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Partial Methylation of Benzyl 4-*O*-Methyl-β-D-Xylopyranoside

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Thin layer chromatography has been used for the quantitative separation of the components obtained on the partial methylation of benzyl 4-*O*-methyl-β-D-xylopyranoside. From the analytical figures obtained, the relative rates of methylation of the hydroxyl groups at C-2 and C-3, k_2 and k_3, respectively, and the effect of substitution at one of these positions upon the reactivity of the other have been determined with good accuracy. The ratio k_2:k_3 was 3.2:1 and after methylation at the C-2 hydroxyl group the reactivity at the C-3 hydroxyl group increased 3.0 times. Methylation at the C-3 hydroxyl group did not affect the reactivity at the C-2 hydroxyl group.

The various alkylation studies previously carried out at this Institute on cellulose, amylose and various glycosides, are summarised in the first reference[1]. It was found that, for methylation, the hydroxyl group at C-2 in cellulose and amylose is the most reactive, and that the hydroxyl group at C-6 is more reactive than that at C-3. For carboxymethylation and hydroxyethylation the primary hydroxyl group was the most reactive while that at C-3 again was the least reactive. In the methylation of some methyl β-D-glucosides, the hydroxyl group at C-6 was the most reactive while that at the C-3 was the least reactive [2]. Exceptions to this are the two acetal derivatives, methyl 4,6-*O*-benzylidene- and methyl 4,6-*O*-ethylidene-β-D-glucopyranosides, where little difference in the reactivities of the two free hydroxyl groups was found [1]. The latter two models differ from the other substances in the conformational rigidity resulting from the two *trans*-fused six-membered rings.

By trying out various ratios for the reactivities at the hydroxyl groups at C-2, C-3 and C-6 respectively and using the equations given by Spurlin [3], the ratio of the reaction constants giving the best agreement between the observed and calculated amount of the various components was obtained. In partial methylation studies, it has been found that the best agreement is obtained by further assuming that the reactivity at the C-3 hydroxyl group is doubled when that at C-2 is substituted, while substitution at the C-3 hydroxyl group has no effect on the reactivity of that at C-2.

In earlier studies the method used has invariably been hydrolysis to a mixture of glucose alkyl ethers, and separation of these on carbon columns followed by further separation and quantitative estimation of the components by paper chromatography and paper electrophoresis. Owing to the number of steps involved in this procedure and the complexity of products arising from the partial alkylations, it has been difficult to obtain an accurate determination of the change in the reactivity at C-2 on alkylating the C-3 hydroxyl group or vice versa.

It was thought desirable to study this effect of adjacent substituents more closely. In a previously reported study on the partial acetylation of benzyl 4-*O*-methyl-β-D-xylopyranoside [4] a complete separation of the four possible components in the partial acetylation mixtures was obtained by the use of thin layer chromatography. This method [5] was therefore applied to the mixture obtained on the partial methylation of this substance [6]. A quantitative separation of the four possible components was obtained, and the individual components were estimated by weighing. This allowed an accurate determination of each compound in the sample.

The benzyl 2,3,4-tri-*O*-methyl-β-D-xylopyranoside, thus obtained, crystallised and was identical to the product obtained on fully methylating benzyl β-D-xylopyranoside [7]. The benzyl 2,4-di-*O*-methyl-β-D-xylopyranoside also crystallised and gave the correct elemental analysis. Paper chromatography and paper electrophoresis on the dimethylxylose obtained after acid hydrolysis, revealed its identity with 2,4-di-*O*-methylxylose. The syrupy benzyl 3,4-di-*O*-methyl-β-D-xylopyranoside obtained was chromatographically identical with the compound obtained by the action of sodium methoxide in methanol upon benzyl 2,3-anhydro-4-*O*-methyl-β-D-ribopyranoside as in the corresponding preparation of methyl 3,4-di-*O*-methyl-β-D-xylopyranoside from methyl 2,3-anhydro-4-*O*-methyl-β-D-ribopyranoside described by Hough and Jones [8]. The identity of the benzyl 3,4-di-*O*-methyl-β-D-xylopyranoside was established by hydrolysis followed by paper chromatography and paper electrophoresis on the dimethylxylose produced, which was thereby identified as 3,4-di-*O*-methylxylose. The benzyl 4-*O*-methyl-β-D-xylopyranoside [6] recovered from the reaction mixture was shown to be identical with the starting material.

