NEIGHBORING-GROUP EFFECTS IN THE REACTIVITIES OF HYDROXYL GROUPS IN D-GLUCOPYRANOSIDES

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ABSTRACT

Glucosides having the hydroxyl groups at C-2 and C-3 individually substituted were treated with *N,N*-diethylaziridinium chloride in the presence of concentrations of sodium hydroxide ranging from 0.1M to 6.0M. Substitution of the hydroxyl group at C-2 greatly enhances the reactivities of the hydroxyl groups at C-3 and C-4 in dilute base but has less effect in more-concentrated base. Substitution of the hydroxyl group at C-2 has little effect upon the reactivity of the hydroxyl group at C-6. Substitution of the hydroxyl group at C-3 depresses the reactivity of the hydroxyl group at C-2 throughout the range of base concentrations, but this substitution enhances the reactivity of the hydroxyl group at C-6 to a great extent in dilute base and to a much smaller extent in the more concentrated base. Proposed explanations for these results are discussed.

INTRODUCTION

In connection with studies of the reactivities of the hydroxyl groups in the D-glucopyranosyl residues of cotton cellulose, it was found that the sites of reaction and distribution of substituent groups among the 2-*O*-, 3-*O*- and 6-*O*-positions are dependent upon the medium in which the reaction occurs[1–4]. More recently, it has been found that the reactivities of the hydroxyl groups at C-2, C-3, and C-4 in methyl D-glucopyranosides decrease with increasing concentration of base in the reaction medium; the reactivity of the hydroxyl group at C-6 is essentially unchanged with increasing concentration of base[5].

This paper describes studies of the following: (*1*) The effects of individual substitutions of the hydroxyl group at C-2 and C-3 in D-glucopyranosides upon the reactivities of the remaining free hydroxyl groups, and (*2*) the effects of base concentration upon the reactivities of the free hydroxyl groups when the hydroxyl groups at C-2 and C-3 are substituted individually.

This work was undertaken in an effort to gain better understanding of the reactivities of the hydroxyl groups of cotton cellulose in various reaction media and

of the different distributions of cross-linkages which may be obtained in the chemical modification of cotton.

RESULTS

The extent of disubstitution in the reactions of 1,2-*O*-ethylene-β-D-glucopyranose (**1**) and methyl 3-*O*-methyl-β-D-glucopyranoside (**2**) was kept to a minimum (less than 5%) by employing a low molar ratio of reagent to glucoside. No evidence was found for the presence of polymeric grafts. The change in the extent of formation of each mono-*O*-[2-(diethylamino)ethyl]-substituted glucoside with change in the base concentration of the reaction medium was calculated from the total d.s. and the fraction of each isomer in the mixture.

1,2-O-Ethylene-β-D-glucopyranose (**1**). — The effect of base concentration upon the reaction of *N,N*-diethylaziridinium chloride with the hydroxyl groups at C-3, C-4, and C-6 in **1** is summarized in Table I. The reactivities of the secondary hydroxyl groups are high relative to that of the primary hydroxyl group at C-6. Each of the

TABLE I

REACTION OF 1,2-*O*-ETHYLENE-β-D-GLUCOPYRANOSE WITH *N,N*-DIETHYLAZIRIDINIUM CHLORIDE

Molarity of NaOH	*Extent of reaction*		*Distribution of substituents*[a]		
	N (%)	*D.s.*	*3*-O-	*4*-O-	*6*-O-
0.1	0.93	0.146	2.37 (0.065)	1.93 (0.054)	1.00 (0.027)
0.5	0.68	0.105	1.75 (0.044)	1.38 (0.035)	1.00 (0.026)
1.0	0.52	0.079	1.22 (0.031)	0.87 (0.022)	1.00 (0.026)
2.0	0.35	0.053	1.11 (0.020)	0.75 (0.014)	1.00 (0.019)
4.0	0.29	0.043	1.00 (0.016)	0.65 (0.011)	1.00 (0.016)
6.0	0.25	0.037	0.92 (0.014)	0.60 (0.009)	1.00 (0.014)

[a]Numbers in parentheses are d.s. values of individual isomers.

secondary hydroxyl groups is considerably more reactive than the corresponding hydroxyl group in methyl β-D-glucopyranoside (**3**). The comparison is shown in Fig. 1-B and 1-C, in which the d.s. values of the individual isomers are plotted as a function of the molarity of the sodium hydroxide involved in the reaction.

