Oxidation of Carbohydrates and A Carbon-13 n.m.r. Study of the Keto Sugars

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Abstract ☐ Three inexpensive oxidation reagents, namely pyridinium chlorochromate, chromium trioxide-dipyridine and nicotinium dichromate were utilized for oxidation of carbohydrates in 78-92% yield. Hydration could be eliminated in the oxidation of pentopyranosides and hexopyranosides, while pentofuranosides had a tendency to be easily hydrated during the oxidation. In the carbon-13 n.m.r. study, the carbonyl function resulted from the oxidation affected on the chemical shifts of α- and β-carbons of methyl 3,4-O-isopropylidene-β-D-arabinopyranosid -2-ulose (8) and 1,2 : 4,5-di-O-isopropylidene-β-D-erythro-2,3-hexodiulo-2,6-pyranose (10) to slightly down fields (0.7-2.6 p.p.m.) compared with the chemical shifts before oxidation. While the carbonyl groups of 1,2-O-isopropylidene-5-O-ethyloxycarbonyl-α-D-erythro -pentofuran-3-ulose (4) and methyl 3,5-O-isopropylidene-α-D-threo-pentofuranosid-2-ulose (6) pushed the α-carbons to up fields (3.2-18.3 p.p.m.). However, the order of signals on the spectra before and after oxidation remained unaltered.

Keto sugars have been utilized as important intermediate in carbohydrate chemistry in expanding carbon numbers (1-3), adding a gemdifluoro group (4,5) and a creation of a new asymmetric center (6,7) by reduction of the ketone.

It is necessary to develop efficient oxidation procedures without hydration involved. Because the hydrate commonly interferes with the next reaction such as a Grignard reaction, fluorination and reduction.

There, in this paper, three different most efficient oxidation reagents will be introduced for synthesis of keto sugars and the identification of each keto sugar by a carbon-13 n.m.r. analysis will be discussed. The three most efficient oxidation reagents used are pyridinium chlorochromate 8-11), chromium troxide-dipyridine (12, 13) and nicotinium dichromate (14, 15).

EXPERIMENTAL METHODS

Melting points were determined with a Mel-Tem apillary melting point apparatus and are uncorected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter at room temperature. Ascending t.l.c. was conducted on plates coated with a 0.25-mm layer of Silica gel 60 PF-254 (E. Merck Co.). The components were located by spraying the plate with 5% H_2SO_4 in ethanol and heating. Carbon-13 n.m.r. spectra were recorded with a Varian XL-100 instrument (100 MHz) with Me_4Si as the internal standard. The chemical shift values are expressed in M values (p.p.m.) relative to Me_4Si.

Methyl 2,3-O-isopropylidene-β-D -ribopentodialdo-1,4-furanoside (2)

Pyridinium chlorochromate (7.76g, 0.036 mol) was suspended in dry dichloromethane (50 ml) and to this was added a solution of methyl 2,3-O -isopropylidene-β-D-ribofuranoside (5g, 0.024 mol) in dry dichloromethane (5 ml) with stirring. The mixture was refluxed for 1.5 hr. Another part of pyridinium chlorochromate (2g) was added to the reaction mixture. After the mixture was cooled to room temperature, dry ether (50 ml) was added to the mixture. The mixture was filtered through a Celite bed and the residue was washed with dry ether (20 ml×2). The combined organic

layer was passed through a short column (230-400 mesh, 5×10cm). After evaporation of the eluent, a solid was obtaind (78%). Pure aldehyde was obtained by a vacuum distillation in 56% yield; b. p. 109° /4.2 mmHg, m.p. 60-61° (lit. (3) 60-61 °), $[\alpha]_D^{20}=-217°$ (c .1.46, chloroform) (lit. (3) $-218°$). Carbon-13 n.m.r. (CDCl₃) : 200.3(C -5), 112.5 (acetal ring carbon), 109.0(C-1), 89.4 (C-4), 83.9(C-2), 80.7(C-3), 55.6(OCH₃), 26.4 and 26.2 (2CH₃).

