION

During the course of this work, it was observed that some of the compounds being studied, notably the dimethylamino compounds, reacted with iodine both reversibly and irreversibly. Because of this, the spectrophometric method was used as the principal, analytical technique. The reactions with iodine will be discussed after the oxidation results.

Methyl 3-amino-4,6-O-benzylidene-3-deoxy-2-O-methyl-α-D-glycopyranosides. — These compounds did not contain a group that would be expected to be readily oxidised by periodate. However, the glucoside **6** consumed 0.8 molar proportion of oxidant at pH 4.04 in 48 days, and 1.0 mol. at pH 6.99 after 3.5 days. The corresponding amino-alcohol consumed[13] 1.0 equivalent of periodate in *ca.* 4 h (pH 4.04). The reactions did not follow simple first- or second-order kinetics, and t.l.c. examination of the oxidation mixture revealed a complex mixture that contained some starting material.

The corresponding altroside (**3**) consumed no periodate at pH 4.04 during 23 days, but at pH 6.99; 2.3 equivalents were reduced in 24 days.

Complex periodate-oxidations of methylated sugars having no "Malapradian-oxidation-site" have been described by Greville and Northcote[31]. It is not considered likely that the benzylidene ring was removed from either compound **3** or **6** at pH 4.04 or pH 6.99.

From these results, it can be concluded that the $-CH(NH_2)-CH(OMe)-$ grouping is, as expected, not readily cleaved by periodate and that if oxidation does occur, it does so at a *very* much lower rate than that for oxidation of a vicinal amino-alcohol.

Methyl 4,6-O-benzylidene-3-deoxy-3-methylamino-α-D-glucoside (**4**). — This compound reacted very rapidly with periodate at pH 6.99 (one equivalent in 9.5 min.) to give a product identical to that obtained[30] from the oxidation of methyl 4,6-*O*-benzylidene-α-D-glucoside. No over-oxidation occurred; the consumption was still 1.0 equivalent after 24 h.

Studies at pH 4.04 yielded values* of K_2 of 119.2 $l.mole^{-1}sec^{-1}$ (spectrophotometric) and 123.2 $l.mole^{-1}sec^{-1}$ (Malaprade). No reaction occurred with iodine, and so the uptake could be measured by both methods; over-oxidation was very slow. The above values of K_2 must be compared with that of 17.95 for the unsubstituted amino-alcohol[13]. Rate increases have been observed by other workers on *N*-methylation of simpler amino-alcohol systems[3,32].

Methyl 4,6-O-benzylidene-3-deoxy-3-methylamino-α-D-altroside. — This compound reacted much more slowly than did the corresponding glucoside **4** at pH 4.04, 0.62 equivalent of oxidant being reduced in 48 days. At pH 6.99, second-order kinetics were followed for an uptake of 0.5 mol. to give 10^3K_2 values of 7.92 $l.mole^{-1}sec^{-1}$ (Muller–Friedberger) and 8.44 $l.mole^{-1}sec^{-1}$ (spectrophotometric). However, considerable over-oxidation occurred, and 0.8 mol. of periodate was taken up after 24 h, 1.0 after 30 h, and 2.3 after 17 days. This behaviour is similar to that reported[14] for methyl 3-amino-4,6-*O*-benzylidene-3-deoxy-α-D-altroside.

Methyl 4,6-O-benzylidene-3-deoxy-3-dimethylamino-α-D-glycosides. — No reaction of the glucoside **5** was observed at pH 4.04 during 14 days (*cf.* the corresponding amino-alcohol[13] and methylamino-alcohol systems). However, at pH 6.99, one mol. of periodate was reduced, the kinetics being second order with a 10^2K_2 value

*For the definition of K_2, see Ref. 13.

of 1.27 $l.mole^{-1}sec^{-1}$ (spectrophotometric); the compound reacted rapidly with iodine and so only the spectrophotometric method was used. Over-oxidation was very slight, 0.9 mol. being consumed in 24 h, and 1.2 in 11 days.

The reaction of the corresponding altroside **2** was very similar. No oxidation occurred at pH 4.04 during 35 days. At pH 6.99, second-order kinetics were followed to give a 10^3K_2 value of 2.48 (spectrophotometric). Again, titrimetric methods could not be used. Over-oxidation was slight, the uptake being 0.85 mol. in 8 days, and 1.1 at 20 and 35 days.

Both the *gluco* and *altro* derivatives gave crystalline compounds having similar i.r. spectra, and which, from elemental analysis, appeared to be *N*-oxides. In the case of the *altro* isomer (**2**), oxidation of the parent sugar with hydrogen peroxide yielded a product identical to that resulting from periodate oxidation, thus substantiating this structural assignment. The n.m.r. spectrum of the dimethylamino-altroside **2** showed signals due to the NMe_2 group at τ 7.54, and no signal between the anomeric proton at 5.51 and the benzylidene methine proton at 4.59. The *N*-oxide, however, had the NMe_2 signal at τ 6.67 and a broad signal of unit intensity at 5.40, which was assigned to H-3. Both these downfield shifts would be expected from the change of character of the nitrogen atom on *N*-oxidation.

Erythromycin[2], which contains an isolated, diequatorial, hydroxy-dimethylamino grouping, was reported to form an *N*-oxide by reaction with periodate, which was identical to the product obtained by reaction of the antibiotic with hydrogen peroxide. The *N*-oxide was further oxidised by periodate, but relatively slowly. Amine oxides from the oxidation of some piperidines with periodate were isolated by Sklarz and Qureshi[33].

The dimethylamino-lyxoside **9**, studied by Overend and co-workers[34], reduced only one equivalent of periodate at pH 4.5. The lyxoside has some structural similarities with desosamine[2] (**10**) and mycaminose[6] (**11**), both of which readily took up one equivalent of periodate to form sugars containing seven carbon atoms; the initial reaction therefore involved the vicinal diol group. Hence, it appeared that protonation of the dimethylamino group, even when it was adjacent to a carbonyl or hemi-acetal group, appreciably slowed oxidation. This effect was also observed by Dahlgren and Rand[3] with 2-dimethylaminoethanol, which was not oxidised by periodate at pH 3–6. trans-2-Dimethylaminocyclohexanol was oxidised[21] only slowly by aqueous sodium periodate (pH 4).

It is concluded, therefore, that the introduction of a second methyl group on to the amine nitrogen atom completely alters the course of the periodate oxidation.

Reactions with iodine. — As stated above, the usual titration techniques could not be used for the oxidation studies, because of the reaction of some of the methylated, amino sugars with iodine in aqueous solution containing potassium iodide. No firm conclusions could be drawn from the results obtained, other than the obvious one that the u.v. method must be used with such systems.

The amount of iodine reacting varied appreciably with the sugar used and with the pH of the system, and was separable into two parts: (*a*) readily reversible

adsorption (iodine that could be removed by titration with arsenite) and (*b*) irreversible reaction (non-titratable iodine). The greatest uptake of iodine was shown by the two dimethylamino sugars **2** and **5**, under both acidic and alkaline conditions. Approximately three equivalents of iodine were taken up, of which one was irreversible. The products of the reaction appeared from i.r. studies to be the complexes of the corresponding methylamino sugars **1** and **4**. The methylamino sugars **1** and **4** reacted irreversibly under alkaline conditions, but reversibly in acid media. Similar behaviour was shown by the 3-amino-2-*O*-methyl-glucoside **6**, but the corresponding altroside (**3**) reacted reversibly under all conditions.

We do not propose to study these reactions any further.

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