Communications to the Editor

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REGIOSELECTIVE MONO-OXIDATION OF NON-PROTECTED GLYCOSIDES BY THE BIS-TRIBUTYLTIN OXIDE-BROMINE METHOD[1)]

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Treatment of methyl glycosides with an excess of bis-tributyltin oxide and molecular sieves 3A in chloroform followed by brominolysis resulted in mono-oxidation to yield oxo-glycosides regioselectively. Thus Me β-D-Glc and Me β-D-Xyl gave the 3-oxo derivatives in more than 90% yield, and Me α-D-Glc, Me α-D-Gal, Me α-D-Xyl, and Me β-L-Ara gave the 4-oxo derivatives in 70-80% yield.

KEYWORDS——methyl glycoside; oxidation; brominolysis; bis-tributyltin oxide; oxo-glycoside; glycopyranosid-3-ulose; glycopyranosid-4-ulose

The O-Sn linkage formed from hydroxyl groups by the action of bis-tributhyltin oxide or dibutyltin oxide is very sensitive to brominolysis and yields a carbonyl compound at the speed of titration, thus providing mild oxidation of a hydroxyl group to the corresponding carbonyl compound.[2)] This method, however, is seldom applied to compounds carrying more than three hydroxyl groups. Only two such examples are reported,[3,4)] in which dibutyltin oxide is used to regioselectively activate a particular hydroxyl group, aided by the formation of a cyclic stannylene derivative. The success of regioselective acylation[5)] and alkylation[6)] of various non-protected glycosides through tin intermediates suggested that the method was worth testing for use with various non-protected carbohydrates.

This communication describes the result when the bis-tributyltin oxide method is applied to glycosides where three or more contiguous hydroxyl groups are present in the molecule.

After several fruitless attempts to apply the previously reported procedure,[2a,b)] we found that the following modification is suitable for oxidizing non-protected glycosides; i. e., stannylation of glycosides in refluxing chloroform with an excess of the reagent and molecular sieves 3A followed by in situ brominolysis, then chromatography without extraction procedure (see General Procedure). Other solvents such as tetrahydrofuran resulted in over-oxidation.

By this modified method, Me β-D-Glc[7)] **1** was oxidized to the 3-oxo derivative **2**, mp 130-134°C, in 96% yield. The product **2** exhibited a single OMe peak in ^{1}H-NMR spectrum (δ 3.62).[8)] The homogeneity of the compound was confirmed by GLC of its trimethylsilyl (TMS) derivative. $NaBH_4$ reduction of **2** in methanol gave back **1** almost quantitatively. The ^{13}C-NMR spectrum (Table I) clearly indicated that the compound is the 3-oxo derivative. The same 3-oxo-glucoside (lit. mp 127-128°C) was previously prepared in low yield by dichromate oxidation of **1** in the presence of oxalic acid.[9)]

The β-D-p-nitrophenyl derivative **3** was also smoothly oxidized (>90%) to the corresponding 3-oxo derivative **4**, mp 190-194°C, although 4 eq of $(Bu_3Sn)_2O$ was necessary for complete reaction in this case.

Me α-D-Glc **5** was similarly oxidized to give exclusively a compound with an OMe peak at δ 3.52 whose intensity ratio suggested that the product was more than 75% homogeneous. $NaBH_4$ reduction

of this product in methanol gave Me α-D-Glc **5** and Me α-D-Gal **7** in a ratio of ca. 7:3 (GLC of TMS derivative) suggesting that the oxidation product is the 4-oxo derivative **6**. The ^{13}C-NMR spectrum confirmed this identification. Me α-D-Gal **7** gave the same product **6** in ca. 70% yield (as judged from the OMe peak at δ 3.52 and confirmed by TLC, GLC of the TMS derivative, and ^{13}C-NMR) by similar oxidation.

