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PARTIAL METHYLATION OF CARBOHYDRATES

PART I. METHYL β-D-XYLOPYRANOSIDE

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ABSTRACT

Partial methylation of methyl β-D-xylopyranoside by the Haworth, Purdie, or Kuhn procedures gave mainly the 2,4-dimethyl ether and revealed the reactivity sequence HO-2 > HO-4 > HO-3. The 4-*O*-methyl derivative preponderated when Hakomori's method was used, and the reactivity sequence was HO-4 > HO-2 > HO-3.

INTRODUCTION

In previous papers[1–9] on the partial methylation of glycosides and polysaccharides, quantitative data have not been reported. However, the accumulated data demonstrated the higher reactivity of HO-2. Both selective[2–6] and non-selective reactions[7–9] have been described.

Partial, Haworth methylation[10] of methyl β-D-xylopyranoside was earlier shown[6] to give a complex mixture, with the dimethyl ether fractions consisting mainly of the 2,4- and 2,3-derivatives. We now report on a detailed study of the partial methylation of methyl β-D-xylopyranoside, using various methods.

EXPERIMENTAL AND RESULTS

Quantitative analysis of the products of partial methylation was performed by g.l.c. of their acetates, using a TSVET 2-65 chromatograph, with flame-ionization detection, an injection-block temperature of 300°, nitrogen as carrier gas (60 ml/min), and a column (1 m, i.d. 3 mm) of 15% poly(butanediol succinate) on silanized Chromosorb W (60–80 mesh) with a temperature programme of 100→225° at 4°/min.

Peak areas were calculated in the usual manner; the relative error was 3–10%. A preliminary, quantitative analysis of the chromatograms for the synthetic mixtures of the acetates of methyl β-D-xylopyranoside and its 2-*O*-, 4-*O*-, 2,4-di-*O*-, and 2,3,4-tri-*O*-methyl derivatives showed the percentages of components to be proportional to the peak areas in the respective chromatograms. Retention times of the methyl ether acetates are given in Table I.

Partial methylation of methyl β-D-xylopyranoside was effected with the Haworth[10], Purdie[11], Kuhn[12,13], and Hakomori[14] procedures. The components of

TABLE I

RELATIVE RETENTION TIMES OF THE ACETATES OF METHYL β-D-XYLOPYRANOSIDE AND ITS METHYLATED DERIVATIVES

Methylated derivative	*Relative retention times*	*Methylated derivative*	*Relative retention times*
2,3,4	0.39	2	1.17
2,3	0.81	4	1.28
3,4	0.93	3	1.33
2,4	1.00 (15.7 min)	Parent compound	1.50

the mixtures of methyl ethers were identified by comparison with authentic samples, using g.l.c., as well as by mass spectrometry of the Me_3Si derivatives.

Haworth methylations. — To a solution of xyloside (0.5 g) in water (2.5 ml), methyl sulphate (5 ml) and 30% aqueous sodium hydroxide (8.5 ml) were added simultaneously and dropwise, the mixture being vigorously stirred at 20° in an atmosphere of nitrogen. Aliquots (0.5 ml) were taken every 30 min and heated for 0.5 h at 95°. They were then diluted with water to 3 ml, treated with Amberlite IR-120(H^+) and Dowex-1 x4 (HCO_3^-) resins, and then evaporated. The residues were acetylated with acetic anhydride and pyridine, the products were isolated in the usual manner, and the final chloroform solutions were used for g.l.c. The results are listed in Table II.

TABLE II

DATA ON PARTIAL, HAWORTH METHYLATION

Time (min)	*Methyl ethers formed (%)*							
	Parent	*2*	*3*	*4*	*2,3*	*2,4*	*3,4*	*2,3,4*
5	72.9	12.0	3.2	10.4	—	1.5	—	—
20	60.7	16.1	3.0	12.6	—	7.6	—	—
30	39.3	22.7	4.2	21.0	1.9	10.9	—	—
60	22.5	24.2	5.7	21.4	4.5	21.7	—	—
90	9.0	26.5	4.9	20.7	6.4	31.6	—	0.9
120	2.2	6.3	1.1	3.9	6.1	26.0	0.8	53.6
240	0.7	6.5	—	3.4	6.2	24.1	0.3	58.8

Kuhn methylations. — (*a*) The xyloside (0.1 g) dissolved in *N,N*-dimethylformamide (3 ml) was stirred with silver oxide (0.6 g) and methyl iodide (0.6 ml) in the dark at 20°. Aliquots (0.2 ml) were poured into methanol (30 ml), filtered, and evaporated. The residues were acetylated and analysed by g.l.c. The results are shown in Table III.

(*b*) The xyloside (0.1 g) dissolved in *N,N*-dimethylformamide (3 ml) was stirred with methyl iodide (0.6 ml), barium oxide (0.6 g), and $Ba(OH)_2.8H_2O$ (48 mg) in the dark at 20°. Aliquots (0.2 ml) were then treated as in (*a*). The results are shown in Table IV.

