Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81; OCH_3, 14.9; neut. equiv., 208. Found: C, 63.72; H, 5.70; OCH_3, 14.7; neut. equiv., 214.

B. Catalytic Hydrogenation of the Potassium Hydroxide Fusion Product from I.—A mixture of 57.2 mg. of fusion product in 3 ml. of 95% ethanol and 5.8 mg. of platinum oxide was shaken at room temperature for 10 minutes in the presence of hydrogen at 1 atmosphere pressure. The hydrogen uptake was quantitative for 1 double bond. The mixture was filtered, the catalyst washed with a little ethanol and the combined washings and filtrate concentrated in vacuum to 1–2 ml. The addition of water caused the precipitation of 51.1 mg., crystalline material, 89%, m.p. 158–162°. Divaricatinic acid, obtained through the courtesy of Dr. Wachtmeister, melted 153–164° (literature value[9] m.p. 150–160°). A mixture of these two preparations had a m.p. 152–163°. The infrared absorption spectra in potassium bromide pellets of the hydrogenation product and of divaricatinic acid were identical in the range from 2–15 μ.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71; OCH_3, 14.8. Found: C, 62.73; H, 6.28; OCH_3, 15.3.

Acknowledgments.—The author wishes to thank Dr. Wachtmeister for the divaricatinic acid, Dr. K. H. Steinkraus for conducting the growth-inhibition tests and Dr. G. T. Newbold for helpful discussions.

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[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, MCGILL UNIVERSITY, AND FROM THE WOOD CHEMISTRY DIVISION, PULP AND PAPER RESEARCH INSTITUTE OF CANADA]

3-*O*-Hydroxyethyl-D-glucose and Some of its Derivatives[1]

BY G. B. CREAMER, H. H. BROWNELL AND C. B. PURVES

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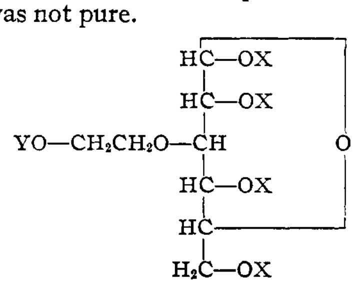
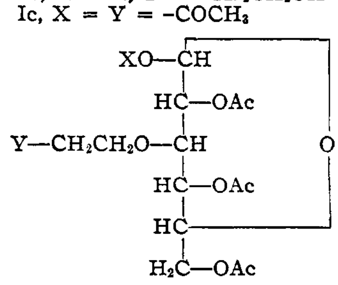
The condensation of ethylene oxide with 1,2;5,6-di-*O*-isopropylidene-β-D-glucofuranose in aqueous alkali was shown to proceed to polyethylene oxide derivatives. Conditions were found for the easy preparation of the monomeric hydroxyethyl derivative, the hydrolysis of which yielded crystalline 3-*O*-hydroxyethyl-α-D-glucose. The sugar was partly decomposed by acetylation with acidic catalysts, and drastic tosylation resulted in partial loss of the hydroxyethyl group. The phenylosazone, β-pentaacetate, acetylated benzyl β-glucoside and a supposed benzyl 3-*O*-iodoethyl-β-glucopyranoside triacetate were obtained in crystalline form. Many other derivatives did not crystallize.

Some years ago,[2b] an attempt was made to determine the mole fraction of primary alcohol units in an *O*-hydroxyethylcellulose by the well known tosylation–iodination method, but some of the hydroxyethyl groups were lost and the results were hard to explain. In order to study the relevant chemistry in a simpler case, a suitable glucose derivative has been hydroxyethylated by the action of ethylene oxide and alkali, and various derivatives of the resulting hydroxyethylglucose have been prepared. The only report of the hydroxyethylation of a sugar found in the literature concerned sucrose; only one of the products was obtained as a pure, crystalline compound, and the structure of this compound was not determined.[3] Crystalline 2-*O*-, 3-*O*- and 6-*O*-hydroxyethyl glucoses have been obtained recently either by the reduction of derivatives of the corresponding carboxymethyl esters (–CH_2-$COOCH_3$) with lithium aluminum hydride,[4] or by the column chromatography of a hydrolyzed hydroxyethylcellulose.[5]

