Reaction of Alkyl Vinyl Ethers with Methyl α-D-Glucopyranoside[1]

M. L. WOLFROM, ANNE BEATTIE, AND SHYAM S. BHATTACHARJEE

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

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Methyl α-D-glucopyranoside was brought into reaction with a series of alkyl vinyl ethers in equimolar quantities, under acid catalysis, and the acetals obtained were analyzed by methylation techniques. After long reaction times the chloroethyl, cyclohexyl, ethyl, and isopropyl vinyl ethers had both C-4 and C-6 hydroxyls blocked by acetal formation. Methyl 4,6-*O*-ethylidene-α-D-glucopyranoside was isolated as the sole product formed, with ethyl and isopropyl vinyl ethers. At short reaction times, formation of methyl 6-*O*-(1-alkoxyethyl)-α-D-glucopyranoside was also observed with ethyl, isopropyl, and methyl vinyl ethers. 6-*O*-(1-Methoxyethyl) and 6-*O*-(1-ethoxyethyl) derivatives could be isolated as major products under defined reaction conditions. Evidence is furnished that the alkyl vinyl ethers react preferentially at the C-6 primary hydroxyl which may be followed by a further reaction of the acetal with an available hydroxyl group at C-4 in the same molecule to form the 4,6-*O*-ethylidene derivative.

Vinyl ethers react with hydroxyl groups under acid catalysis to form mixed acetals.[2-4] Acetals formed in this manner have been used in carbohydrate chemistry to serve as blocking groups, easily removable by dilute acid.[5,6] The cyclic vinyl ether 2,3-dihydropyran has been most widely used in reactions of this type. The formation of stereoisomers on the acetal carbon has been shown to occur;[7] however, this does not interfere with the use of the formed acetal as a blocking group, which is subsequently removed. Vinyl thioethers have been demonstrated to be suitable protective agents for hydroxyl groups; the hydroxyl group could be regenerated with silver ion under neutral conditions.[8] It has been observed[9] that the *O*-(1-methoxyethyl) group can be more readily removed than the *O*-tetrahydropyran-2-yl group.

Starch acetals of various degrees of substitution have been prepared in this laboratory[10] and also by other workers.[11] Before studying the distribution of substituents in starch derivatives of a low degree of substitution (preferably 1.0) it was deemed necessary to determine whether vinyl ethers undergo preferential reaction with any hydroxyl group of a simple monomer model, for example, methyl α-D-glucopyranoside. It is also of interest in synthetic carbohydrate chemistry to examine the possibility of using vinyl ethers for any selective or preferential reaction. With this objective, the reaction of several alkyl vinyl ethers with methyl α-D-glucopyranoside has been studied.

The reaction of equimolar proportions of a vinyl ether with methyl α-D-glucopyranoside in *N,N*-dimethylformamide solutions was performed, under catalysis by *p*-toluenesulfonic acid, over a period of days (Table I). The use of chloroethyl, cyclohexyl, ethyl, and isopropyl vinyl ethers was first investigated. The products obtained were then fully methylated and the acetal was later removed by a mild acid hydrolysis. Identification of the resulting methyl ethers of methyl α-D-glucopyranoside or D-glucose indicated the location of the acetal attachment.

TABLE I

REACTION OF METHYL α-D-GLUCOPYRANOSIDE WITH 1 MOLAR EQUIV OF VARIOUS VINYL ETHERS

			Methylated D-glucose	
Vinyl ether	Reacn time[a]	Acetal yield, %	Me Glycoside, yield, %	Identity[b]
Chloroethyl	4 days	54	90	2,3-Di-*O*-methyl
Cyclohexyl	7 days	65	90	2,3-Di-*O*-methyl
Ethyl	7 days	67	95	2,3-Di-*O*-methyl
Isopropyl	30 min	23	95	2,3-Di-*O*-methyl (~90%); 2,3,4-Tri-*O*-methyl (~10%)
	7 days[c]	60	60	2,3-Di-*O*-methyl[c]

[a] Ambient temperature (25 ± 3°); *p*-toluenesulfonic acid catalyst. [b] By paper chromatography (solvents A and B) in comparison with authentic specimens. [c] See Experimental Section.