1, 2-*O*-*Isopropylidene*-5-*O*-*ethyloxycarbonyl* - α -*D*-*erythro*-*pentofuran*-3-*ulose* (4)

1, 2-O-Isopropylidene-α -D-xylofuranoside (22) was protected (23) on the position 5 with ethyl chloroformate to give 1, 2-O-isopropylidene-5-O -ethyloxycarbonyl- α -D-xylofuranoside; m.p. 104-106° , $[\alpha]_D^{20}=15.7°$ (c 2.04, chloroform). To a suspended refluxing mixture of pyridinium chlorochromate (9.9g, 0.046 mol) and molecular sieves (3A, 8-12 mesh, 10g) in dichloromethane (200 ml) was added 1,2-O-isopropylidene-5-O-ethyl -oxycarbonyl- α-D-xylofuranoside (6g, 0.024 mol) in one portion and the mixture was stirred at room temperature for 2 hr. Two portions (10g each) of pyridinium chorochromate were added to the reaction mixture with an interval of 1.5 hr. After 16 hr stirring at room temperature, the reaction mixture was filtered through a Celite bed, the gummy residue was washed with ether (200 ml) and filtered. The combined filtrate was evaporated to a dark gummy syrup. The residue was dissolved in toluene/acetone (20 : 1) mixture (20 ml) applied to a column of Silica gel (230-400 mesh, 2. 5×50cm). The column was eluted with toluene/ acetone (20 : 1). The appropriate fractions were collected, evaporated and dried in vacuo to give crystals; yield 4.9g (83.6%), Rf=0.64 on Silica gel in benzene/ethyl acetate (1 : 1), Rf=0.20 on Silica gel in toluene/acetone (19 : 1), m.p. 53-54 ° , $[\alpha]_D^{20}=+142.1°$ (c 2.02, chloroform). Carbon -13 n.m.r. (CDCl₃) : 207.1(C-3), 154.3(OC(O)O), 114.2 (acetal ring carbon), 103.1(C-1), 76.9(C-4), 76.2(C-2), 65.8(C-5), 64.4(OCH₂CH₃), 27.4 and 27.0(2CH₃), 14.1(OCH₂CH₃).

Methyl 3, 5-*O*-*isopropylidene*- α -*D*-*threo* -*pentofuranosid*-2-*ulose* (6)

Chromium trioxide (7.83g, 0.0784 mol) was added to a solution of pyridine (12.67 ml, 0.157 mol) in dichloromethane (200 ml). After 15 min stirring, a solution of methyl 3,5-O-iso-propylidene-m-D-xylofuranoside (4g, 0.0195 mol)(1,24) in dichloromethane (50 ml) was added dropwise with stirring at room temperature for 1 hr. Acetic anhydride (7.4 ml) was added to the reaction mixture at once. The reaction mixture

was refluxed for 2 hr and then allowed to room temperature. The mixture was poured into ethyl acetate (600 ml) and the resulting mixture was poured onto a Silica gel column (230-400 mesh, 5× 30cm). The eluent (1 liter) was evaporated to a syrup (black). The syrup was chromatographed on a column of Silica gel (230-400 mesh, 2×40cm). The column was eluted with toluene/acetone (30 : 1). The appropriate fractions were collected, evaporated and dried *in vacuo* to give a solid; yield 3.4g (79.2%). The crude one was recrystallized from toluene and pet. ether. m.p. 71-72° (hydrate)(lit. (1, 24) 69-70°), $[\alpha]_D^{20}=+111°$ (c 1.07, chloroform)(lit. (1, 24) 111°). Carbon-13 n.m.r. (CDCl₃) : 203.7(C-2), 106.4(C-1), 98.8(acetal ring carbon), 73.5(C-4), 70.4(C-3), 60.7(C-5), 56.6(OCH₃), 28.7 and 19.4(2CH₃).
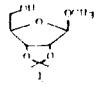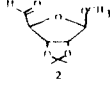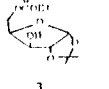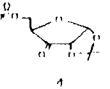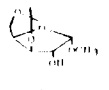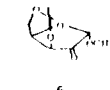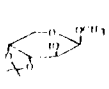
Methyl 3, 4-*O*-*isopropylidene*- β -*D* -*arabinopyranosid*-2-*ulose* (8)