Condensation of ethylene oxide with 1,2;5,6-di-*O*-isopropylidene-D-glucofuranose (diacetone glucose, mole ratio 16:1) in aqueous 5% sodium hydroxide solution, followed by extraction with chloroform, yielded a crude product which was fractionally distilled *in vacuo* to separate 26% of the more volatile, unchanged starting material. The next three fractions, which had specific rotations of −37 to −38° in water, consisted of pure or nearly pure 3-*O*-hydroxyethyl-1,2;5,6-di-*O*-isopropylidene glucofuranose, because when hydrolyzed with acid to remove the isopropylidene groups all yielded a solid mass of crystalline 3-*O*-hydroxyethyl glucose (Ia). Neither the diisopropylidene derivative, nor its acetate, benzoate, *p*-toluenesulfonate and iodoethyl analog, could be induced to crystallize and a description of these compounds has been omitted from this article. All were levorotatory compounds and the first three had the expected compositions, the last was not pure.



Ia, X = Y = H
Ib, X = H, Y = $-CH_2CH_2OH$
Ic, X = Y = $-COCH_3$



IIa, X = CH_3; Y = OAc
IIb, X = $C_6H_5CH_2$; Y = OAc
IIc, X = $C_6H_5CH_2$; Y = O − $SO_2C_7H_7$
IId, X = $C_6H_5CH_2$; Y = I

Since the less volatile fractions, with smaller specific rotations of −36 to −32°, failed to give

(1) Abstracted from Ph.D. Theses submitted to the University by G.B.C. in September, 1950, and by H.H.B. in October, 1953.

(2) C. W. Tasker and C. B. Purves, THIS JOURNAL, (a) **71**, 1017 (1949); (b) **71**, 1023 (1949).

(3) J. W. LeMaistre and R. B. Seymour, *J. Org. Chem.*, **13**, 782 (1948).

(4) W. P. Shyluk and T. E. Timell, *Can. J. Chem.*, **34**, 571 (1956).

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the crystalline hydroxyethyl glucose when hydrolyzed, it was supposed that they were contaminated with the diisopropylidene derivatives of 3-*O*-hydroxyethoxyethyl glucose (Ib) and higher polymers. To verify this supposition, the still residue from the fractional distillation was separated into three main fractions by chromatography on an alumina column (Fig. 1) and the fractions were

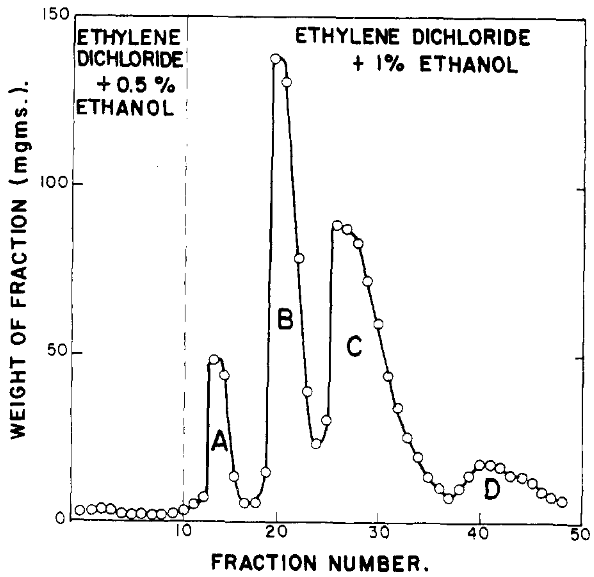

Fig. 1.—Chromatographic fractionation of still-residue remaining after fractional distillation, *in vacuo*, of crude 3-*O*-hydroxyethyl-1,2;5,6-di-*O*-isopropylideneglucofuranose.

then separately hydrolyzed by acid. The hydrolyzates of Fractions A and B were chromatographed on paper for prolonged periods with water-saturated butanol as the eluent and yielded only the single spot of R_f 0.180 characteristic of 3-*O*-hydroxyethyl glucose (R_f for glucose, 0.09). Hydrolysate C, however, gave a single spot of R_f 0.187, and when admixed with 3-*O*-hydroxyethyl glucose the additional spot at R_f 0.180 appeared. Analyses suggested that this hydrolysate contained from three to four ethylene oxide units for each glucose residue.