Methylation and hydrolysis of the reaction product of isopropyl vinyl ether with methyl α-D-glucopyranoside gave a crystalline methyl di-*O*-methyl-α-D-glucopyranoside, not susceptible to oxidation by sodium periodate, the physical properties of which were in good agreement with those of methyl 2,3-di-*O*-methyl-α-D-glucopyranoside. Hydrolysis gave a syrupy di-*O*-methyl-D-glucose having chromatographic and electrophoretic values identical with those of an authentic specimen of 2,3-di-*O*-methyl-D-glucose. Formation of the crystalline *N*-phenylglycosylamine derivative characterized the sugar as 2,3-di-*O*-methyl-D-glucose.

Chromatographic evidence indicated that methylation and hydrolysis of the reaction products of chloroethyl, cyclohexyl, and ethyl vinyl ethers with methyl α-D-glucopyranoside all gave 2,3-di-*O*-methyl-D-glucose as the only final product of this procedure (Table I). This shows that both C-4 and C-6 hydroxyls of methyl α-D-glucopyranoside had been blocked to methylation by acetal formation. The acetal product formed in each of the long-term reactions with isopropyl and ethyl vinyl ethers was purified from traces of methyl α-D-glucopyranoside by

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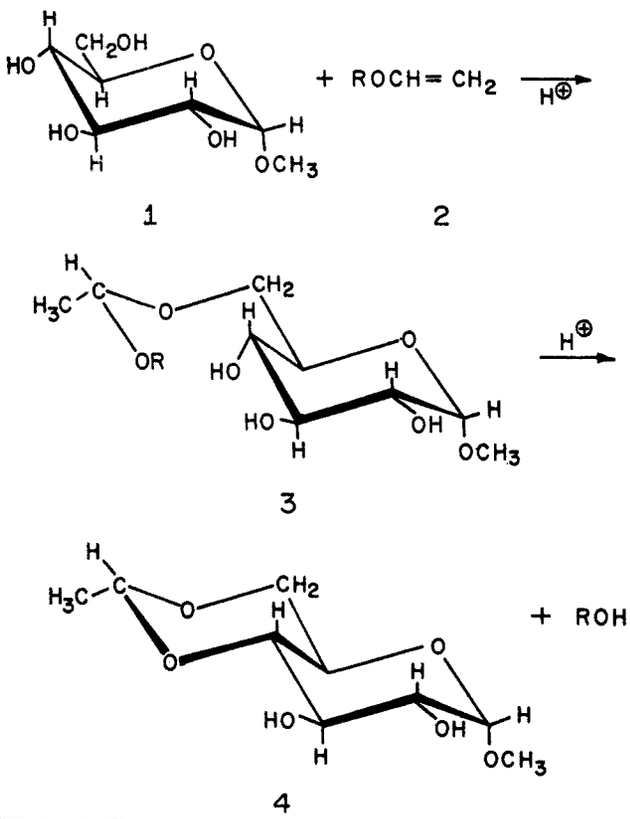
preparative thin layer chromatography and isolated. The sole product obtained was the crystalline methyl 4,6-*O*-ethylidene-α-D-glucopyranoside which also confirms the methylation results. When the reaction time of isopropyl vinyl ether with methyl α-D-glucopyranoside was reduced from several days to 30 min, a methylation assay showed 2,3-di-*O*-methyl-D-glucose as the main product with some tri-*O*-methyl-D-glucose tentatively identified as 2,3,4-tri-*O*-methyl-D-glucose (Table I).