The reactivity of each of the secondary hydroxyl groups in **1** is considerably greater in dilute base than that of the corresponding hydroxyl group in **3**. However, the decreases in the reactivities of the hydroxyl groups at C-3 and C-4 with increasing base concentration are much greater in **1** than in **3**.

The effect of base concentration upon the reactivity of the hydroxyl group

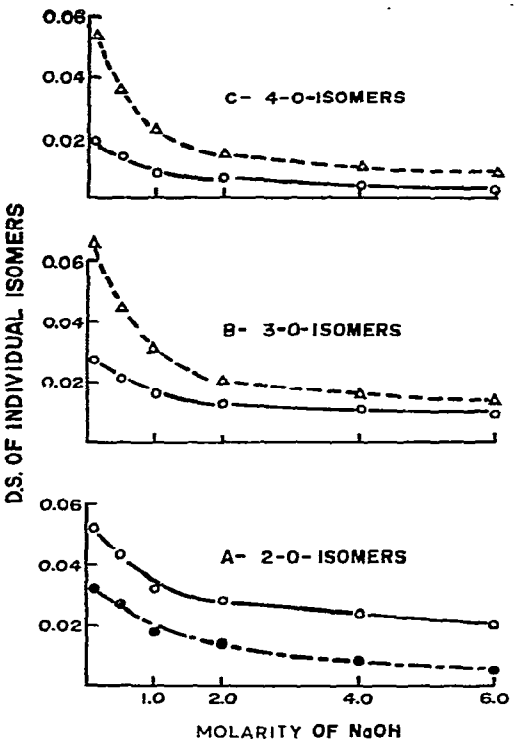

Fig. 1. Effects of base concentration and neighboring group upon the extent of formation of secondary isomeric mono-*O*-[2-(diethylamino)ethyl]-substituted glucopyranosides: ----------, 1,2-*O*-ethylene-*β*-D-glucopyranose; – – – –, methyl 3-*O*-methyl-*β*-D-glucopyranoside; ————, methyl *β*-D-glucopyranoside from ref. 5.

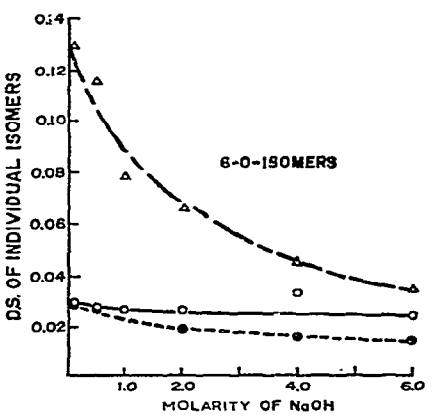

Fig. 2. Effect of substitution of the hydroxyl groups at C-2 and C-3 individually upon the extent of formation of 6-*O*-[2-(diethylamino)ethyl]-substituted glucopyranosides as a function of base concentration in the reaction medium: ----------, 1,2-*O*-ethylene-*β*-D-glucopyranose; – – – –, methyl 3-*O*-methyl-*β*-D-glucopyranoside; ————, methyl *β*-D-glucopyranoside from ref. 5.

at C-6 in **1** as compared with that of the corresponding hydroxyl group in **3** is shown in Fig. 2. In this case the reactivities of the hydroxyl groups at C-6 in both compounds are almost equal at low concentration of base. The decrease in reactivity of the hydroxyl group at C-6 in **1** in more-concentrated base is greater than that of the corresponding hydroxyl group in **3**.

