FURTHER STUDIES OF RUTHENIUM TETROXIDE AS AN OXIDANT FOR CARBOHYDRATE DERIVATIVES

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ABSTRACT

An extension is reported of the evaluation of ruthenium tetroxide as an oxidant for the conversion of partially protected carbohydrates into glycosulose derivatives. It has been demonstrated that free hydroxyl groups in benzoic and toluene-*p*sulphonic esters, and in *N*-acetamido derivatives of glycosides can all be oxidised successfully by the reagent. It has been shown also that the oxidant converts 1,4:3,6dianhydrohexitols into the corresponding 2,5-dione; no significant selectivity in the oxidation of *endo* and *exo* hydroxyl groups was noted.

Comment is made on the abnormally high optical rotation of the bis(2,4dinitrophenylhydrazone) of 1,4:3,6-dianhydro-D-threo-hexo-2,5-diulose.

INTRODUCTION

Recently, we reported^{1,2} on ruthenium tetroxide as an oxidant for a single hydroxyl group in partially protected sugars. Generally, yields of oxidation products were very good with alkylidene or arylidene derivatives, and this has been confirmed by other workers³. Apart from our report¹ of the successful oxidation of methyl 3,4,6-tri-O-benzoyl- α -D-glucoside to methyl 3,4,6-tri-O-benzoyl- α -D-arabino-hexopyranosidulose, less work seems to have been done with sugars partially protected by acyl groups. In this paper, we report on the oxidation of some partially acylated glycosides and of some 1,4:3,6-dianhydrohexitols.

RESULTS AND DISCUSSION

Both methyl 2,3,6-tri-O-benzoyl- α -D-galactopyranoside⁴ (1) and the analogous glucoside⁵ 2 could be oxidised with ruthenium tetroxide to give pure, crystalline methyl 2,3,6-tri-O-benzoyl- α -D-xylo-hexopyranosid-4-ulose (3) in good yield (81 and 79%, respectively). The pyranosidulose 3 afforded a 2,4-dinitrophenylhydrazone 4. These yields of the ulose 3 were better than that obtained when methyl sulphoxide and acetic anhydride were used; it is noteworthy that Gabriel⁶ recently reported difficulty in isolating this pyranosidulose from the Me₂SO-Ac₂O oxidising medium.

These oxidations further exemplify the conclusion² that ruthenium tetroxide appears to oxidise axial and equatorial hydroxyl groups with equal ease.

Other benzoates which can be oxidised successfully with ruthenium tetroxide are methyl 3,6-di-O-benzoyl-2-deoxy- α -D-*arabino*-hexopyranoside and phenyl 3,6-di-O-benzoyl-2-deoxy- α -D-*lyxo*-hexopyranoside.

The toluene-*p*-sulphonyl group is stable towards the oxidant, since methyl 4,6-*O*-benzylidene-2-*O*-toluene-*p*-sulphonyl- α -D-glucoside can be converted into the hexopyranosidulose 5 with ruthenium tetroxide. However, in this case, the oxidation procedure has no advantage over the method used previously⁷.

The reagent can be used to oxidise acetamidoglycosides. For example, methyl 2-acetamido-4,6-O-benzylidene-2-deoxy- α -D-glucoside yielded the acetamidoglycosidulose 6, in this case, by use of a catalytic amount of the tetroxide in the presence of metaperiodate solution. The method gives a reasonable yield, but not so good as that reported⁸ by the use of the Pfitzner-Moffatt reagent.

Although ruthenium tetroxide will oxidise two suitably located hydroxyl groups within a molecule, attempts⁹ to thus prepare an ' α -diketone' from methyl 4,6-O-benzylidene- α -D-glucopyranoside have failed so far. The product remains strongly attached to the ruthenium oxide. On the other hand, 1,4:3,6-dianhydro-hexitols are oxidised, but there is no useful discrimination between *endo* and *exo* hydroxyl groups. This lack of selectivity contrasts with the selective, platinum-catalysed oxidation of *endo*-hydroxyl groups¹⁰.

We were interested in studying the oxidation of the dianhydrohexitols, because of the dearth of information available about the related carbocyclic system, bicyclo-[3.3.0]octa-2,6-dione. Consequently, 1,4:3,6-dianhydro-D-mannitol (7), -L-iditol (8), and -D-glucitol (9) were oxidised by RuO_4 under identical conditions, and, in each case, the oxidation product (10) was isolated as the bis(2,4-dinitrophenylhydrazone) (11) (yields, 53, 43, and 48%, respectively). Although a trend indicating some preference for oxidation of *endo* over *exo* hydroxyl groups might be read into these results, we prefer not to do so, because the variation is only *ca*. 10% for the oxidation of the *endo-endo* derivative 7 and the *exo-exo* compound 8, and, in no case, was a 2,4-dinitrophenylhydrazone of a mono-ulose obtained.