Treatment of methyl α-D-glucopyranoside in about 3 *M* excess with methyl vinyl ether in the presence of boron trifluoride etherate gave a homogeneous (by thin layer chromatography), amorphous compound, in a good yield (70–75% of the crude reaction product), which has been identified as methyl 6-*O*-(1-methoxyethyl)-α-D-glucopyranoside on the basis of the following facts. This product could be partially converted into the known methyl 4,6-*O*-ethylidene-α-D-glucopyranoside; methylation and subsequent hydrolysis afforded 2,3,4-tri-*O*-methyl-D-glucose identified through its crystalline anilide; this material was chromatographically identical with a compound obtained from methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside by its reaction with methyl vinyl ether followed by deacetylation. Similar treatment of methyl α-D-glucopyranoside with ethyl vinyl ether in the presence of boron trifluoride etherate furnished a chromatographically homogeneous, noncrystalline product (yield ~80% of the crude product) which could likewise be identified as methyl 6-*O*-(1-ethoxyethyl)-α-D-glucopyranoside. This shows that the glycosidic group, a monocyclic acetal, does not exhibit to any significant extent the complex reactions described[12] for simple, acyclic acetals with vinyl ethers. Using again the same reaction conditions but replacing the boron trifluoride with *p*-toluenesulfonic acid, methyl 4,6-*O*-ethylidene-α-D-glucopyranoside was formed as a major product instead of methyl 6-*O*-(1-ethoxyethyl)-α-D-glucopyranoside. Reaction of equimolar proportions of methyl vinyl ether with methyl α-D-glucopyranoside, in the presence of *p*-toluenesulfonic acid for a 1- or 2-hr reaction period furnished methyl 6-*O*-(1-methoxyethyl)-α-D-glucopyranoside and methyl 4,6-*O*-ethylidene-α-D-glucopyranoside in approximately equal amounts, although, as noted before (Table I), the latter was formed as a major product when isopropyl vinyl ether was utilized under nearly the same conditions.



These results show that alkyl vinyl ethers (**2**) react preferentially as the C-6 hydroxyl of methyl α-D-glucopyranoside (**1**) followed by a subsequent reaction with the available C-4 hydroxyl group to form methyl 4,6-*O*-ethylidene-α-D-glucopyranoside (**4**). The 6-*O*-monosubstituted acetal (**3**) could, however, be trapped partially (*p*-toluenesulfonic acid catalysis) or almost completely (boron trifluoride etherate catalysis), depending on the reaction conditions.

Experimental Section[13]

Reaction of Methyl α-D-Glucopyranoside with 1 Molar Equiv of Several Vinyl Ethers.—A typical reaction was carried out in the following manner. Methyl α-D-glucopyranoside (15 g) was dispersed in dry *N*,*N*-dimethylformamide (30 ml) over Drierite (2 g). The vinyl ether (1 molar equiv) was added, followed by a catalytic amount of *p*-toluenesulfonic acid (80 mg). The reaction mixture was stirred for the desired reaction period (Table I) at ambient temperatures. Drierite and unreacted methyl α-D-glucopyranoside were removed by filtration; sodium hydrogen carbonate (100 mg) and water (2.0 ml) were added to the filtrate, which was concentrated to a syrup. The syrup was shaken with diethyl ether and filtered. The filtrate was concentrated to a syrup. The yields of the acetals obtained from various vinyl ethers are shown in Table I.

Methylation of the Reaction Product.—The above syrup (15 g) was dissolved in methyl iodide (100 ml) and silver oxide (25 g) was added. The mixture was shaken overnight at room temperature (or alternatively refluxed), filtered, and concentrated. The methylation procedure was repeated (4–5 times) until the infrared spectrum of the syrup showed the hydroxyl peak to be negligible. A portion of the above methylated syrup was hydrolyzed with 2 *N* sulfuric acid for 4 hr under reflux. Paper chromatographic examination (solvent A or B) of the neutralized (barium carbonate) hydrolyzate indicated the sugars resulting from the reactions with the various vinyl ethers (Table I).

Identification of 2,3-Di-*O*-methyl-D-glucose Following Methylation and Hydrolysis of the Reaction Product of Isopropyl Vinyl Ether with 1 Molar Equiv of Methyl α-D-Glucopyranoside.—The methylated acetal reaction product (3.0 g) from isopropyl vinyl ether was prepared as described above (7 days reaction time). Hydrolysis of this product with methanolic hydrogen chloride for 2 hr at reflux, followed by concentration and redistillation with

(12) R. I. Hoaglin and D. H. Hirsch, *J. Amer. Chem. Soc.*, **71**, 3468 (1949); R. I. Hoaglin and S. F. Clark, U. S. Patent 2,564,760 (1951); *Chem. Abstr.*, **46**, 2566 (1952).