The sodio derivative of 3-*O*-hydroxyethyl-1,2;5,6-di-*O*-isopropylideneglucose was then condensed in benzene solution with an equimolecular amount of ethylene chlorohydrin, and the product was hydrolyzed to form the hydroxyethoxyethyl glucose Ib. This hydrolysate when chromatographed yielded the single spot of R_f 0.187. Another uncrystallized sample of Ib, synthesized by an alternative method that formed no higher homologs, was also reported to move very slightly faster than Ia on a paper developed by ethyl acetate–acetic acid–water.[4]

The recognition that the R_f values of Ia and Ib, and presumably of higher homologs, differed by only 3 to 4%, and that these compounds often gave a single elliptical spot on a paper chromatogram, made it possible to show that the hydroxyethoxyethyl derivative formed very readily in condensations of ethylene oxide with 1,2;5,6-di-*O*-sopropylidene glucose. When a mixture of the ast two substances in the molar ratio of 16:1 originally used was shaken at 100° in a sealed tube, the crude product after hydrolysis yielded a chromatogram with both spots. The same result was obtained with a mixture of mole ratio 79:1 made up with triethylamine instead of sodium hydroxide as the base and kept at 70° until the diisopropylidene glucose had reacted completely (6.5 hr.). Blank experiments containing none of the glucose derivative resulted in neither of these spots, and the chromatographic behavior of the non-carbohydrate polyethylene glycols formed was markedly different.

The above observations suggested that a convenient method of preparing pure 3-*O*-hydroxyethylglucose would be to reduce the molar ratio of the initial mixture to about 5:1 and thereby reduce the formation of higher homologs. Unchanged diisopropylidene glucose was then recovered in a simple distillation and recycled, while the still residue was hydrolyzed and fermented with yeast to remove residual glucose. The remaining sirup readily crystallized when seeded, giving Ia in 30% yield based on unrecovered diisopropylidene glucose. A crystalline phenylosazone was prepared from 3-*O*-hydroxyethylglucose (Ia), and acetylation with anhydrous sodium acetate yielded a crystalline, slightly levorotatory pentaacetate which was presumably the β-isomer of Ic. Acetylations with zinc chloride or sulfuric acid as catalysts gave black mixtures from which strongly dextrorotatory, dark colored, sirupy pentacetates were isolated in high yield.

Treatment of an uncrystallized sample of the β-pentaacetate with hydrogen bromide in glacial acetic acid gave the corresponding glucosyl bromide as a clear amber, unstable sirup. When condensed with methanol in the presence of silver carbonate, this sirup yielded the uncrystallized tetraacetate of methyl 3-*O*-hydroxyethyl-β-D-glucoside (IIa), but the corresponding benzyl derivative IIb crystallized. Careful deacetylation of these two products gave the uncrystallized non-reducing glucosides, and re-acetylation of benzyl 3-*O*-hydroxyethyl-β-D-glucoside regenerated the crystalline tetraacetate IIb in 93% yield. Thus no unexpected change had occurred during the saponification or reacetylation. A catalytic hydrogenolysis of the benzyl glucoside gave 3-*O*-hydroxyethyl glucose as a strongly reducing, colorless sirup which crystallized spontaneously.

Benzyl 3-*O*-hydroxyethyl-β-D-glucoside, when condensed with an excess of *p*-toluenesulfonyl chloride (tosyl chloride) in pyridine for eight days at room temperature gave a clear, straw-colored glass whose sulfur content was close to that required by the tetratosylate. The hydroxyethyl content, however, was only about one-third of that expected, and it was obvious that the greater portion had been eliminated during the prolonged tosylation. Since the unit partly removed was a monomer directly attached to the third po ition of the glucose residue, there was no justification for the assumption[2b] that similar units in hydroxyethylcellulose were stable during tosylation, and that only those in the polyethylene oxide chains were removed. The previous interpretation of the tosylation-iodination reaction as applied to hydroxyethylcellulose was therefore invalid.

Although benzyl 3-*O*-hydroxyethyl-β-D-glucoside was unstable to tosylation under the above drastic conditions, the use of only one molar equivalent of tosyl chloride for two hours at 0° gave a monotosylate which was isolated in more than 90% yield and analyzed as an uncrystallized triacetate (IIc). The primary alcohol group in methyl β-glucopyranoside required about 24 hr. to be tosylated in similar conditions,[6] and the shorter period effective in the present case was similar to that successful with the mono-alkyl ethers of ethylene and polyethylene glycols.[2a,7] As in the last cases, and also in tosylations of 1,2;5,6-di-*O*-isopropylidene-3-*O*-hydroxyethylglucose not recorded here in detail, there was an unusually rapid replacement of tosyloxy groups by chlorine from the by-product pyridine hydrochloride. The partial tosylation of benzyl 3-*O*-hydroxyethyl-β-D-glucoside thus probably involved the primary alcohol group in the hydroxyethyl rather than that in the glucose residue, as indicated in IIc.