Chromium trioxide (43.06g, 0.428 mol) was added to a magnetically stirred solution of pyridine (69.7 ml, 0.856 mol) in dichloromethane (1 liter). After 15 min, a solution of methyl 3, 4-O-isor-propylidene- β -D-arabinopyranoside (22g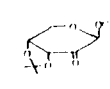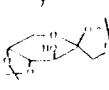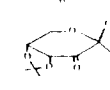, 0.107 mol)(25, 26) in dichloromethane (150 ml) was added dropwise to the mixture at room temperature with vigorous stirring for 15 min. Acetic anhydride (40.7 ml) was added to the mixture at once and the mixture was stirred at room temperature for 2 hr. After evaporating the mixture to ca 400 ml, the residue was poured into ethyl acetate (2 liters) and the whole mixture was poured onto a Silica gel column (230-400 mesh, 7×100cm). The eluent (3.2 liters) was collected and evaporated to dryness. The crude one was recrystallized from toluene and pet. ether to give 19.9g (92.0%) which was not hydrated one; m.p. 87-88° (lit. (26) 114° hydrate), $[\alpha]_D^{20}=-155.8$ (c 0.69, chloroform)(lit. (26) −161° hydrate). Carbon-13 n.m.r. (CDCl₃) : 198.5(C-2), 110.3(acetal ring carbon), 100.8(C-1), 77.6(C-3), 75.3(C-4), 58.3(C-5), 55.6(OCH₃), 27.1 and 26.1(2CH₃).

1, 2 : 4, 5-*Di*-*O*-*isopropylidene*- β -*D*-*erythro* -2, 3-*hexodiulo*-2, 6-*pyranose* (10)

To a solution of benzene (400 ml) and pyridine (38.4 ml, 0.48 mol) were added nicotinium dichromate (112g, 0.24 mol)(14, 15) and 1,2 : 4, 5-di-O-isopropylidene- β-D-fructopyranoside (20.84g, 0.08 mol)(27) consecutively at room temperature. The mixture was stirred for 15 min and then refluxed for 3.5 hr. The mixture was cooled to room temperature, filtered through a Celite (300 G) bed and the brownish filter cake was washed with benzene (160 ml×2). The combined filtrate (clear yellow solution) was evaporated to

Table I. Oxidation of Carbohydrates.

Substrate	Product	Reagent	Yield
		Pyridinium chlorochromate	78% (56%)*
		Pyridinium chlorochromate	84%
		Chronium trioxide-dipyridine	79%
		Chromium trioxide dipyridine	92%
		Nicotinium dichromate	87%

*After distillation

dryness and dried *in vacuo* to give crude crystals. The crude one was dissolved in anhydrous ether (150 ml) and the ether solution was passed through a Silica gel column (230-400 mesh, 5×25 cm). The column was further eluted with anhydrous ether. The total eluent (500 ml) was collected, evaporated under deminished pressure to dryness and dried *in vacuo* to give white crystals; yield 17. 9g (86. 6%), m.p. 100-101° (lit. (16) 102-103 °), $[\alpha]_D^{20}=-119.6°$ (c 1. 1 chloroform)(lit. (16) —119. 6°). Carbon-13 n.m.r. (CDCl$_3$) ; 196. 8(C -3), 113. 7 and 110. 7(2 acetal ring carbon), 104. 3 (C-2), 77. 9(C-4), 76. 0(C-5), 70. 3(C-1), 60. 5(C -6), 27. 2, 26. 6, 26. 1 and 26. 1(4CH$_3$).

RESULTS AND DISCUSSION

Oxidations of five chosen carbohydrates by three different reagents adapted in this experiment went in high yields (78-92%) which were much higher compared with the oxidation by methyl sulfoxide (44%) (16) in compound 12(Table I). Pyridinium chlorochromate as well as RuO$_2$-NaIO$_4$-K$_2$CO$_3$ (not shown in this paper) oxidized compound 3 to compound 4 in 84% yield in both cases. However, pyridinium chlorochromate was inexpensive and easier to handle compared with RuO$_2$.