(13) Paper chromatography was carried out on Whatman No. 1 filter paper in solvent systems 1-butanol–ethanol–water (4:1:5, v/v, solvent A), 1-butanone–1% ammonium hydroxide (10:1, v/v, solvent B) with indication by *p*-anisidine hydrochloride solution [L. Hough, J. K. N. Jones, and W. H. Wadman, *J. Chem. Soc.*, 1702 (1950)] or with silver nitrate and alkali [W. E. Trevelyan, D. P. Procter, and J. S. Harrison, *Nature*, **166**, 444 (1950)]. Solutions were concentrated under reduced pressure. Melting points were determined in a Thomas–Hoover capillary melting point apparatus. Infrared spectra were recorded with a Perkin-Elmer Infracord infrared spectrometer. Thin layer chromatography was ascending and was effected on 0.25–1.25 mm layers of silica gel G (E. Merck, Darmstadt, Germany) activated at 110°, using the solvent systems benzene–ethanol–water–10 *N* ammonium hydroxide (200:47:15:1, v/v, solvent D), methanol–ether (1:6, solvent D), and chloroform–acetone (1:1, v/v, solvent E) with indication by iodine vapor (preparative) or sulfuric acid. Microanalytical determinations were made by W. N. Bond. Acknowledgment is made to the experimental assistance of G. G. Parekh.

additional methanol, gave a crystalline glycoside (yield 1.85 g, 60%), mp 75–78°. Pure material was obtained on two recrystallizations from ethyl acetate (mp 82–83°, $[\alpha]^{22}D$ +150° (*c* 1.0, water) (lit.[14] mp 83–85°, $[\alpha]D$ +150° (water)) for 2,3-di-*O*-methyl α-D-glucopyranoside. The substance consumed no periodate during 24 hr at 35°.

Hydrolysis of the above methyl glycoside with 1 *N* sulfuric acid for 2 hr at reflux, followed by neutralization with barium carbonate, filtration, and concentration, afforded a di-*O*-methyl-D-glucose syrup: $[\alpha]^{20}D$ +58° (*c* 1.0 in water); R_G 0.6 (solvent A) and 0.4 (solvent B) identical with those of an authentic specimen[15] of 2,3-di-*O*-methyl-D-glucose. Electrophoresis in borate buffer at pH 10 for 5 hr at 600 V showed M_G 0.12 as did the authentic specimen, lit.[16] M_G 0.12. The crystalline anilide was prepared, mp 133° (lit.[17] mp 134°).

Acetal Isolation. A. From Isopropyl Vinyl Ether Reaction Products.—The reaction product (1.5 g) from isopropyl vinyl ether was isolated as described before and was subjected to preparative thin layer chromatography by two ascents with solvent C and extraction with methanol. The resultant syrup was crystallized from diethyl ether and the product was identified as methyl 4,6-*O*-ethylidene-α-D-glucopyranoside: yield 0.9 g (60%); mp 75°; $[\alpha]^{20}D$ +111.5° (*c* 0.5, methanol), lit.[18] mp 75–76°.

Anal. Calcd for $C_9H_{16}O_6$: C, 49.09; H, 7.27. Found: C, 49.34; H, 7.63.

Hydrolysis of the acetal reaction product (151 mg) with 2 *N* hydrochloric acid and distillation of the hydrolyzate into a solution of 2,4-dinitrophenylhydrazine in dilute hydrochloric acid[10] gave 1 molar equiv (93%) of acetaldehyde 2,4-dinitrophenylhydrazone.

B. From Ethyl Vinyl Ether.—The reaction product from ethyl vinyl ether was treated as described above and the product was identified as methyl 4,6-*O*-ethylidene-α-D-glucopyranoside in the same manner.