The molecular rotations for some anils derived from the diulose 10 are listed in Table I. It is clear that the bis(2,4-dinitrophenylhydrazone) 11 has a remarkably high optical rotation and one much larger than that $([\alpha]_D + 466^\circ)$ of the *p*-nitrophenylhydrazone of 4,6-O-ethylidene-1,2-O-isopropylidene-D-xylo-hexopyran-3-ulose, which was the subject of recent comment¹¹. Also, it is much larger than that $([\alpha]_D + 100^\circ)$ of the 2,4-dinitrophenylhydrazone (4) derived from the uloside 3 or that $([\alpha]_D + 238^\circ)$ of the 2,4-dinitrophenylhydrazone prepared from methyl 3,4,6-tri-Obenzoyl- α -D-xylo-hexopyranosidulose¹. The explanation of the large rotation of compound 11 must be that the light used (sodium D-line, λ 589 nm) for the measurement was of a wavelength close to that at which the compound exhibited a Cotton effect. Compound 11 gives a typical ultraviolet spectrum for the 2,4-dinitrophenylhydrazone chromophore (Fig. 1). The o.r.d. curve (also shown in Fig. 1) shows several Cotton effects in the wavelength range 220-330 nm, but, at 385 nm, a positive Cotton effect of large amplitude (a = 111,300) is centred^{*}. This appears to be associated with the electronic transition which gives rise to the shoulder on the

TABLE I

SPECIFIC AND MOLECULAR ROTATIONS OF SOME NITROGENOUS DERIVATIVES OF 1,4:3,6-DIANHYDRO-Dthreo-hexo-2,5-Diulose

Derivative	$[\alpha]_{\mathrm{D}}$ (degrees)	Solvent	[M] (degrees)
Bis(2,4-dinitrophenylhydrazone)	+ 1670	CHCl ₃ (c 0.1)	8383
Bis(p-nitrophenylhydrazone)	+ 582	Me ₂ CO (c 0.02)	2400
Bis(phenylhydrazone)	+ 770	CHCl ₃ (c 0.1)	2480
Bis(1-naphthylhydrazone)	+ 934	CHCl ₃ (c 0.04)	3940
Dioxime	+ 207	EtOH (c 0.06)	356



Fig. 1. Ultraviolet and o.r.d. curves of compound 11 in p-dioxane.

^{*}It is because of the large amplitude that this o.r.d. spectrum could be measured with such a strongly absorbing compound.



Fig. 2. O.r.d. curve of the bis(p-nitrophenylhydrazone) of the diulose 10. measured in p-dioxane-



Fig. 3. Ultraviolet and o.r.d. curves of compound 4 in p-dioxane.

long-wavelength absorption band. The bis(*p*-nitrophenylhydrazone) of the diulose 10 shows only a weak Cotton effect at shorter wavelength (Fig. 2).

The 2,4-dinitrophenylhydrazone of the uloside 3 has the ultraviolet spectrum shown in Fig. 3. The o.r.d. curve of the compound shows a Cotton effect with a large amplitude (a = 78,000), but this is centred at shorter wavelength (*i.e.*, 238 nm) than for compound 11.

Although the large, specific rotation of compound 11 is explicable by reference to its o.r.d. curve, the reason why this compound should exhibit a long-wavelength Cotton effect is, at present, a matter for speculation. Little work in this connection

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has been done with 2,4-dinitrophenylhydrazones. Although Guthrie and co-workers¹² have found interesting results with phenylazo sugars, comparisons with our work are not meaningful, because of the difference in complexity of the two types of chromophore.



In some way, the large optical rotation of compound 11 would seem to be attributable to the *o*-nitro group, since the bis(p-nitrophenylhydrazone) of the diulose 10 does not have such a large rotation. However, the effect is not due solely to the presence of the 2,4-dinitrophenylhydrazone residue, regardless of its molecular environment, since the optical rotation of compound 4 is unexceptional. It is note-worthy that *o*-nitrophenyl glycosides have been found to have abnormally high optical rotations which exhibit a marked dependence on temperature, but the reason for this behaviour is not understood¹³. The phenomenon is being further investigated.