Methyl 3-O-methyl-β-D-glucopyranoside (**2**). — The effect of base concentration upon the reaction of *N,N*-diethylaziridinium chloride with the hydroxyl group at C-2 and C-6 in **2** is summarized in Table II. The results show that the reactivity of

TABLE II

REACTION OF METHYL 3-*O*-METHYL-β-D-GLUCOPYRANOSIDE WITH *N,N*-DIETHYLAZIRIDINIUM CHLORIDE

Molarity of NaOH	*Extent of reaction*		*Distribution of substituents*[a]	
	N (%)	*D.s.*	2-O-	6-O-
0.1	1.00	0.160	0.25 (0.032)	1.00 (0.128)
0.5	0.91	0.144	0.24 (0.028)	1.00 (0.116)
1.0	0.62	0.096	0.23 (0.018)	1.00 (0.078)
2.0	0.50	0.080	0.21 (0.014)	1.00 (0.066)
4.0	0.36	0.055	0.19 (0.009)	1.00 (0.046)
6.0	0.27	0.040	0.18 (0.006)	1.00 (0.034)

[a]The numbers in parentheses are d.s. values of individual isomers. No 4-*O*-isomer was detected in the products of these reactions.

the hydroxyl group at C-2 is low relative to that of the hydroxyl group at C-6. That the reactivity of this hydroxyl group at C-2 is lower than that of the same hydroxyl group of **3** is shown in the curves of Figure 1-A; in each case the d.s. of the 2-*O*-derivative is plotted as a function of the molarity of the sodium hydroxide involved in the reaction. The extent of reaction of the hydroxyl group at C-2 in **2** was lower than that in **3**; the decreases in reactivities of these hydroxyl groups with increasing base concentration occurred approximately in parallel.

The effect of base concentration upon the reactivity of the hydroxyl group at C-6 in **2** as compared with that in **3** is shown in Fig. 2. It is obvious from these curves that the reactivity of the hydroxyl group at C-6 in **2** is much greater than that in **3** especially at low concentrations of base. The reactivity of the hydroxyl group at C-6 in **2** decreased rapidly and considerably with increasing base concentration, whereas that in **3** decreased very little under the same conditions.

The extent of reaction at the hydroxyl group at C-4 in **2** was below the level of detection by gas–liquid chromatography.

DISCUSSION

In a previous publication[5], we have shown that the reactivities of the hydroxyl groups at C-2, C-3, and C-4 in methyl β-D-glucopyranoside (**3**) with *N,N*-diethylaziridinium chloride are sharply decreased by increasing the base concentration in the reaction medium. On the other hand, the reactivity of the hydroxyl group at C-6 is not significantly changed under these conditions. The result of reaction in dilute basic medium (0.1M) was to produce about 60% as much substitution in the 6-*O*-position as in the 2-*O*-position, but the result in concentrated basic medium (6.0M) decreased the 2-*O*-substituion to approximately 60% of that at the 6-*O*-position.

It was proposed that the reactivity of the hydroxyl group at C-2 in basic media is accentuated by its proximity to the oxygen atoms on C-1 *and* by hydrogen bonding from the hydroxyl group at C-3 to the oxyanion at C-2. It was also suggested that increasing concentration of base promotes formation of adducts between base and vicinal hydroxyl groups, such as at C-2, C-3, and C-4 (ref. 6), and that the stability of these adducts is sufficiently high to reduce the degree of oxyanion formation at these sites; the result is a decrease in the extent of reactions at these hydroxyl groups. It was further proposed that, in these aqueous media, the reactivity of the hydroxyl group at C-6 is generally repressed (by comparison to the reactivities of the hydroxyl groups at C-2, C-3, and C-4) by a strong solvent-sheath around the oxyanion but that, being without a vicinal hydroxyl group, it is essentially free of the "adduct effect" as the concentration of base in the reaction medium is increased.