Reaction of Methyl α-D-Glucopyranoside with Methyl Vinyl Ether Using Boron Fluoride as Catalyst.—Methyl α-D-glucopyranoside (50 g, 0.25 mol) was dissolved in anhydrous dimethyl sulfoxide (100 ml) to which boron trifluoride etherate (4 drops) was added followed by the addition of methyl vinyl ether (5 ml, ~0.06 mol). The mixture was stirred magnetically in a closed flask for 2 hr at 35–40° (bath temperature). The catalyst was neutralized with an excess of powdered anhydrous sodium carbonate (stirred for 4 hr at room temperature). The mixture was filtered, the residue was washed with dimethyl sulfoxide, and the combined filtrates were concentrated to a syrup. This syrup was mixed thoroughly with chloroform whereupon unreacted methyl α-D-glucopyranoside (42 g) separated. The remaining methyl α-D-glucopyranoside and dimethyl sulfoxide were removed by repeating the concentration and addition of chloroform. The syrup (5.1 g) obtained from the chloroform solution, still containing traces of methyl α-D-glucopyranoside, consisted of one major and two minor components as shown by thin layer chromatography (solvents D and E). The major component (3.7 g, ~75% of the crude reaction product) was isolated by preparative thin layer chromatography (solvent D). In one experiment, further purification by thin layer chromatography (solvent E) was necessary. This solid material, methyl 6-*O*-(1-methoxyethyl)-α-D-glucopyranoside, did not crystallize, $[\alpha]^{20}D$ +46° (*c* 1.0, chloroform); 1 molar equiv of acetaldehyde formed on acid hydrolysis.

Anal. Calcd for $C_{10}H_{20}O_7$: C, 47.61; H, 7.93. Found: C, 48.03; H, 7.78.

A portion (100 mg) of the above compound was dissolved in chloroform (20 ml) to which *p*-toluenesulfonic acid (2.5 mg) was added. The solution became turbid after 2 min. After 15 min, the precipitate formed was filtered, washed with chloroform, and identified as methyl α-D-glucopyranoside (60 mg). The acid was neutralized with sodium carbonate after the total reaction period of 30 min and filtered. The filtrate showed only one spot by thin layer chromatography (solvents D and E) which had identical mobility with that of methyl 4,6-*O*-ethylidene-α-D-glucopyranoside. The chloroform solution was evaporated to dryness and the residue was crystallized from carbon tetrachloride and light petroleum ether (mp 74–76°, undepressed on admixture with a specimen of methyl 4,6-*O*-ethylidene-α-D-glucopyranoside, prepared by a known method,[19] which had mp 74–76°).

Anal. Calcd for $C_9H_{16}O_6$: C, 49.09; H, 7.27. Found: C, 48.84; H, 7.19.

This reaction was also performed in the presence of Drierite, using *N*,*N*-dimethylformamide and methylene chloride as solvents, and was found to follow the same course as described above.

Another portion (0.3 g) of the above amorphous compound, $[\alpha]^{20}D$ +46° ($CHCl_3$), was methylated with methyl iodide and silver oxide in the same way as described before. The completely methylated product (0.6 g) was hydrolyzed by refluxing with 1 *N* sulfuric acid for 10 hr, neutralized (barium carbonate), filtered, and evaporated to a syrup which showed one main spot with a very faint spot of slow moving component by paper chromatography (solvent A). These components were separated by paper chromatography and the main fraction (97 mg) was found to constitute about 97% of the mixture. The minor component (~2 mg) was not further investigated. A portion (50 mg) of the major component and distilled aniline (40 mg) were dissolved in ethanol (10 ml) and the solution was boiled under reflux for 4 hr. After evaporation of the aniline, the residue was left in the cold overnight for crystallization and the product was recrystallized from ether–petroleum ether (bp 30–60°): yield 48 mg; mp 143–145°, undepressed on admixture with an authentic specimen[20] of 2,3,4-tri-*O*-methyl-*N*-phenyl-D-glucopyranosylamine; $[\alpha]^{20}D$ −101° (*c* 1.0, ethanol, lit.[21] −103°).

Reaction of Methyl α-D-Glucopyranoside with 1 Molar Equiv of Methyl Vinyl Ether.—Methyl α-D-glucopyranoside (5 g) was dissolved in dry *N*,*N*-dimethylformamide (50 ml) to which *p*-toluenesulfonic acid (100 mg) and methyl vinyl ether (1.5 g) were added. The mixture was stirred for 1 hr at room temperature. The acid was neutralized with sodium carbonate, filtered, washed with *N*,*N*-dimethylformamide, and the combined filtrates were concentrated to a syrup. Unreacted methyl α-D-glucopyranoside was removed by mixing the syrup with chloroform, as mentioned in the previous case. The remaining portion was composed of two components in an approximate ratio 1:1, as shown by thin layer chromatography (solvent D), and these were chromatographically identical with methyl 6-*O*-(1-methoxyethyl)-α-D-glucopyranoside and methyl 4,6-*O*-ethylidene-α-D-glucopyranoside, respectively. The same results were obtained using a 2-hr reaction time and on variation of the quantity of *p*-toluenesulfonic acid.