EXPERIMENTAL

Unless stated to the contrary, optical rotations were measured on chloroform solutions. Infrared spectra were determined with a Perkin-Elmer Infracord model 137; solids were dispersed in KBr discs, and gums were smeared on such discs. Ultraviolet spectra were measured with a Unicam SP 500 or 700 spectrometer on solutions in 'Spectrosol' grade solvents. N.m.r. spectra were obtained with a Varian A-60 spectrometer. O.r.d. curves were measured (solutions in *p*-dioxane) with a Bellingham and Stanley (Polarmatic 62) instrument. T.l.c. plates were coated with silica gel G (Merck), and compounds were located¹⁴ with an ethanolic solution of anisaldehyde (0.1%) and sulphuric acid (5%).

Methyl 2,3,6-tri-O-benzoyl- α -D-xylo-hexopyranosid-4-ulose (3). — (a) Methyl 2,3,6-tri-O-benzoyl- α -D-glucopyranoside (2) (6 g) in methylene chloride (50 ml) was oxidised with ruthenium tetroxide (from 3.1 g of RuO₂) in carbon tetrachloride

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(200 ml) for 4 h. Recrystallisation of the product from light petroleum (b.p. 60–80°)– ether gave the title compound (4.8 g, 79%) as needles, m.p. 121°, $[\alpha]_D + 172^\circ$ (c 1.8, methylene dichloride), v_{max} 1700 cm⁻¹.

Anal. Calc. for C28H24O9: C, 66.6; H, 4.8. Found: C, 65.6; H, 5.0.

The same compound was obtained in 64% yield by carrying out the oxidation of the glucoside 2 (5 g) with methyl sulphoxide (25 ml) and acetic anhydride (18 ml).

(b) Likewise, methyl 2,3,6-tri-O-benzoyl- α -D-galactopyranoside (1, 3 g) could be oxidised in methylene chloride with ruthenium tetroxide (from 1.5 g of RuO₂) in carbon tetrachloride. After 4 h at room temperature, excess of oxidant was destroyed by addition of isopropyl alcohol (1 ml), and the filtered solution was washed with water (2 × 50 ml), dried (Na₂SO₄), and evaporated. The residue was recrystallised as above to give the ulose (2.3 g, 81%), m.p. 121°. Oxidation of compound 1 (2 g) with methyl sulphoxide (8 ml) and acetic anhydride (5 ml) for 8 h gave the ulose (1.41 g) in 72% yield.

Treatment of crude ulose 3 (0.4 g) with 2,4-dinitrophenylhydrazine (0.16 g) in ethanol (50 ml) containing hydrochloric acid (0.002M) for 1 h at 75° gave the 2,4-dinitrophenylhydrazone 4 (0.2 g) as yellow crystals, m.p. 131–132°, $[\alpha]_D + 100^\circ$; v_{max} 3370 (NH), 1730 (ester C = O), and 1600 cm⁻¹; n.m.r. data [(CD₃)₂SO]: τ 6.41 (3H, methoxyl); 5.0 (3H, H-6, H-6', and H-5); 4.67 (1-proton doublet, 3.5 Hz, H-1); 4.2 (1-proton quartet, 3.5 and 7.8 Hz, H-2); 3.62 (1-proton doublet, 7.8 Hz, H-3); 1.7–2.8 (17-proton multiplet, three benzoyl groups and two protons of the dinitrophenylhydrazino residue); 0.97 (1-proton doublet, 2.5 Hz, proton situated between the two nitro groups); δ 11.8 (broad NH signal).

Anal. Calc. for C₃₄H₂₈N₄O₁₂: C, 59.6; H, 4.1; N, 8.2. Found: C, 59.6; H, 4.4; N, 7.8.

Methyl 3,6-di-O-benzoyl-2-deoxy- α -D-thrco-hexosid-4-ulose. — A solution of methyl 3,6-di-O-benzoyl-2-deoxy- α -D-arabino-hexopyranoside¹⁵ (5 g) in dry carbon tetrachloride (40 ml) at 0° was treated for 5 h with ruthenium tetroxide (from 3 g of the dioxide) in carbon tetrachloride. Excess of oxidant was eliminated by addition of isopropyl alcohol (1.5 ml), and the filtered solution was dried (Na₂SO₄) and concentrated to a syrup which was triturated with 60% ethanol. The resulting prisms were recrystallised from light petroleum (b.p. 60–80°)-ether to afford the title compound (3.4 g, 68%), m.p. 88–89°, $[\alpha]_D$ +125° (c 1, methylene dichloride), ν_{max} 1700 cm⁻¹.

Anal. Calc. for C21H20O7: C, 65.6; H, 5.3. Found: C, 65.5; H, 5.3.