No basis was found in the preceding study (or this study) to raise suspicion that the conformation of the β-D-glucosidic units in these queous media are different from the *C1* conformation shown by Reeves[7], Lenz and Heeschen[8], and Michell and Higgens[9] to characterize **2** and **3**. It is expected that solvation and adduct formation will, perhaps at most, contribute to a slight flattening of the chair form. A substantial degree of intramolecular hydrogen bonding between hydroxyl groups of the D-glucopyranosyl residues is considered to provide the primary explanation for the reactivities of these hydroxyl groups.

Our interpretation of the present results of reactions of **1** and **2** is such as to strengthen and extend our previous proposals, as indicated in the following paragraphs.

Upon substitution of the hydroxyl group at C-2, as in **1**, the reactivities of the hydroxyl groups at C-3 and C-4 are increased: that is, the reactivities of the former and latter hydroxyl groups approach, respectively, the reactivities of the hydroxyl groups at C-2 and C-3 in **3**. It is interpreted that the hydroxyl group at C-3 in **1** occupies a position of general similarity to that of the hydroxyl group at C-2 in **3** with regard to intramolecular bonding (namely, 4-OH···$^{-}$O-3 in **1**, and 3-OH···$^{-}$O-2 in **3**) to reinforce the oxyanions. However, the hydroxyl group at C-3 in **1**, being more removed from C-1, receives less activating contribution from C-1 than does C-2 in **3**. Thus, oxyanion formation at C-3 in **1** and at C-2 in **3** are expected to be similar, with the former being smaller as a result of a smaller inductive effect from C-1. Similar

reasoning relates the reactivity of the hydroxyl group at C-4 in **1** to that at C-3 in **3**.

There is only little difference in reactivity between the hydroxyl groups at C-6 in **1** and **3**; this is consistent with the absence in structural change in this part of the D-glucopyranosyl residue.

Upon substitution of the hydroxyl group at C-3, as in **2**, the reactivity of the hydroxyl group at C-2 drops below that of the corresponding hydroxyl group in **3** to a level very similar to that of the hydroxyl group at C-3 in **3**. This low reactivity is consistent with the absence of a hydroxyl group at C-3 in **2** and the consequent loss of activation by hydrogen bonding to reinforce the oxyanion at C-2.

The lack of evidence for reaction of the hydroxyl group at C-4 in **2** is surprising, indeed. It is suggested that the chain of intramolecular hydrogen bonds as it exists in **3** (in the direction from the hydroxyl group at C-4 to that at C-3 to the oxyanion at C-2) is broken by the methyl substituent at C-3. Then, it is tentatively proposed that the hydroxyl group at C-4 is hydrogen bonded in the alternative direction: namely, to the primary hydroxyl group at C-6, with sufficient tenacity to decrease the reactivity of the hydroxyl group at C-4 below our levels of detection. Consistent with this interpretation is the observation of Norrman[10] that the hydroxyl group at C-4 in D-glucopyranosyl residues exhibits lower reactivity when the hydroxyl group at C-6 is unsubstituted; he suggested that this might be due to the formation of a strong hydrogen-bond between the oxyanion at C-4 and either a hydroxyl group on an adjacent D-glucopyranosyl residue (of a polysaccharide) or the hydroxyl group at C-6.

The reactivity of the hydroxyl group at C-6 in **2** is unique compared with that of the corresponding hydroxyl group in **3** and in **1**. One difference lies in the more pronounced reactivity of the hydroxyl group at C-6 in **2** and another lies in the effect that increasing concentrations of base have upon lowering the reactivity of this hydroxyl group in **2**. Since this is the same hydroxyl group at C-6 that was proposed as the recipient of a hydrogen bond from the hydroxyl group at C-4, it is with the same tentativeness as before that we propose that the increased reactivity of this hydroxyl group at C-6 is due to the reinforcement of its oxyanion through hydrogen bonding from the hydroxyl group at C-4.

