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Studies on Glycosylation. II.[1] A S-Glycosylation by Use of Stannic Chloride

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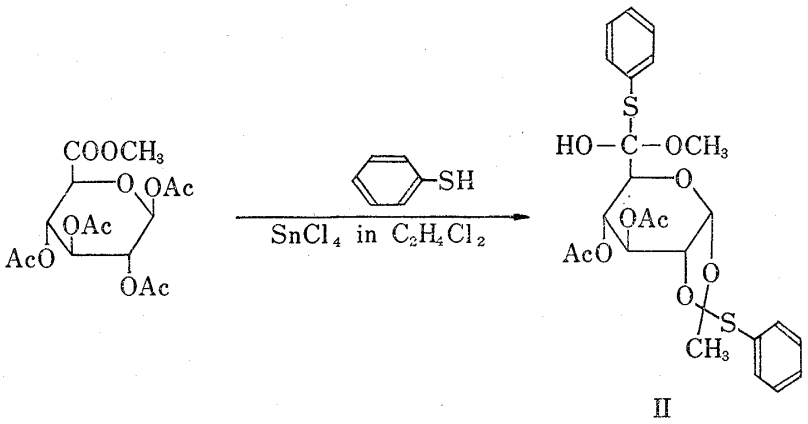
Application of the Helferich method to the preparation of thioglycosides was performed in dichloroethane at room temperature by use of $SnCl_4$ as catalyst. The reaction gave 1-thio-β-D-glucopyranoside from penta-O-acetyl-β-D-glucopyranose and thiophenol in good yield. However, the similar reaction with methyl 1,2,3,4-tetra-O-acetyl-β-D-glucopyranuronate and thiophenol gave an unpredicted product, 3,4-di-O-acetyl-6-methoxy 6-thiophenyl-α-D-glucopyranose 1,2-(phenylthio orthoacetate). The structure was confirmed by analytical and spectral data.

The application of the Helferich method to the preparation of thioglycosides was carried out by Hurd and Bonner,[3] who obtained phenyl-1-thio-β-D-glucopyranoside from penta-O-acetyl-β-D-glucopyranose and thiophenol with *p*-toluenesulfonic acid as catalyst. Lemieux converted this acetate into ethyl-2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside by zinc chloride-catalyzed ethanethiolysis.[4] In connection with the previous study on a facile O-glycosidation using stannic chloride,[1] we have attempted S-glycosidation by similar reaction.

The condensation of penta-O-acetyl-β-D-glucopyranose with thiophenol in dichloroethane in the presence of $SnCl_4$ at room temperature afforded the acetylated 1-thiophenyl glucoside (I), mp 116—117°, $[\alpha]_D$ +16.7°, in 47% yield. The structure was confirmed by the nuclear magnetic resonance (NMR) spectrum, the analytical data, and by the comparison with the literatural values in mp and $[\alpha]_D$.



II

Chart 1

The reaction of methyl-1,2,3,4-tetra-O-acetyl-β-D-glucopyranuronate and thiophenol with $SnCl_4$ in dichloroethane at room temperature following purification by silica gel column chromatography gave a product as colorless prisms (II), mp 120—121°, $[\alpha]_D$ +42°, in about

1) Part I: K. Honma, K. Nakazima, T. Uematsu, and A. Hamada, *Chem. Pharm. Bull.* (Tokyo), **24**, 394 (1976).
2) Location: 5–8, *Hatanodai 1-chome, Shinagawa-ku, Tokyo.*
3) C.D. Hurd and W.A. Bonner, *J. Org. Chem.*, **11**, 50 (1946).
4) R.U. Lemieux, *Can. J. Chem.*, **29**, 1079 (1951).