The replacement of the tosyloxy group in IIc by an iodine atom was brought about by heating with an excess of sodium iodide in acetonylacetone, and proceeded normally. The product, presumably benzyl 2,3,6-tri-*O*-acetyl-3-*O*-iodoethyl-β-D-glucoside (IId), was obtained in a crystalline, analytically pure condition. A parallel series of preparations from the uncrystallized methyl glucoside derivative IIa yielded only sirups whose compositions were usually close to the expected values. There seems to be little advantage in describing these sirups in detail.

Experimental

Materials and Methods.—The preparation of 1,2;5,6-di-*O*-isopropylidene-β-D-glucose by one published method[8] gave an 85% yield of pure material after two recrystallizations from hexane and one from isopropyl ether; a recent modification[9] resulted in a slightly greater yield that was more difficult to purify. Commercial ethylene oxide was used, but other reagents and most solvents were specially purified. Evaporation of solutions was invariably carried out under diminished pressure at the lowest convenient temperature.

Prior to analyses, viscous sirups were dried *in vacuo* over phosphorus pentoxide for one to four weeks in order to remove traces of solvent that were often tenaciously retained. Sulfur, chlorine and iodine were determined by a semi-micro Carius method,[10] acetyl by a semi-micro method,[10] and combined ethylene oxide by Morgan's modification[11] of the Zeisel method. All paper chromatograms were developed by the descending flow technique,[12] with *n*-butyl alcohol saturated with water, and were sprayed with an aniline phthalate solution. Specific rotations were observed at 20° and with the D line of sodium.

Condensations with Ethylene Oxide.—(a) Pure 1,2;5,6-di-*O*-isopropylidene-D-glucose (20 g., 0.077 mole) was dissolved in 300 ml. of aqueous 5% sodium hydroxide. Liquid ethylene oxide (57 g., 1.3 mole) was vaporized and passed through fritted glass for 43 min. into the solution, whose temperature during this time rose slowly to 92° and then fell rapidly. The solution was extracted with three 100-ml. volumes of chloroform, the combined extracts were washed with five 40-ml. volumes of water, were dried over anhydrous sodium sulfate and evaporated to a sirup. This sirup, 23.1 g., was fractionally distilled through a 60-cm. vacuum-jacketed column of the Cooke-Bower type[13] near 10^{-2} mm. pressure and with a bath temperature of 200–250°. The first fraction, 5.32 g., was nearly unchanged, crystalline 1,2;5,6-di-*O*-isopropylidene-D-glucose, which when pure had a specific rotation of −18.7° in water. Fractions 2 to 7 weighed 3.63, 3.66, 2.05, 3.74, 1.34 and 0.20 g. and their specific rotations in water (*c* 2.3 to 2.8) were −37.1, −36.8, −38.0, −36.5, −31.2 and −32.1°, respectively. The still residue, 2.12 g., had the specific rotation −24.6° after the aqueous solution had been clarified with adsorbent carbon.

Portions of fractions 2 to 6 were hydrolyzed separately by heating for 3 hr. near 100° with 9 parts of 0.1% hydrochloric acid, which was then removed by passing the solution through a column of Amberlite IRA-410 (OH) resin. Evaporation, drying and seeding produced 71 to 92% yields of crystalline 3-*O*-hydroxyethyl-α-D-glucose, m.p. 110 to 127°, from fractions 2, 3 and 4, but fractions 5 and 6 remained as sirups. A 1.24-g. sample of the still residue was placed on a column containing 300 g. of alumina and was developed with 3700 ml. of ethylene dichloride containing 1% of ethanol, the eluate being collected in 100-ml. fractions. Essentially all of the material was removed, and a plot of fraction weight against fraction number exhibited the sharp peaks A, B and C and a diffuse peak D (Fig. 1). Elutions with carbon tetrachloride–benzene and with ethylene dichloride–benzene mixtures were unsuccessful, and ethylene dichloride containing only 0.5% of ethanol failed to elute the sample.