To this point, we have associated the substantial decreases in reactivities of vicinal hydroxyl groups that occur as a result of increasing concentrations of base in the reaction media with formation of adducts at the vicinal hydroxyl groups. Now, it appears reasonable to attribute the substantial decrease in reactivity of the hydroxyl group at C-6 in **2** with increasing base concentration to formation of an adduct at the 4-OH···O-6 grouping.

According to the concepts developed here, the reactivities of the hydroxyl groups of D-glucopyranosyl residues in basic media are rationalized on the basis of inductive effects from the C-1 position and intramolecular hydrogen-bonding from the hydroxyl group at C-4 toward the oxyanion at the most remote unsubstituted hydroxyl group (namely, that at C-2 in **3** or C-3 in **1**). On substitution of the hydroxyl group at C-3, it is proposed that the direction of hydrogen-bond formation is redirected toward the hydroxyl group at C-6. Those hydroxyl groups that are donors in hydrogen

bonding are low in reactivity and both hydroxyl groups that participate in hydrogen bonds are susceptible to decreased reactivity through formation of adducts. It is pertinent (*a*) that the reactivities of the hydroxyl groups of decrystallized cellulose show the same trends as those of **3**, as reaction is conducted in media of higher base concentrations[4], and the same interpretation of data as that described above is applicable, and (*b*) that the reactivity of the hydroxyl group at C-3 increases substantially in reactions of cellulose with a variety of reagents in basic media after etherification has occurred[11–15] with the hydroxyl group at C-2, and, again, the foregoing interpretation is applicable.

EXPERIMENTAL

N,N-Diethylaziridinium chloride. — The *N,N*-diethylaziridinium chloride solutions were prepared by dissolving 7.5 g (55 mmoles) of 2-chloroethyldiethylamine in about 75 ml of water and diluting the solution to 100 ml, as described by Roberts, Wade, and Rowland[5].

1,2-O-Ethylene-β-D-glucopyranose (**1**). — This inner glucoside of 2-*O*-(2-hydroxyethyl)-β-D-glucopyranose was prepared from 2-chloroethyl-β-D-glucopyranoside in 81% yield as described by Roberts and Rowland[16], it had m.p. 215–217° and showed a single peak on g.l.c.

Methyl 3-O-methyl-β-D-glucopyranoside (**2**). — Prepared from 1,2,5,6-di-*O*-isopropylidene-α-D-glucofuranose in 11.3% overall yield by the procedure of Helferich and Lang[17], this compound distilled at 152° at 150 torr at the rate of 30 drops per min and showed a single peak on g.l.c.

Reaction of D-glucopyranosides with N,N-diethylaziridinium chloride. — The inner glucoside **1** (2.06 g, 10 mmoles) was dissolved in 25 ml of sodium hydroxide solution of the desired final molarity in a 50-ml volumetric flask. To this solution was added 5 ml (2.50 mmoles) of *N,N*-diethylaziridinium chloride solution. Then 5 ml of sodium hydroxide solution of double the final desired molarity was added, and the volume was adjusted to 50 ml with sodium hydroxide of the final desired molarity. The solutions were 0.20M in glucoside and 0.05M in *N,N*-diethylaziridinium chloride, and ranged from 0.10 to 6.0M in sodium hydroxide. The solution was transferred to a 100-ml, round-bottomed flask and shaken for 16 h at 25°. The product was isolated as described by Roberts, Wade and Rowland[5] for the reaction of **3**.

The 3-*O*-methyl derivative **2** (2.08 g, 10 mmoles) was treated with 5 ml (2.50 mmoles) of *N,N*-diethylaziridinium chloride solution under the same conditions employed for **1**.