Reaction of Methyl α-D-Glucopyranoside (Excess) with Ethyl Vinyl Ether. A. Boron Trifluoride as Catalyst.—Methyl α-D-glucopyranoside (25 g, 0.12 mole) was dissolved in anhydrous dimethyl sulfoxide (50 ml) to which were added successively boron trifluoride etherate (2 drops) and ethyl vinyl ether (2.3 g, 0.03 mol). The mixture was stirred for 2 hr at 35–40° and then anhydrous sodium carbonate (excess) was added, the mixture was stirred for another 4 hr, filtered, and washed with dimethyl sulfoxide. After removal of unreacted methyl α-D-glucopyranoside and dimethyl sulfoxide in the same manner as described in the case of the methyl vinyl ether reaction, the syrupy reaction product (2.4 g) afforded only one homogeneous solid material (1.9 g, ~80% crude reaction product) by preparative thin layer chromatography (solvent D). Trace amounts of another fast-moving component were present in the original mixture and were not investigated. The main reaction product, methyl 6-*O*-(1-ethoxyethyl)-α-D-glucopyranoside, failed to crystallize: $[\alpha]^{20}D$ +38° (*c* 1.0, chloroform).

Anal. Calcd for $C_{11}H_{22}O_7$: C, 49.62; H, 8.27. Found: C, 49.11; H, 8.25.

The above compound (100 mg) was dissolved in methylene chloride or chloroform (20 ml) to which *p*-toluenesulfonic acid (2.5 mg) was added. The reaction was followed by thin layer chromatography (solvent D) and after 30 min at room temperature there was no starting material present. The products were methyl α-D-glucopyranoside (major) and methyl 4,6-*O*-ethylidene-α-D-glucopyranoside.

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(16) Reference 14, p 129.

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(19) H. Appel, W. N. Haworth, E. G. Cox, and F. J. Llewellyn, *ibid.*, 793 (1938).

(20) Obtained from the collection of the late F. Smith through the courtesy of S. Kirkwood, University of Minnesota, St. Paul.

(21) J. D. Geerdes, B. A. Lewis, and F. Smith, *J. Amer. Chem. Soc.*, **79**, 4209 (1957).

B. *p*-Toluenesulfonic Acid as Catalyst.—To a magnetically stirred solution of methyl α-D-glucopyranoside (2.5 g, 0.12 mol) in anhydrous dimethyl sulfoxide (50 ml) was added *p*-toluenesulfonic acid (500 mg) followed by the addition of ethyl vinyl ether (2.3 g, 0.03 mol). Stirring was continued for 2 hr at 35–40°, sodium carbonate was added, and the mixture was agitated for 4 hr at room temperature. The reaction mixture was processed as described above. The major product was identical with methyl 4,6-*O*-ethylidene-α-D-glucopyranoside and the minor component was methyl α-D-glucopyranoside, as shown by thin layer chromatography (solvents D and E).

Preparation of the Methyl 6-*O*-(1-Alkoxyethyl)-α-D-glucopyranoside from Methyl 2,3,4-Tri-*O*-acetyl-α-D-glucopyranoside.—Methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (0.7 g), prepared by a known method,[22] was dissolved in diethyl ether (20 ml) to which *p*-toluenesulfonic acid (10 mg) and methyl vinyl ether (0.5 ml) were added. The reaction appeared to be complete after the mixture had been shaken for 10 min, as indicated by thin layer chromatography (solvents D and E), and was stopped after 15 min by neutralizing the acid with sodium carbonate. The reaction mixture was filtered, and the salts were washed with ether. The combined filtrates were decolorized with carbon and concentrated to a syrup (0.790 g) with no hydroxyl group (ir spectroscopy) which was homogeneous by thin layer chromatography (solvents D and E) but resisted crystallization.

Anal. Calcd for $C_{16}H_{26}O_{10}$: C, 50.79; H, 6.87. Found: C, 50.62; H, 6.82.