The yields of material from peaks A to D were 10, 37, 44 and 10%, respectively, and the specific rotations of the first three samples were −21.0, −22.5 and −18.1° in ethanol (*c* 2.1). Material, 0.38 g., from peak C was intensively dried *in vacuo* to remove any traces of ethylene dichloride before being hydrolyzed as described above. The resulting neutral sirup was thoroughly dried. *Anal.* Calcd. for glucose with 3 polyethylene oxide units $C_6H_{12}O_6(OCH_2CH_2)_3$: OCH_2CH_2, 42.3. Calcd. for $C_6H_{12}O_6(OCH_2CH_2)_4$: OCH_2CH_2, 48.5. Found: OCH_2CH_2, 46.2.

The chromatographic behavior of hydrolyzates from peaks A, B and C already has been described.

(b) Ethylene oxide gas, 26.7 g. (0.61 mole), was passed at 70° into a solution of 2 g. (0.0077 mole) of 1,2;5,6-di-*O*-isopropylidene-β-D-glucose in 10 ml. of triethylamine during 6.5 hr. The solution was evaporated to an oil, which was dissolved in water and passed through a column of Amberlite IR-120 (H) to remove the remaining base. Evaporation of the resulting neutral solution left 2.52 g. of a dry sirup which was hydrolyzed in 0.1% hydrochloric acid at 100° for 3 hr. After de-ionization, an aliquot containing 0.5 mg. was chromatographed for 12 days on Whatman No. 1 filter paper. The spot for 3-*O*-hydroxyethyl-α-D-glucose of R_f 0.180 was accompanied by another of R_f 0.187.

To identify the latter spot, 1 g. (0.0033 mole) of 3-*O*-hydroxyethyl-1,2;5,6-di-*O*-isopropylideneglucose was dissolved in 10 ml. of dry benzene and 0.08 g. (0.0035 mole) of sodium wire was added. The mixture was boiled under reflux and with exclusion of moisture until almost all of the sodium had dissolved. The clear, red supernatant liquor was then boiled under reflux for 6 hr. with 0.27 g. (0.0033 mole) of redistilled ethylene chlorohydrin to form the hydroxyethoxyethyl derivative Ib of the diisopropylideneglucose. After isolation, the latter weighed 0.79 g. An 0.13-mg. sample when chromatographed on paper for 4.4 days gave a single spot of R_f 0.187.

Preparation of 3-*O*-Hydroxyethyl-α-D-glucose (Ia).—Pure 1,2;5,6-di-*O*-isopropylideneglucose (100 g., 0.385 mole) was dissolved in 1500 ml. of 5% aqueous sodium hydroxide, and gaseous ethylene oxide (78.7 g., 1.79 moles) was passed into the solution during 1.5 hr. The temperature rose to only 55°. After standing for a further 2 hr., the solution was extracted with three 500-ml. volumes of chloroform. The

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combined extract was washed with three 500-ml. volumes of water, was dried and evaporated to a sirup. Unreacted 1,2;5,6-di-*O*-isopropylideneglucose was removed by distilling this sirup *in vacuo* and without a fractionating column from a bath at 150° until the distillate ceased to crystallize in the receiver. The still residue, 78 g., was shown to retain a further 24 g. of diisopropylideneglucose by the hydrolysis and fermentation of a small aliquot.

The still residue, 78 g., was hydrolyzed in 0.1% hydrochloric acid and de-acidified as previously described. After being washed with two 100-ml. volumes of chloroform, the neutral aqueous solution was evaporated to 200 ml., and was fermented with yeast until a paper chromatogram showed that glucose was no longer present. The liquor was filtered, and evaporated to a sirup, which was diluted with 600 ml. of absolute ethanol. A filtration removed inorganic salts and the filtrate yielded a colorless sirup (39.7 g.). A solution of this sirup in 100 ml. of anhydrous methanol became turbid when diluted with 175 ml. of ethyl acetate and, after clarification with the minimum amount of methanol, was seeded with 3-*O*-hydroxyethyl-α-D-glucose. The crude crystals weighed 21 g. after an extraction with cold acetone, and their melting point of 110–112° was raised to 122–123° by two recrystallizations from ethanol. The highest melting point observed for the 3-*O*-hydroxyethyl glucose was 134–135°.

Anal. Calcd. for $C_6H_{11}O_6 \cdot CH_2CH_2OH$: C, 42.8; H, 7.2; OCH_2CH_2, 19.65. Found for an uncrystallized sample, n^{20}_D 1.500: C, 42.7, 42.4; H, 7.3, 7.1; OCH_2CH_2, 18.9, 19.1. Found for a sample melting at 134–135°; OCH_2CH_2, 19.6, 19.4.