4,6-O-Benzylidene-1,2-O-ethylene-β-D-glucopyranose. — A mixture of 2.0 g (7.70 mmoles) of **1**, 2.0 g of fused zinc chloride, and 15 g of benzaldehyde was shaken for 16 h at 25°. The solution was poured into 200 ml of ice and water with stirring, 100 ml of petroleum ether was added with continued stirring, and the petroleum ether layer was removed. The extraction of benzaldehyde was continued with four additional 100-ml portions of petroleum ether, at the end of which time the product

crystallized from the aqueous phase. After being washed with small portions of petroleum ether, the crystals were recrystallized from methanol, yielding 2 g (71%) of product m.p. 196–197°. Another crystallization raised the m.p. to 197–198°; unchanged by further recrystallization.(Found: C, 61.9; H, 6.1. $C_{15}H_{18}O_6$ calc.: C, 61.2; H, 6.1%). The product showed a single peak on g.l.c. with the OV-1 column (details in later section) operated isothermally at 240°.

4,6-O-Benzylidene-3-O-[2-(diethylamino)ethyl]-1,2-O-ethylene-β-D-glucopyranose. — To 50 ml of dry *p*-dioxane were added (1.0 g (3.4 mmoles) of 4,6-*O*-benzylidene-1,2-*O*-ethylene-β-D-glucopyranose, 1.17 g (6.8 mmoles) of 2-chloroethyldiethylamine hydrochloride, 2.0 g of powdered sodium hydroxide, and 5.0 g of Drierite. The mixture was stirred for 4 h under reflux. The solid was filtered off on a sintered-glass filter and washed with *p*-dioxane. The solvent was removed from the combined *p*-dioxane solutions by freeze-drying to yield 1.8 g of amorphous, solid product.

3-O-[2-(Diethylamino)ethyl]-1,2-O-ethylene-β-D-glucopyranose. — The product from the immediately preceding reaction was dissolved in 50 ml of ethanol, 2.0 ml of acetic acid was added, and the benzylidene group was removed by hydrogenation over palladium-on-carbon. The catalyst was filtered off, the alcohol was removed under diminished pressure, and the residue was dissolved in 15 ml of water. After freeze-drying, there was obtained 1.2 g (90%) of an amorphous solid. When trimethylsilylated, this product showed a single peak (retention time 32.0 min, OV-1 column, isothermal at 210°) in addition to a small peak corresponding to the original starting material, **1**.

1,2-O-Ethylene-6-O-trityl-β-D-glucopyranose. — This compound was prepared from 3.0 g (14.6 mmoles) of **1** and 4.06 g (14.6 mmoles) of chlorotriphenylmethane by the procedure of Helferich and Becker[18]. The amorphous product was dissolved in *p*-dioxane and freeze-dried to yield 6.0 g of solid.

Mixed 3-O- and 4-O-[2-(diethylamino)ethyl]-1,2-O-ethylene-6-O-trityl-β-D-glucopyranose. — To 50 ml of dry *p*-dioxane was added the product of the preceding reaction, 2.29 g (1.33 mmoles) of 2-chloroethydiethylamine hydrochloride, 4.0 g of powdered sodium hydroxide, and 2 g of Drierite. The mixture was refluxed with stirring for 3 h, filtered, and the filtrate was concentrated and finally freeze-dried to yield 7.0 g of an amorphous solid.

Mixed 3-O- and 4-O-[2-(diethylamino)ethyl]-1,2-O-ethylene-β-D-glucopyranose. — The product of the preceding reaction was dissolved in 50 ml of 80% (w/w) aqueous acetic acid. The solution was refluxed for 30 min to remove the trityl group[19], and then evaporated under diminished pressure to yield a solid mass, which was extracted several times with water. Triphenylcarbinol, which remained undissolved, was removed by filtration. The filtrate was freeze-dried to yield 3.7 g of amorphous solid. When trimethylsilylated and subjected to g.l.c. (OV-1 column, isothermal at 210°), this product showed two peaks, at 28.7 min retention time and at 32.0 min, in the ratio of 1.13:1.00. By reference to results described in a preceding section for 3-*O*-[2-(diethylamino)ethyl]-1,2-*O*-ethylene-β-D-glucopyranose, it is evident that **1** having a 2-(diethylamino)ethyl substituent at the 3-*O*-position is eluted in the chromato-

gram at a retention time of 32.0 min. It is concluded, therefore, that the first peak eluted from the chromatogram of the product described in this section is the isomer having the 2-(diethylamino)ethyl substituent in the 4-*O*-position of **1**.