A portion (0.350 g) of the above syrup was dissolved in absolute methanol (10 ml) to which was added 0.5 *N* sodium methoxide solution (1.5 ml). The mixture was shaken occasionally for 45 min at room temperature. After being treated with Amberlite IR-120 (H^+), the methanolic solution was concentrated to a syrup, which was found to contain trace amounts of methyl α-D-glucopyranoside by thin layer chromatography (solvents D and E). The syrup was shaken with chloroform and filtered and the filtrate was evaporated to dryness. The resultant solid compound was chromatographically identical with methyl 6-*O*-(1-methoxyethyl)-α-D-glucopyranoside obtained directly from methyl α-D-glucopyranoside, as described before, and on treatment with *p*-toluenesulfonic acid in chloroform this material was converted into methyl α-D-glucopyranoside (major) and methyl 4,6-*O*-ethylidene-α-D-glucopyranoside as shown by thin layer chromatography (solvent D).

Similarly, a compound was prepared from methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside, by reaction with ethyl vinyl ether followed by deacetylation, and was found to be chromatographically (thin layer chromatography, solvents D and E) identical with the mono-*O*-(1-ethoxyethyl) derivative obtained from methyl α-D-glucopyranoside by boron trifluoride catalysis.

Registry No.—**1**, 97-30-3; **3** (R = Me) ($C_{10}H_{20}O_7$), 15717-31-4; **3** (R = Et) ($C_{11}H_{22}O_2$), 15649-43-1; **4**, 13225-11-1.

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Purine Nucleosides. XIX. The Synthesis of Certain 8-Chloropurine Nucleosides and Related Derivatives[1]

JOHN F. GERSTER,[2] BARBARA C. HINSHAW, ROLAND K. ROBINS, AND LEROY B. TOWNSEND

Department of Chemistry, University of Utah, Salt Lake City, Utah 84112

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A new and improved procedure for the preparation of 8-bromo-2′,3′,5′-tri-*O*-acetylguanosine (II) has been accomplished using bromine water. The first displacement of bromine with chlorine on a purine nucleoside was successfully achieved with phosphorus oxychloride to furnish 2-amino-6,8-dichloro-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)purine (III) which, with subsequent deblocking, yielded 2-amino-6,8-dichloro-9-(β-D-ribofuranosyl)purine (VI). Nucleophilic displacement of the chloro groups on VI was demonstrated to occur preferentially at position 6 to afford several 8-chloro-2,6-disubstituted purine nucleosides. Nucleophilic displacement of both chloro groups was accomplished with thiourea to yield 2-amino-9-(β-D-ribofuranosyl)purine-6,8-dithione (VIII) and the completely deblocked 2,6,8-trichloro-9-(β-D-ribofuranosyl)purine (IX) was prepared for the first time *via* diazotization of VI.

The direct bromination of various purine nucleosides to afford the corresponding 8-bromopurine nucleosides has been recently reported[3–6] and was prompted primarily by the direct bromination studies of certain nucleic acids[7–9] (RNA and DNA). However, the first direct chlorination of a nucleic acid, soluble ribonucleic acid from yeast, with N-chlorosuccinimide has only recently been reported.[9] It was postulated[10] that 8-chloroguanosine was present as an intermediate prior to subsequent degradation. This is similar to other reports[11,12] which have previously described the degradation of guanine and guanosine when left in contact with an excess of brominating agent for an extended period of time. The present study describes the synthesis and chemical reactivity of several new and interesting 8-chloro-2,6-disubstituted purine nucleosides starting with readily available 2′,3′,5′-tri-*O*-acetylguanosine (I).

We have now developed a new and improved preparation of 8-bromo-2′,3′,5′-tri-*O*-acetylguanosine in 90% yield from commercially available 2′,3′,5′-tri-*O*-acetylguanosine (I) using saturated bromine water. The crystalline nucleoside (II) prepared in this investigation was found to be identical in every respect with II prepared previously[5] (64%) by the direct bromination of I, using a mixture of glacial acetic acid, sodium acetate, and bromine. The anomeric configuration of all nucleosides reported herein is definitely established as β since the starting material in all cases was guanosine.

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