Pure 3-*O*-hydroxyethyl-α-D-glucose mutarotated in water (*c* 1.13) from an extrapolated initial specific rotation of +93° to an equilibrium value of +51.4°, the change obeying first-order kinetics. The substance was not affected by the enzymes in yeast, and 1 mg. was equivalent in Shaffer–Somogyi[14] copper reducing power to 0.345 mg. of glucose.

3-*O*-Hydroxyethyl-D-glucose Phenylosazone.—Fischer's procedure[15] and the use of 1 g. of the sugar gave the osazone as an oil which solidified on cooling. Two recrystallizations from 20% aqueous ethanol left a 42% yield of yellow crystals melting with decomposition at 163°.

Anal. Calcd. for $C_{20}H_{26}O_5N_4$: C, 59.7; H, 6.5; N, 13.9; OCH_2CH_2, 11.0; mol. wt., 402. Found: C, 59.9, 59.9; H, 6.6, 6.4; N[10], 13.9, 14.0; OCH_2CH_2, 11.0, 11.3; mol. wt. (Rast[10]), 410, 379.

3-*O*-Acetoxyethyl-1,2,4,6-tetra-*O*-acetyl-β-D-glucose.—The crystalline sugar, 1 g., fused sodium acetate, 0.4 g., and acetic anhydride, 4 g., were heated together near 100° for 2.3 hr. When the solution was poured into a stirred mixture of ice and water, the oily product soon redissolved and the solution was neutralized with sodium bicarbonate. The solution was extracted three times with chloroform, and the combined extracts (100 ml.) after being dried yielded 2.0 g. (103%) of the pentaacetate as an oil. Crystallization from aqueous methanol left 1.2 g. (62%) as needles whose melting point of 60–76° was raised to 82.5° by three further recrystallizations. The specific rotation in chloroform was −3.7° (*c* 1.5).

Anal. Calcd. for $C_8H_{11}O_7(COCH_3)_5$: C, 49.8; H, 6.0; acetyl, 49.5; OCH_2CH_2, 10.1. Found: C, 49.9, 49.8; H, 6.0, 6.2; acetyl, 50.6, 49.6; OCH_2CH_2, 10.2.

Benzyl 3-*O*-Acetoxyethyl-2,4,6-tri-*O*-acetyl-β-D-glucoside (IIb).—A solution of 38.8 g. of uncrystallized 3-*O*-hydroxyethylglucose pentaacetate in 20 ml. of glacial acetic acid was mixed with 50 ml. of glacial acetic acid containing 42% of hydrogen bromide gas. The solution rapidly developed a dark color which prevented observation of its optical rotation. One hour later, the solution was poured into 1 l. of ice-water and the product recovered by extraction with chloroform. This extract was quickly shaken with aqueous sodium bicarbonate and water, was dried and cautiously evaporated, but the acetobromo derivative decomposed when the red-brown sirup (45 g.) was even gently heated. A 2-g. portion was purified by solution in chloroform, passage through a small column of alumina and cautious evaporation *in vacuo* at room temperature to a clear amber sirup. The specific rotation in chloroform was +130° (*c* 1.58).

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(15) E. Fischer, *Ber.*, **17**, 579 (1884).

Anal. Calcd. for $C_8H_{11}O_6(COCH_3)_4Br$: acetyl, 37.8. Found: acetyl, 37.9, 37.5.

Following a published procedure,[16] 15 g. of the crude acetobromo derivative was added in three portions during 15 min. to a stirred suspension of Drierite, 20 g., and silver carbonate, 6 g., in 200 ml. of pure benzyl alcohol. A 3-necked flask with a mercury sealed stirrer, a guard tube with anhydrous calcium chloride, and a stopper was used. The mixture was filtered 3 hr. later, and benzyl alcohol was removed from the filtrate by steam distillation, leaving the product as a water-insoluble oil which crystallized on cooling. Three recrystallizations from ethanol raised the melting point to 113–114°, unchanged by a fourth recrystallization. The glycoside did not reduce Fehling solution and had a specific rotation of −57.4° in chloroform (*c* 2.39).