TABLE III

DATA ON PARTIAL KUHN METHYLATION (Ag_2O + MeI)

Time (min)	*Methyl ethers formed* (%)							
	Parent	*2*	*3*	*4*	*2,3*	*2,4*	*3,4*	*2,3,4*
20	87.6	5.2	2.2	4.3	—	—	—	—
30	84.4	7.3	3.3	5.0	—	—	—	—
45	64.7	13.5	9.4	11.1	—	1.3	—	—
60	54.4	15.5	11.3	13.3	1.3	4.2	—	—
90	8.3	14.4	11.1	11.0	10.6	29.6	0.1	14.9
120	0.2	2.8	0.6	0.4	8.5	33.3	—	54.2
240	—	0.8	—	0.2	0.6	17.0	—	81.4
480	—	—	—	—	—	7.1	—	92.9
960	—	—	—	—	—	—	—	100

TABLE IV

DATE ON PARTIAL KUHN METHYLATION (BaO + MeI)

Time (min)	*Methyl ethers formed* (%)							
	Parent	*2*	*3*	*4*	*2,3*	*2,4*	*3,4*	*2,3,4*
3	83.2	3.8	4.5	8.5	—	—	—	—
6	73.0	7.0	6.6	13.4	—	—	—	—
7.5	66.3	10.2	7.0	16.5	—	—	—	—
10	53.4	12.2	12.6	20.5	—	1.4	—	—
15	37.2	20.5	18.6	19.8	0.4	3.5	—	—
20	30.3	20.9	16.6	22.3	1.7	8.2	—	—
35	8.4	19.5	15.4	17.6	8.3	25.8	—	5.0
45	1.5	1.8	0.7	3.2	4.0	19.5	—	69.3
60	—	—	—	—	—	—	—	100

Purdie methylations. — The xyloside (0.1 g) was dissolved in dry methanol (2 ml), silver oxide (0.7 g) and methyl iodide (0.38 ml) were added, and the mixture was stirred in the dark at 20°. Aliquots (0.1 ml) were poured into methanol (30 ml), filtered, and evaporated to dryness. The residues were acetylated and analysed by g.l.c. The data obtained are given in Table V.

Hakomori methylations. — Sodium hydride (1.9 g) in dry methyl sulphoxide (20 ml) was stirred at 58–65° for 1.5 h in a nitrogen stream. The resulting solution of methylsulphinyl carbanion was used for methylation. The xyloside (0.1 g) dissolved in methyl sulphoxide (3 ml) was treated with a solution of methylsulphinyl carbanion [0.65 or 1 ml for procedures (*a*) and (*b*), respectively, into xyloside solution] introduced with a syringe. After shaking the mixture, methyl iodide was added in amounts indicated in Tables VI and VII. After 30 min, the solution was neutralized with methanolic hydrogen chloride and poured into 10 vol. of methanol. The filtered solution was evaporated, and the residue was acetylated and analysed by g.l.c. The results are given in Tables VI and VII.

TABLE V

DATA ON PARTIAL PURDIE METHYLATION

Time (*min*)	*Methyl ethers formed* (%)							
	Parent	*2*	*3*	*4*	*2,3*	*2,4*	*3,4*	*2,3,4*
5	66.2	11.5	9.3	13.0	—	—	—	—
10	37.5	19.1	14.4	16.4	1.0	11.6	—	—
20	25.7	24.6	18.6	21.7	—	9.3	—	—
30	13.9	26.3	20.1	18.2	2.7	18.8	—	—
45	5.8	24.9	18.4	13.3	6.0	31.6	—	—
60	3.1	19.9	18.1	10.8	8.3	37.2	0.1	2.5
90	2.3	15.2	14.4	4.4	12.1	45.6	0.4	5.6
120	1.8	12.0	10.1	2.5	13.8	45.5	—	14.3

TABLE VI

DATA ON PARTIAL, HAKOMORI METHYLATION (*a*)

MeI ($ml \times 10^3$)	*Methyl ethers formed* (%)							
	Parent	*2*	*3*	*4*	*2,3*	*2,4*	*3,4*	*2,3,4*
32	66.6	7.2	4.6	7.7	1.2	2.7	—	10.0
38	61.4	6.9	5.0	9.7	1.6	2.1	—	13.3
46	57.8	5.2	4.6	10.2	1.7	2.5	—	17.8
53	50.9	8.0	6.0	12.7	2.0	3.6	—	16.8
61	45.3	6.1	3.5	13.2	2.5	3.5	—	25.9
72	46.1	3.8	4.9	11.8	1.6	3.3	—	28.5
92	25.5	4.5	4.9	17.0	3.4	5.5	—	39.2
110	15.4	6.1	5.2	14.7	6.0	9.7	—	42.9
130	9.5	4.4	4.7	12.7	6.9	11.8	—	50.0
149	8.9	7.3	5.5	13.0	5.9	16.0	—	43.4