20% yield, (Chart 1). On the NMR spectrum, a signal corresponding to C-CH_3 group was observed at 1.72 ppm as a singlet, and ten aromatic protons due to two thiophenyl groups were observed at 7.25—7.65 ppm. Further, the spectrum exhibited signals due to two acetyl groups at 2.10 and 2.15 ppm. In addition, the anomeric proton was observed at 4.39 ppm as a doublet with a small coupling constant, (J=3.0 Hz). These data on NMR spectrum proposed compound II to be 1,2-phenylthio orthoester-like structure. Further, decoupling procedure and addition of D_2O revealed that the other thiophenyl group was attached to the C-6 position, and one hydroxy group was present also on the C-6 position. Infrared (IR) spectrum of II showed absorbance of OH group near 3400 cm^{-1}, and the Rf value (Rf=0.22) on thin-layer chromatography (TLC) with benzene-ether (10: 1) showed lower than that of the parent sugar (Rf=0.40) with the effect of OH group. Acetylation of II was carried out in the usual manner to give the product with Rf 0.67 on the TLC. The NMR spectrum showed one additional acetyl group at 2.15 ppm. In addition, acetylated II showed the molecular ion peak at m/e 578 on the mass spectrum. These results established the structure of II to be 3,4-di-O-acetyl-6-methoxy 6-thiophenyl-α-D-glucopyranose 1,2-(phenylthio orthoacetate).

The nucleophilicity of sulfur caused introduction of a thiophenyl group to the cationized C-6 position of methyl glucopyranuronate. Sagar orthoesters are usually prepared from sugar halide in the reaction medium buffered against acids by pyridine derivative and they have high sensitivity against acids.[5] However, II was isolated under acidic conditions with $SnCl_4$. Lemieux, *et al.*[5a] prepared tri-O-acetyl-α-D-glucopyranose 1,2-(phenyl orthoacetate) and described that the *exo*- and *endo*-isomers showed the signals of orthoacetyl group at 1.78 and 1.58 ppm, respectively. But, it is not possible to determine the *exo*- or *endo*-configuration of the phenylthio orthoacetate (II) from the NMR spectrum.

Experimental

General Procedure——Melting points were determined on a H_2SO_4 bath and were uncorrected. $[\alpha]_D$ values were determined on a Yanagimoto OR 50 and ORD spectra on a Jasco model ORD/UV-5 polarimeter. NMR spectra were recorded on a Hitachi R-22 apparatus using TMS as an internal standard. Thin layer chromatography (TLC) was performed on Kiesel gel F254 (Merck) with benzene–ether (10: 1).

Phenyl-2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside (I)——A solution of penta-O-acetyl-β-D-glucopyranose (2.0 g, 5.1 mmoles)[6] and thiophenol (1.0 ml) in dichloroethane (20 ml) was treated with $SnCl_4$ (1.5 ml) at room temperature for 1 hr. The reaction mixture was diluted with dichloroethane, and washed with water. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was crystallized from isopropanol to afford I as colorless needles (1.07 g, 47%), mp 116—117°, $[\alpha]_D^{22}$ −16.7° (c=1.8, $CHCl_3$) (lit.[7] mp 117°, $[\alpha]_D$ −17.5°). ORD (c=0.2, $CHCl_3$) $[\alpha]^{22}$ (nm): −180° (290) (trough). NMR ($CDCl_3$) δ: 2.00—2.10 (12H, 4×AcO), 3.74 (1H, m, H-5), 4.20 (2H, d, J=4.0 Hz, H-6,6′), 4.65—5.33 (4H, m, H-1, H-2, H-3, H-4), 7.26—7.53 (5H, m, aromatic H). *Anal.* Calcd. for $C_{20}H_{24}O_9S$: C, 54.53; H, 5.49. Found: C, 54.78; H, 5.38.

3,4-Di-O-acetyl-6-methoxy 6-thiophenyl-α-D-glucopyranose-1,2-(phenylthio orthoacetate) (II)——A solution of methyl 1,2,3,4-tetra-O-acetyl-β-D-glucopyranuronate (2.0 g, 5.3 mmoles)[8] and thiophenol (1.0 ml) in dichloroethane (20 ml) was treated with $SnCl_4$ (1.5 ml) at room temperature for 1 hr. The reaction mixture was diluted with dichloroethane and washed with water. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel (100 mesh) (2.0×30 cm) with increasing proportions of ether in benzene (benzene→benzene: ether=5: 1). The major fractions corresponding to Rf 0.22 on TLC were collected and evaporated under reduced pressure. The residue was crystallized from isopropanol to afford II as colorless prisms (540 mg, 19%), mp 120—121°. $[\alpha]_D^{22}$ +42° (c=1.0, $CHCl_3$). ORD (c=0.21, $CHCl_3$): $[\alpha]^{22}$ (nm): +238° (314) (peak). NMR ($CDCl_3$) δ: 1.72 (3H,