The methylations were performed with dimethyl sulphate in 19 % aqueous sodium hydroxide. It was found necessary to add one part of ethanol to four parts of the aqueous alkali in order to prevent the precipitation and accumulation of dimethyl ethers, and the consequent distorted substitution pattern. Three degrees of substitution were obtained by varying the amount of dimethyl sulphate added. The resulting mixtures were separated into their four components. The overall yields from starting material to separated and weighed compounds ranged from 95—100 %. The results are given in the Table. For the present example Spurlin's equations are simplified to

$$s_0 = \mathrm{e}^{-(k_2+k_3)t}$$

$$s_2 = \frac{k_2}{k_2 + k_3 - k_{3\mathrm{a}}}(\mathrm{e}^{-k_{3\mathrm{a}}t} - s_0)$$

$$s_3 = \frac{k_3}{k_2 + k_3 - k_{2\mathrm{a}}}(\mathrm{e}^{-k_{2\mathrm{a}}t} - s_0)$$

$$s_{2,3} = 1 - (s_0 + s_2 + s_3)$$

in which s_0, s_2, s_3 and $s_{2,3}$ are the molar fractions of unsubstituted and of 2-, 3- and 2,3-substituted compounds respectively, k_2 is the rate constant at the C-2 hydroxyl group and k_3 the rate constant at the C-3 hydroxyl group. The rate constant at the C-2 hydroxyl group when that at C-3 is substituted is denoted k_{2a} and that at the C-3 hydroxyl group when that at C-2 is substituted k_{3a}.

From the observed values of s_0, s_2, s_3 and $s_{2,3}$ at two degrees of substitution, relative k-values could be calculated. The three sets of relative k-values thus obtained differed only slightly from each other. The average values, giving k_3 the value 1, were $k_2 = k_{2a} = 3.2 \pm 0.1$ and $k_{3a} = 3.0 \pm 0.1$. As seen in Table 1, there is good agreement between the experimental values and those calculated from these relative k-values.

The effect, observed in previous studies [1,2] on methylation of glucosides, and xylosides that the reactivity at C-3 is considerably increased on substitution of the C-2 hydroxyl has hereby been established as well as the finding that the reactivity at the C-2 hydroxyl group is virtually unaffected by methylation of that at C-3. A reduction in reactivity in one of these positions when the other is substituted has been observed in the carboxymethylation of cellulose. This is certainly due to repulsion, by the ionic substituent of the ionic reagent and to steric hindrance caused by these bulky substituents. The observed enhancement of reactivity at the C-3 hydroxyl group when that at C-2 is methylated must have a different cause. It seems reasonable to assume that a considerable proportion of the hydroxyls in the glycoside is present in the strongly alkaline medium as alkoxide ion, and that the methylating agent reacts with the alkoxide ions. The inductive effects from the two acetal oxygens at C-1 would imply that the C-2 hydroxyl group should be the more acidic and thus preferentially ionised. When this group is ionised, the acidity at the C-3 hydroxyl group

Table 1. Composition of the reaction mixtures from partially methylated benzyl 4-*O*-methyl-β-D-xylopyranoside.

Compound	D.S. 0.43 Mole %		D.S. 0.70 Mole %		D.S. 0.99 Mole %	
	Found	Calc. *	Found	Calc. *	Found	Calc. *
Benzyl 4-*O*-methyl-β-D-xylopyranoside, (s_0)	63.3	63.3	44.9	44.9	28.9	28.9
Benzyl 2,4-di-*O*-methyl-β-D-xylopyranoside, (s_2)	23.0	23.5	30.7	30.7	33.6	33.1
Benzyl 3,4-di-*O*-methyl-β-D-xylopyranoside, (s_3)	7.0	7.2	9.2	9.4	9.6	10.0
Benzyl 2,3,4-tri-*O*-methyl-β-D-xylopyranoside, ($s_{2,3}$)	6.7	6.0	15.2	15.0	27.9	28.0

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* Calculated using the solution $k_2{:}k_3 = 3.2$, $k_{2a}{:}k_2 = 1.0$ and $k_{3a}{:}k_3 = 3.0$. The observed values of s_0 are taken as a basis for the calculation of the other s-values.

should be considerably decreased. Methylation at the C-2 hydroxyl group removes this effect, but methylation at the C-3 hydroxyl group should not have a similar effect on the C-2 hydroxyl group.