Me β-D-Xyl **8** was oxidized to the 3-oxo derivative[10] **9** in more than 90% yield. The product **9** (^{13}C-NMR, see Table I), on reduction with $NaBH_4$, regenerated **8**, while on catalytic hydrogenation over Pt in AcOH gave Me β-D-Rib **10** and Me β-D-Xyl **8** in a ratio of 9:1 as confirmed by TLC and GLC (TMS derivative).

On similar oxidation, Me α-D-Xyl **11** and Me β-L-Ara **12** gave the same product **13** (>80% yield). However, their ^{1}H- and ^{13}C-NMR were complex, suggesting that the product is a mixture of at least three compounds. This was eventually found to be identical with the oxidation product of Me β-L-

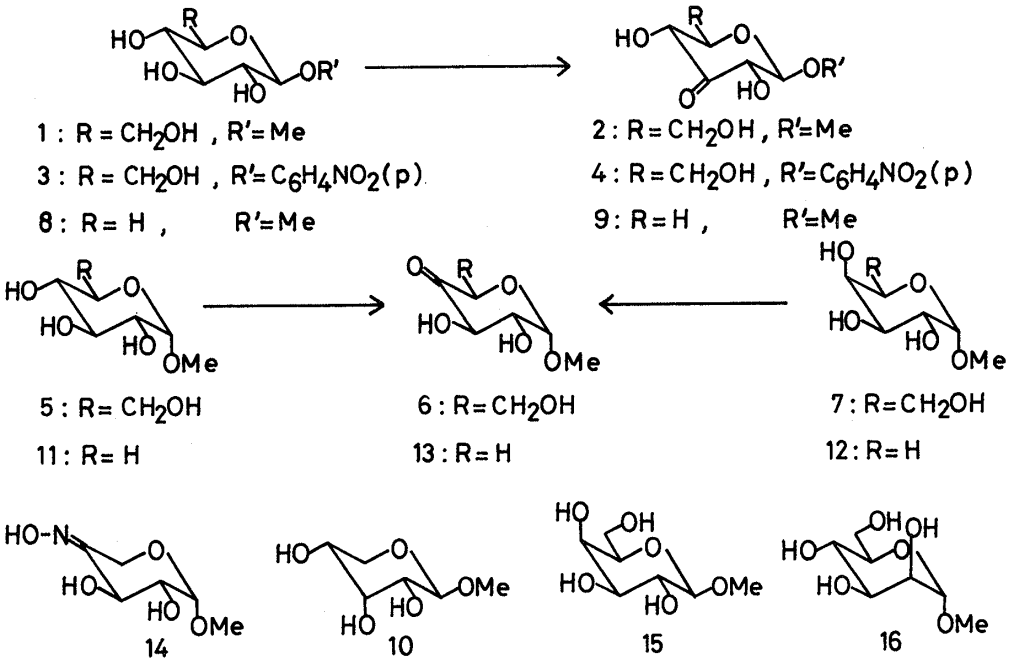

Table I. ^{13}C-NMR Spectra of Oxo-Glycosides in Pyridine-d_5
(Parenthical values indicate the shifts from the corresponding Me β- or α-D-Glc or D-Xyl).

Compds	C-1	C-2	C-3	C-4	C-5	C-6	OMe
2	106.4	78.2[a)]	207.4	73.5	78.0[a)]	62.0	56.9
	(+0.9)	(+2.7)	--	(+2.1)	(-0.3)	(-0.6)	(+0.2)
4	102.4	77.7	206.4	73.5	79.0	61.9	--
6	101.0	74.6	77.4	205.8	76.1	60.5	55.8
	(-0.3)	(+0.9)	(+2.1)	--	(+2.1)	(-2.1)	(+0.8)
9	107.5	78.2	206.9	73.2	66.9	--	56.8
	(+1.4)	(+3.5)	--	(+2.2)	(+0)		(+0.2)

2: methyl β-D-ribo-hexopyranosid-3-ulose, **6**: methyl α-D-xylo-hexopyranosid-4-ulose;
9: methyl β-D-erythro-pentopyranosid-3-ulose.
a) Assignment may be interchanged.