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s, C-CH_3), 2.10 (3H, s, AcO), 2.15 (3H, s, AcO), 3.08 (1H, d, J=7.0 Hz, C_6-OH) (This signals disappeared on addition of D_2O.), 3.70 (3H, s, OCH_3), 4.11 (1H, t, $J_{4,5}$=7.0 Hz, H-5) [This signals shifted to 4.15 (1H, d, $J_{4,5}$=7.0 Hz) on addition of D_2O], 4.39 (1H, d, $J_{1,2}$=3.0 Hz, H-1), 5.18 (1H, dd, $J_{4,5}$=7.0 Hz, $J_{3,4}$=3.0 Hz, H-4), 5.42 (1H, dd, $J_{2,3}$=7.0 Hz, $J_{1,2}$=3.0 Hz, H-2), 5.89 (1H, dd, $J_{2,3}$=7.0 Hz, $J_{3,4}$=3.0 Hz, H-3), 7.25—7.65 (10H, m, aromatic H). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1750 (C=O), 1445, 1380, 1258, 1230, 1080, 1040. *Anal.* Calcd. for $C_{25}H_{28}O_9S_2$: C, 55.96; H, 5.26; S, 11.94. Found: C, 56.06; H, 5.20; S, 11.88.

II (30 mg) was acetylated with acetic anhydride (1 ml) and pyridine (1 ml) overnight at room temperature. Usual working up gave the sirupy product (32 mg). This showed one spot (Rf=0.67) on TLC. NMR ($CDCl_3$) δ: 1.71 (3H, s, C-CH_3), 2.05 (3H, s, AcO), 2.15 (6H, s, 2×AcO), 3.72 (3H, s, OCH_3), 4.39 (1H, d, $J_{1,2}$=3.0 Hz, H-1), 5.05 (1H, d, $J_{4,5}$=8.0 Hz, H-5), 5.47 (1H, dd, $J_{4,5}$=8.0 Hz, $J_{3,4}$=3.0 Hz, H-4), 5.54 (1H, dd, $J_{2,3}$=8.0 Hz, $J_{1,2}$=3.0 Hz, H-2), 5.95 (1H, dd, $J_{2,3}$=8.0 Hz, $J_{3,4}$=3.0 Hz, H-3), 7.25—7.65 (10H, m, aromatic H). Mass Spectrum[9] *m/e*: 578 (M^+), 469 (M^+-SC_6H_5), 409 (M^+-SC_6H_5-CH_3COOH), 367 (M^+-SC_6H_5-CH_3COOH-$COCH_3$).

9) The mass spectrum was determined on a Hitachi Model RMV-6E spectrometer at an ionizing voltage of 70 eV.

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A Novel Synthesis of α-Halo Carbonyl Compounds using Metal Halides

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The α-position of active methylene compounds which were activated by the carbonyl group was halogenated using metal halides in the presence of peroxides.

Various Halogenation methods, such as the reaction of carbonyl compounds with bromine[2] or chlorine,[3] with N-bromosuccinimide[4] or with sulfuryl chloride,[5,6] *etc.*,[7] have been reported for the preparation of α-halo carbonyl compounds. The reaction of carbonyl compounds with two mole equivalents of copper (II) halide[8,9] under reflux in various solvents has also been applied to prepare α-halo aldehydes and α-halo ketones. In this reaction, the use of two mole equivalents of copper(II) halide is necessary and the reaction solution becomes strongly acidic owing to evolution of hydrogen halide as follows:

$$(CH_3)_2CH\text{-}CHO + 2CuCl_2 \longrightarrow 2CuCl + HCl + (CH_3)_2\overset{Cl}{\overset{|}{C}}\text{-}CHO$$

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