Anal. Calcd. for $C_{23}H_{30}O_{11}$: C, 57.3; H, 6.3; acetyl, 35.7; OCH_2CH_2, 9.14; mol. wt., 482. Found: C, 57.5, 57.4; H, 6.3, 6.3; acetyl, 35.7, 35.8; OCH_2CH_2, 9.3, 9.3; mol. wt. (ebullioscopic[17]), 480, 461.

Benzyl 3-*O*-Hydroxyethyl-β-D-glucose.—A solution of 10 g. of the above crystalline tetraacetate in 150 ml. of absolute methanol was deacetylated[18] at 0° by admixture with 5 ml. of 0.228 *M* barium methylate in absolute methanol. After 24 hr. at 0°, the solution was diluted with 30 ml. of water and saturated with carbon dioxide to remove barium as the carbonate. Evaporation of the clear filtrate left 6.5 g., or an almost quantitative yield, of a straw-colored sirup which did not reduce Fehling solution and had a specific rotation of −44.9° in water (*c* 2.06).

Anal. Calcd. for $C_{15}H_{22}O_7$: OCH_2CH_2, 14.0. Found: OCH_2CH_2, 14.5, 14.2.

A sample when acetylated with acetic anhydride–pyridine for 18 hr. near 20° gave a 93% yield of the original tetraacetate whose melting point of 113–114° was unchanged when mixed with authentic benzyl 3-*O*-acetoxyethyl-β-D-glucopyranoside triacetate.

Another sample (1.62 g., 0.00515 mole) was dissolved in 50 ml. of absolute ethanol containing 0.1 g. of palladium black catalyst.[19] This suspension absorbed 0.0203 mole of hydrogen when shaken for 8 hr. at room temperature with the gas at 2 atm. pressure. Hence 3.96 moles of hydrogen per mole of glycoside were required, one mole to cleave the benzyl ether bond and three moles to reduce the aromatic ring.[20] After filtration from the catalyst and evaporation of the filtrate, 3-*O*-hydroxyethylglucose remained as a clear, colorless sirup. The yield of 1.17 g. was quantitative. The sirup crystallized spontaneously on standing and provided the seed crystals for the other preparations.

Drastic Tosylation of Benzyl 3-*O*-Hydroxyethyl-β-D-glucoside.—The conditions were similar to those used in the tosylation of a hydroxyethylcellulose.[2b] A 2.65-g. (0.0084 mole) sample of the glucoside was dissolved in 26.5 ml. of anhydrous pyridine containing 18.7 g. (0.098 mole) of recrystallized *p*-toluenesulfonyl chloride. After being kept at room temperature for 8 days, the solution was poured into ice-water, and the mixture was extracted three times with chloroform. The combined extracts were washed in succession with dilute sulfuric acid, aqueous sodium bicarbonate and with water, were dried and evaporated. A clear, straw-colored glass, 5.96 g., remained with a specific rotation in chloroform of −4.2° (*c* 2.74).

Anal. Calcd. for a tetratosylate of benzyl 3-*O*-hydroxyethylglucoside, $C_{43}H_{46}O_{15}S_4$: S, 13.8; Cl, 0.0; OCH_2CH_2, 4.73. Found: S, 12.1, 12.2; Cl, 1.88, 1.95; OCH_2CH_2, 1.57, 1.56. Thus two-thirds of the hydroxyethyl groups were absent and some of the tosyl groups had been replaced by chlorine.

Benzyl 2,4,6-Tri-*O*-acetyl-3-*O*-tolylsulfonyloxyethyl-β-D-glucoside (IIc).—A solution of the benzyl hydroxyethylglucoside (2.52 g., 0.008 mole), in 9 ml. of dry pyridine was cooled to 0° and mixed with 1.53 g. (0.008 mole) of pure tosyl chloride. After being kept at 0° for 2 hr.,[7] the solution was diluted with 10.5 ml. of acetic anhydride and kept at room temperature overnight. The method of isolating

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the product was as just described, and a pale yellow sirup resulted in 92% yield. The specific rotation in chloroform was −43.6°.

Anal. Calcd. for a monotosyl triacetyl derivative, $C_{23}H_{33}O_{12}S$: S, 5.4; Cl, 0.0; CH_3CO, 21.7; OCH_2CH_2, 7.4. Found: S, 4.9, 5.0, 5.1; Cl, 1.53, 1.58, 1.54; CH_3CO, 21.8, 22.1; OCH_2CH_2, 7.7, 7.9. A preparation made at 21° instead of 0° had S, 4.7, 4.8; Cl, 2.09, 2.30.