EXPERIMENTAL

Evaporations were performed at reduced pressure at a bath temperature below 40°. All melting points are corrected.

The benzyl 4-*O*-methyl-β-D-xylopyranoside used had m.p. 79—80.5 , $[\alpha]_D^{20}$ $-110°$ (*c*, 1.0 in chloroform)[6]. It gave xylose and traces of di- and oligosaccharides on demethylation with boron trichloride[9] and the phenylosazone of the 4-*O*-methyl-D-xylose obtained after hydrogenation[4,7] had m.p. 160—162°. Hough and Jones[8] report m.p. 160—161° for this compound.

Chromatography. Paper: Whatman No. 1, solvent: butanol-ethanol-water, 10:3:5. Ascending thin layer chromatography[5]. Absorbent: Kieselgel G nach Stahl, E. Merck AG. Solvent: ethyl ether. Paper electrophoresis. Paper: Whatman No. 3MM. Buffer: 0.1 M borate buffer at pH 10.

The spots on the thin layer chromatograms were detected with iodine vapour, the reducing sugars on the papers with anisidine hydrochloride.

*Benzyl 2,3,4-tri-O-methyl-β-*D*-xylopyranoside.* Benzyl β-D-xylopyranoside (1.0 g m.p. 110.5—113.5° $[\alpha]_D^{20}$ $-76°$ (*c*, 1.0 in ethanol)[7]) was dissolved in anhydrous dioxan (50 ml). Powdered sodium hydroxide (10 g) was added, followed by the addition of dimethyl sulphate (6 ml) in anhydrous dioxan (10 ml) with stirring. The mixture was allowed to stand with stirring at 60°, overnight, filtered, and the solids were washed with anhydrous dioxan. The filtrate was concentrated to dryness. Spontaneous crystallisation occurred. The crystals were dissolved in hot isopropyl ether and filtered to remove the last traces of inorganic material. A thin layer chromatogram gave a single, fast-moving spot. The filtrate was concentrated to dryness and the resulting crystals were recrystallised from ligroin to give crystals (0.88 g), m.p. 42.5—44°, $[\alpha]_D^{20}$ $-81°$ (*c*, 2.1 in chloroform). From the mother liquor a further 0.15 g crude material was obtained with m.p. 37.5—43°. (Found: C 63.5; H 7.92; O 28.2. Calc. for $C_{15}H_{22}O_5$: C 63.8; H 7.86; O 28.3).

*Benzyl 3,4-di-O-methyl-β-*D*-xylopyranoside.* Benzyl 2,3-anhydro-4-*O*-methyl-β-D-ribopyranoside (68.1 mg, m.p. 101—102.5°)[6] was refluxed for 24 h in methanol (5 ml) containing sodium methoxide (from 0.3 g sodium). The solution was concentrated to 0.5 ml, diluted with water and extracted continuously with chloroform. The chloroform extract was dried over anhydrous sodium sulphate, filtered, and concentrated to dryness Yield 77.0 mg syrup, $[\alpha]_D^{20}$ $-108°$ (*c*, 1.9 in chloroform). The substance gave a single spot on thin layer chromatography. The acetate of the substance was also amorphous.

From the methylation experiments described below a substance with the identical mobility on thin layer chromatography as that described above was obtained. Hydrolysis of this xyloside, with 0.5 N sulphuric acid overnight, followed by neutralisation with aqueous barium hydroxide, filtration and concentration yielded a compound which on paper chromatography had the expected R_F value for a dimethylxylose. Its paper electrophoretic mobility was the same as that previously reported for 3,4-di-*O*-methylxylose [4].