Ara **12** by dibutyltin oxide and bromine, where the product was shown to be in equilibrium between the monomer **13** and dimers.[4] The GLC of the above product (TMS derivative) verified that this is actually the case. The structure of the product was finally confirmed by converting it to the single oxime **14**, mp 138-139°C, which was identical with the authentic specimen[4] in all respects. Thus, regioselective C-4 oxidation was established for **11** and **12**.

The oxidation of Me β-D-Gal **15** and Me α-D-Man **16** was not highly regioselective. They give a mixture of two regio-isomeric oxo-derivatives (probably 4-oxo and 3-oxo derivatives from **15**, and 2-oxo and 4-oxo derivatives from **16**).

In conclusion, most of glycosides are smoothly oxidized regioselectively by the bis-tributyltin oxide-bromine method to yield the mono-oxo derivative in high yield without protection of the other hydroxyl groups. Oxidtion takes place at C-3 for the glycosides which have an equatorial glycosidic linkage (usually β-glycosides) and at C-4 for those which have an axial glycosidic linkage (usually α-glycosides). At the present we can not explain the reason for this. The above obtained oxo-glycosides should be useful intermediates for synthesis in the carbohydrate field, particularly for the synthesis of amino, branched, and the other unusual sugars.

GENERAL PROCEDURE—— Dried methyl glycoside (0.5-1 g), $(n\text{-}Bu_3Sn)_2O$ (ca. 2 eq), and an excess of molecular sieves 3A in chloroform (20-40 ml) were heated under reflux until the glycoside dissolved completely (2-3 h required), then cooled. To this mixture, bromine (ca. 2 eq required) was added at 0°C with stirring until the solution was faintly colored (5-8 min), then the mixture was poured onto a column of silica gel. The column was washed thoroughly with chloroform to remove tin compound(s), then eluted with ethyl acetate to yield the oxo-derivative (70-96%) which is pure enough in ^{13}C-NMR (in most cases) and can be used without further purification. Further elution of the column with methanol gave a small amount of the starting material (if present).

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REFERENCES AND NOTES

1) Utilization of Sugars in Organic Syntheses. XV. Part XIV: ref. 6).
2) a) K. Saigo, A. Morikawa, and T. Mukaiyama, Bull. Chem. Soc. Jpn., 49, 1656 (1976); b) Y. Ueno and M. Okawara, Tetrahedron Lett., 1976, 4597; c) S. David and A. Thieffry, J. Chem. Soc. Perkin Trans. 1, 1979, 1568.
3) S. Hanessian and R. Roy, J. Am. Chem. Soc., 101, 5839 (1979).
4) Y. Tsuda, M. Hanajima, and K. Yoshimoto, Chem. Pharm. Bull., 31, 3778 (1983).
5) Y. Tsuda, Md. E. Haque, and K. Yoshimoto, Chem. Pharm. Bull., 31, 1612 (1983).
6) Md. E. Haque, T. Kikuchi, K. Yoshimoto, and Y. Tsuda, Chem. Pharm. Bull., 33, 2243 (1985).
7) Abbreviations: Me (methyl), Glc (glucoside), Gal (galactoside), Xyl (xyloside), Ara (arabinoside), Rib (riboside), and Man (mannoside).
8) ^1H- and ^{13}C-NMR spectra were taken in pyridine-d_5 solution.
9) B. Lindberg and O. Theander, Acta Chem. Scand., 8, 1870 (1954).
10) Preparation of the same 3-oxo derivative (mp 85-88°C) in 80% yield by DMSO-Ac_2O oxidation of the 2,4-phenylboronate was reported [B. Lindberg and K. N. Slessor, Acta Chem. Scand., 21, 910 (1967)].

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