Benzyl 2,4,6-Tri-*O*-acetyl-3-*O*-iodoethyl-β-D-glucoside (IId).—A 1-g. sample of the tosyloxyethyl triacetate and 1 g. of sodium iodide were heated in 20 cc. of dry acetonylacetone at 110–115° for 2 hr. The solution was poured into 300 ml. of water and the mixture was extracted with ether; the extract was washed with dilute aqueous sodium thiosulfate to remove free iodine, was dried and evaporated. The residual amber sirup (yield 90%) crystallized, and after three recrystallizations from ethanol the white needles melted sharply at 114–115° and had a specific rotation in chloroform of −26.8°.

Anal. Calcd. for a benzyl iodoethyl glucose triacetate, $C_{21}H_{27}O_9I$: I, 23.1. Found: I, 22.7, 22.8.

When the tosyloxy derivative was iodinated for five hours in boiling acetone (56°), the uncrystallized product had only 10.9% of iodine.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Derivatives of D-Glucose Containing the Sulfoamino Group[1]

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Methyl 2-deoxy-2-sulfoamino-α-D-glucopyranoside (sodium salt monohydrate, XIII) was prepared from methyl 2-amino-*N*-(benzoxycarbonyl)-2-deoxy-α-D-glucopyranoside (I) by acetylation followed by hydrogenolysis of the *N*-blocking group, sulfation (without deacetylation) and final deacetylation. Analogous reactions were carried out with the corresponding trimethyl ether of I. Sulfation and subsequent deacetylation of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucose (III) yielded 2-sulfoamino-2-deoxy-D-glucose (IX).

The sulfoamino group is present in the 2-amino-2-deoxy-D-glucose (D-glucosamine, chitosamine) unit of heparin.[4] The only derivatives of this sulfoamino sugar hitherto described are the amorphous 2-deoxy-2-sulfoamino-D-glucose (ammonium salt)[5] and the amorphous barium salt of methyl 2-deoxy-2-sulfoamino-β-D-glucopyranoside trisulfate dihydrate.[6] The first compound was obtained by the direct sulfation of 2-amino-2-deoxy-D-glucose base and was believed to be a mixture of sulfate and sulfoamino derivatives having some 80% of the sulfur function on the nitrogen atom. We describe herein the synthesis of the crystalline sodium salt (monohydrate) of methyl 2-deoxy-2-sulfoamino-α-D-glucopyranoside (XIII), its triacetate XI, and the crystalline sodium salt of tetra-*O*-acetyl-2-deoxy-2-sulfoamino-β-D-glucose (VI). Our preparation of 2-deoxy-2-sulfoamino-D-glucose (IX) was an amorphous anomeric mixture but was analytically pure and was obtained through crystalline intermediates. Our methyl 2-deoxy-3,4,6-tri-*O*-methyl-2-sulfoamino-α-D-glucopyranoside (XII), although obtained through crystalline intermediates, was amorphous and contained extraneous ash (not sulfate).

Methyl 2-amino-*N*-(benzoxycarbonyl)-2-deoxy-α-D-glucopyranoside (I), prepared by the glycosidation of 2-amino-*N*-(benzoxycarbonyl)-2-deoxy-D-glucose according to Neuberger and Rivers,[7] was acetylated, the amino blocking group was removed by catalytic hydrogenation and the resultant amine was isolated as the hydrochloride V. When the reaction contained the equivalent amount of hydrogen chloride to exactly neutralize the amine, the product V was obtained in good yield without deacetylation. In one experiment wherein slightly more than one equivalent of acid was present, a crystalline monoacetyl derivative of methyl 2-amino-2-deoxy-α-D-glucopyranoside hydrochloride was obtained. The amino-blocked glycoside I was also methylated by treatment with methyl iodide and thallous hydroxide followed by reaction with methyl iodide and silver oxide. The crystalline trimethyl ether IV then was converted to the hydrochloride VII by catalytic hydrogenation. Utilizing a different synthetic route, Cutler, Haworth and Peat[8] have recorded the same substance (VII).

For the purposes of *N*-sulfation, a study was first made of the conditions required to sulfate the 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucose (III) of Bergmann and Zervas.[9] This free base was sulfated with sulfur trioxide in pyridine. The product VI was isolated as the crystalline sodium salt which contained acid-hydrolyzable sulfate and exhibited negative tests for the amino

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