*Benzyl 2,4-di-O-methyl-β-*D*-xylopyranoside.* From the methylation experiments described below a crystalline compound was obtained with m.p. 73—74°, $[\alpha]_D^{20}$ $-80°$ (*c*, 0.7 in chloroform). (Found: C 63.0; H 7.53; O 29.7. Calc. for $C_{14}H_{20}O_5$: C 62.7; H 7.51; O 29.8). Hydrolysis of a small sample as described above yielded a dimethylxylose which was indistinguishable from 2,4-di-*O*-methylxylose on paper chromatography and which, like 2,4-di-*O*-methylxylose, did not migrate on paper electrophoresis in borate.

Partial methylation studies. Benzyl 4-*O*-methyl-β-D-xylopyranoside (100.0 mg) was dissolved in 19 % aqueous sodium hydroxide (20 ml). Ethanol (5 ml) was added and then, dropwise, dimethyl sulphate (1 ml) while stirring. After 1 h at room temperature one further addition of dimethyl sulphate (1 ml) was made, the reaction was then allowed to proceed at room temperature for 2 h. The clear solution was neutralised with 6 N sulphuric acid and the solution was extracted continuously with chloroform overnight. The chloroform solution was dried over anhydrous sodium sulphate, filtered and concentrated to a syrup which was dried over silica gel and calcium chloride in a vacuum. Yield 104.2 mg.

The mixture was dissolved in benzene and streaked on to four thin layer chromatography plates (20 × 20 cm) which were then developed in ethyl ether. The four bands were located by the briefest possible exposure to iodine vapour. The iodine colour was allowed to disappear in air and the bands were scraped off. Whenever one band was developed noticeably faster than the others, it was marked out and removed from the plates before the other bands were located. Corresponding bands were combined and kept under ethanol (25 ml) overnight. Each ethanol extract was filtered, the absorbent was thoroughly washed with ethanol and the filtrate and washings concentrated to dryness and the syrup was dried in a vacuum as above. The following yields of chromatographically pure compounds, in order of their mobility on the chromatograms, were obtained. Syrupy benzyl 2,3,4-tri-*O*-methyl-β-D-xylopyranoside, $s_{2,3}$ (16.9 mg) yielding from ligroin, on seeding, crystals (16.3 mg) with m.p. 38–43°. Two further recrystallisations gave crystals (13.3 mg), m.p. and mixed m.p. with the above authentic material 41–43°. Benzyl 3,4-di-*O*-methyl-β-D-xylopyranoside, s_3, (9.7 mg) did not crystallise. Benzyl 2,4-di-*O*-methyl-β-D-xylopyranoside, s_2, (32.4 mg) crystallised, m.p. 70–73°. One recrystallisation from isopropyl ether-ligroin gave crystals (28.5 mg) with m.p. 73–74°. Benzyl 4-*O*-methyl-β-D-xylopyranoside, s_0, (45.0 mg) in isopropyl ether, on seeding, gave crystals (37.8 mg) with m.p. 70–78° and after two recrystallisations 26.7 mg with m.p. 78–80.5° unchanged on admixture with authentic material.

The other two methylations were performed as above, with different amounts of dimethyl sulphate. To obtain a lower D.S. only one addition (1 ml) was made and the reaction was then allowed to proceed for 2 h. A higher D. S. than that described above was obtained by adding more dimethyl sulphate (1 ml) 1 h after the second addition and then allowing the reaction to proceed for a further 2 h. The yields obtained were 103.2 and 101.3 mg, respectively.

The efficiency of the above fractionation was checked by separating a mixture of s_0 (25.2 mg) and $s_{2,3}$ (23.6 mg) on one plate as described above. The yield of recovered s_0 was 24.8 mg, from which crystals (20.0 mg) with m.p. and mixed m.p. 77.5–80° were obtained. The yield of recovered, syrupy $s_{2,3}$ was 22.1 mg, this gave crystals (21.4 mg) with m.p. 40–43° undepressed on admixture with authentic material.

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