TABLE VII

DATA ON PARTIAL, HAKOMORI METHYLATION (*b*)

MeI ($ml \times 10^3$)	*Methyl ethers formed* (%)							
	Parent	*2*	*3*	*4*	*2,3*	*2,4*	*3,4*	*2,3,4*
40	68.8	6.5	1.9	11.2	1.0	2.3	—	8.3
80	50.3	8.4	0.4	16.4	1.1	2.0	—	21.4
120	25.4	1.0	—	27.6	0.1	0.1	—	45.8
140	16.3	0.2	—	26.8	—	—	—	56.7
170	9.7	0.1	—	12.4	1.2	3.2	—	73.4
180	7.8	0.2	—	10.5	1.0	3.3	—	77.2
200	7.2	1.2	—	11.0	3.3	5.2	—	72.1
220	3.4	0.9	—	8.7	3.5	8.1	—	75.4
240	3.0	0.6	0.6	5.1	2.1	6.3	—	82.3
300	0.7	0.8	0.6	4.3	3.0	6.9	—	83.7

DISCUSSION

The data noted in Tables II–VII demonstrate that partial, Haworth methylation of methyl β-D-xylopyranoside gave virtually no 3,4-dimethyl ether (except for traces after 2 h) and that the 3-*O*-methyl derivative was formed in small amounts only. The dimethyl ether fraction contained the 2,4- and 2,3-isomers in the ratio (4–5:1). The monomethyl ether fraction consisted of approximately equal amounts of the 2- and 4-isomers. Methylation in the presence of barium oxide yielded, in the early stages, approximately twice the quantity of 4-methyl ether compared to either of the two other mono-ethers, although later they were present in approximately equal amounts. The dimethyl ether fraction consisted of the 2,4- and 2,3-isomers, with the former preponderating. It is noteworthy that, after 1 h, the 2,3,4-trimethyl ether was the only compound present.

Kuhn methylation in the presence of silver oxide gave monomethyl ethers in approximately equal proportions, but with the sequence 2>4>3. The dimethyl ether fraction again consisted mainly of the 2,4-isomer (33.3% after 2 h). The 2,3-di-*O*-methyl derivative was further methylated more rapidly than the 2,4-isomer and was present in very small amount after 4 h, whereas 17% of the 2,4-di-*O*-methyl derivative was still present. Therefore HO-3 is more difficult to methylate than HO-4. It is interesting to note that Kuhn methylation in the presence of barium oxide was 16 times faster than in the presence of silver oxide.

The results of the Purdie methylation demonstrate that, in the initial stages, the monomethyl ether fraction consisted of approximately equal amounts of all the possible isomers. However, inspection of the relative ratios of the mono-ethers at later stages showed that the 4-isomer was methylated more quickly than the others. The dimethyl ether fraction consisted of the 2,4- and 2,3-isomers, the former comprising, after 2 h, ~45% of the total mixture. It is noteworthy that only Purdie's procedure led to a low content of the permethylated compound (~15% by the end of the reaction). With reaction times exceeding 2 h, the composition of the product mixture did not change significantly. Table V shows that partial, Purdie methylation may be used to obtain 2,4-di-*O*-methyl-D-xylose on a preparative scale.

Partial, Hakomori methylation was conducted with 3.3 and 5.8 equiv. of carbanion per equiv. of xyloside. The methylation proceeded very quickly, and methyl iodide was added in portions in order that the methylation might be followed. In the first procedure, the monomethyl ether fraction contained approximately equal amounts of isomers. Initially, on the addition of methyl iodide, the concentration of the 4-methyl ether increases, attaining 17% of the total mixture and 65% of the mono-ether fraction. The dimethyl ether fraction consisted of the 2,4- and 2,3-isomers in a ratio of 2:1 throughout most of the reaction. It is interesting to note that the Hakomori methylation procedure, unlike other methods, yielded the 2,3,4-trimethyl ether in the early stages of the reaction but only a small proportion of dimethyl ethers. In the second procedure, the content of 4-methyl ether increased to a maximum of 27.6% after the addition of 3.12 equiv. of methyl iodide. Further methylation of the

4-methyl ether appeared to be slower than that of other mono-ethers. The initially formed 2-*O*-, 3-*O*-, and di-*O*-methyl derivatives disappeared with increase in methyl iodide concentration but were detected again an adding more than 3.75 equiv. of methyl iodide. Taking into account the difficulty of preparing 4-*O*-methyl-D-xylose[15], partial, Hakomori methylation of the xyloside, followed by chromatographic separation of the 4-*O*-methyl derivative and subsequent hydrolysis, is a practical method of synthesis.

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