Phenyl 3,6-di-O-benzoyl-2-deoxy- α -D-threo-hexosid-4-ulose. — A solution of phenyl 3,6-di-O-benzoyl-2-deoxy- α -D-lyxo-hexopyranoside (2 g) in methylene chloride (20 ml) was treated at 0° with a solution of ruthenium tetroxide (from 1.2 g of the dioxide) in carbon tetrachloride for 45 min. The product was isolated as described previously and was recrystallised from light petroleum (b.p. 60-80°)-ether to give the title compound (0.91 g, 48%) as needles, m.p. 118°, $[\alpha]_D + 153°$ (c 1, methylene dichloride), which soon became hydrated.

Anal. Calc. for C₂₆H₂₂O₇: C, 69.7; H, 5.0. Found: C, 69.7; H, 5.1.

Methyl 4,6-O-benzylidene-2-O-toluene-p-sulphonyl- α -D-ribo-hexopyranosid-3ulose (5). — Methyl 4,6-O-benzylidene-2-O-toluene-p-sulphonyl- α -D-glucopyranoside (2 g) was oxidised for 20 h in the usual manner with ruthenium tetroxide (prepared from 0.66 g of the dioxide). The crude material (1.46 g) isolated was recrystallised from methylene dichloride (8 ml) and light petroleum (b.p. 40–60°) (25 ml) to yield starting material (0.91 g). The mother liquors were concentrated to a residue which, after recrystallisation (twice) from ethanol, gave compound 5 (0.3 g), m.p. 164–166°, $[\alpha]_D + 42^\circ$ (c 0.5, N,N-dimethylformamide); lit.⁷, m.p. 165–167°, $[\alpha]_D + 45^\circ$ (N,Ndimethylformamide).

Treatment of the starting material with sodium metaperiodate and a catalytic amount of ruthenium dioxide afforded less product.

Methyl 2-acetamido-4,6-O-benzylidene-2-deoxy- α -D-ribo-hexopyranosid-3-ulose (6). — A solution of sodium metaperiodate (2.3 g) in water (150 ml) containing ruthenium dioxide (0.06 g) was mixed with methyl 2-acetamido-4,6-O-benzylidene-2deoxy- α -D-glucoside (1.5 g) in methylene chloride (300 ml). The mixture was stirred for 4 h at room temperature, and the pH was maintained at 6-7 by addition of 2N aqueous sodium hydroxide. When t.l.c. monitoring showed the absence of starting material, the solution was treated with isopropyl alcohol (1 ml), filtered, and concentrated to a solid residue (1.1 g) which, on recrystallisation from acetone-light petroleum (b.p. 40-60°), afforded compound 6 (0.87 g, 58%), m.p. 227-229° (dec.), $[\alpha]_D^{20} + 88°$ (c 1.1); ν_{max} 3400 (NH), 1770 (C = O), 1660 and 1565 (amide) cm⁻¹; lit.⁸, m.p. 227-228° (dec.), $[\alpha]_D + 110° \pm 4°$ (N,N-dimethylformamide).

Anal. Calc. for C₁₆H₁₉NO₆: C, 59.8; H, 5.96; N, 4.4. Found: C, 59.4; H, 6.45; N, 4.2.

1,4:3,6-Dianhydro-D-threo-hexo-2,5-diulose bis(2,4-dinitrophenylhydrazone) (11). — This compound was prepared from the 1,4:3,6-dianhydrides of D-mannitol¹⁶ (7), L-iditol¹⁷ (8), and D-glucitol¹⁸ (9), in separate experiments under identical conditions. The dianhydride (0.58 g) in methylene chloride (500 ml) was treated, in the usual way, with ruthenium tetroxide prepared from ruthenium dioxide (1.1 g). After 4 h, the reaction was terminated by addition of isopropyl alcohol (0.5 ml). The mixture was filtered, and the dioxide was washed with acetone. The combined filtrate and washings were evaporated to a residue which was treated with 2,4-dinitrophenyl-hydrazine. The bis(dinitrophenylhydrazone) had m.p. 245–246° (dec.), $[\alpha]_D + 1670°$ (c 1), irrespective of the starting material; lit.¹⁰ m.p. 248°. N.m.r. data [(CD₃)₂SO]: τ 5.24 (4-proton, broad signal, pair of methylene groups); 4.16 (2-proton, broad signal, two bridge-head methine protons); 2.12 (1-proton doublet, 10 Hz, proton adjacent to the hydrazino substituent); 1.09 (1-proton doublet, 2.5 Hz, the proton between the two nitro-groups); 1.54 (1-proton quartet, 10 and 2.5 Hz, the remaining aromatic ring proton); δ 11.6 (broad NH signal).

Anal. Calc. for C₁₈H₁₄N₈O₁₀: C, 43.0; H, 2.8; N, 22.3. Found: C, 43.0; H, 2.7; N, 21.95.

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