All three oxidation reagents were efficient at room temperature in aprotic solvents such as dichloromethane, benzene, toluene and acetonitrile. Chromium trioxide–dipyridine required a large amount of solvent for the purification and provided messy stain on the reaction vessels. While oxidation by pyridinium chlorochromate and nicotinium dichromate needed less solvent for the purification

Table II. Carbon-13 n.m.r. chemical shifts in p.p.m. from Me$_4$Si.

Compd.	C-1	C-2	C-3	C-4	C-5	C-6	OCH$_3$	$\overset{O}{\underset{O}{>}}C\overset{\nearrow}{\searrow}$		CH$_3$
1	109. 5	85. 4	81. 4	87. 8	63. 6		55. 0	111. 9	26. 2	24. 6
2	109. 0	83. 9	80. 7	89. 4	200. 3		55. 6	112. 5	26. 4	26. 2
3 *	104. 5	79. 2	75. 1	85. 2	65. 8			111. 6	26. 5	26. 0
4 **	103. 1	76. 2	207. 1	76. 9	65. 8			114. 2	27. 4	27. 0
5	103. 2	71. 3	75. 4	76. 7	60. 4		56. 4	97. 3	28. 5	19. 4
6	106. 4	203. 7	70. 4	73. 5	60. 7		56. 6	98. 8	28. 7	19. 4
7	99. 1	70. 1	76. 0	73. 0	59. 2		55. 5	108. 9	28. 0	26. 0
8	100. 8	198. 5	77. 6	75. 3	58. 3		55. 6	110. 3	27. 1	26. 1
9	70. 5	104. 6	72. 6	77. 2	73. 4	61. 1		111. 7	27. 9	26. 5
								109. 3	26. 3	25. 9
10	70. 3	104. 3	196. 8	77. 9	76. 0	60. 5		113. 7	27. 2	26. 6
								110. 7	26. 1	26. 1

OC(O)O(153. 3), $\underline{C}$H$_2$CH$_3$(64. 4), CH$_2$$\underline{C}H_3$(14. 1)
*OC(O)O(154. 3), $\underline{C}$H$_2$CH$_3$(64. 4), CH$_2$$\underline{C}H_3$(14. 1)

and did not give messy stain. Nicotinium dichromate and pyridinium chlorochromate are more convinient for the large scale oxidation due to ease to handle and smaller solvent needed than chromium trioxide-dipyridine.

The assignment of signals in carbon-13 n.m.r. spectra followed the empirical rules established in earlier publications (17, 18). (a) The anomeric carbon atoms in pyranoses and furanoses, and in their derivatives, resonate at lowest field (90-110 p.p.m.). (b) Carbon atoms carrying primary hydroxy groups are found at 60-64 p.p.m.. (c) Carbon atoms bearing secondary hydroxy groups, in pyranoses and furanoses, give signals at 65-85 p.p.m.. Signals of alkoxylated carbon atoms, including C-5 in petopyranoses and C-4 in furanoses, are shifted 5-10 p.p.m. to lower field when compared with the correspponding, hydroxy-substituted carbon atoms.

Carbon atoms of the furanoses, compound 2, 4 and 6 were assigned according to the above rules. C-3 and C-4 of compound 10 were assigned compared with corresponding pentopyranoses (19, 20) in which C-3 appeared at slightly lower field than C-4. The same assignment rule was applied to compound 12 in which the signal of C-4 was lower than that of C-5 (Table II).

The 6-membered acetal ring carbon (6) resonated in higher field than the 5-membered acetal ring carbons (2, 4, 8 and 10), which was well agreed with the previous obserbation (21). The oxidation (C=O) of the alcohols in pyranoses (8 and 10) affected on the chemical shifts of the α and β-carbons to slightly down field (0.7-2.6 p.p.m.) and the oxidation (C=O) of the alcohols in furanoses (4 and 6) moved the α-carbons to up field (3.2-18.3 p.p.m.) compared with their chemical shifts before oxidation. The large change of the chemical shift (18.3 p.p.m.) of C-4 in 4 seemed to be due to the confirmation change from endo (alcohol; a possible formation of hydrogen bond) to exo (keto; a repulsion between two keto groups) form.

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