Methyl 4,6-O-benzylidene-3-O-methyl-β-D-glucopyranoside. — This compound was prepared from 5.0 g (16.9 mmoles) of **2**, 20 g of benzaldehyde, and 5 g of fused zinc chloride by the same procedure described in a preceding section under the heading of 4,6-*O*-benzylidene-1,2-*O*-ethylene-β-D-glucopyranose; yield 5.0 g (70%). After crystallization from methanol, the product melted at 164–165°; further crystallization did not alter the melting point. (Found: C, 60.9; H, 6.8. $C_{15}H_{20}O_6$ calc.: C, 60.8; H, 6.8%). This compound showed a single peak on g.l.c. (OV-1 column, isothermal at 210°).

Methyl 4,6-O-benzylidene-2-O-[2-(diethylamino)ethyl]-3-O-methyl-β-D-glucopyranoside. — This compound was prepared from 1.0 g (3.38 mmoles) of the product from the preceding reaction together with other reagents, precisely as described under the heading of 4,6-*O*-benzylidene-3-*O*-[2-(diethylamino)ethyl]-1,2-*O*-ethylene-β-D-glucopyranose; yield 1.9 g of amorphous product.

Methyl 2-O-[2-(diethylamino)ethyl]-3-O-methyl-β-D-glucopyranoside. — The product from the reaction immediately preceding was dissolved in 50 ml of ethanol and the benzylidene groups were removed as described under the heading of 3-*O*-[2-(diethylamino)ethyl]-1,2-*O*-ethylene-β-D-glucopyranose; yield 1.1 g (85%). The trimethylsilylated product showed a single peak on g.l.c. (retention time 21.5 min OV-1 column, isothermal at 190°) in addition to a small peak corresponding to the original starting material **2**.

Methyl 3-O-methyl-6-O-trityl-β-D-glucopyranoside. — This compound was prepared from 2.5 g (12.0 mmoles) of **2** and 3.34 g (12.0 mmoles) of chlorotriphenylmethane by the procedure of Helferich and Becker[18]. The product did not crystallize; it was dissolved in 20 ml of *p*-dioxane and freeze-dried to yield 5.0 g of amorphous solid.

Mixed methyl 2-O- and 4-O-[2-(diethylamino)ethyl].-3-O-methyl-6-O-trityl-β-D-glucopyranosides. — The product from the preceding reaction was dissolved in *p*-dioxane and treated with 2-chloroethyldiethylamine hydrochloride as described under the heading of mixed 3-*O*- and 4-*O*-[2-(diethylamino)ethyl]-1,2-*O*-ethylene-6-*O*-trityl-β-D-glucopyranose; yield 5.4 g of freeze-dried product.

Mixed methyl 2-O- and 4-O-[2-(diethylamino)ethyl]-3-O-methyl-β-D-glucopyranosides. — The mixed product of the preceding reaction was dissolved in 80% (w/w) acetic acid for removal of the trityl group as described in under the heading of mixed 3-*O*- and 4-*O*-[2-(diethylamino)ethyl]-1,2-*O*-ethylene-β-D-glucopyranose; yield 2.7 g of amorphous, freeze-dried solid. The trimethylsilylated product showed two peaks on g.l.c., in addition to that of the original starting material **2**. The two peaks were eluted at retention times of 14.7 and 21.5 min (OV-1 column, isothermal at 190°); ratio 1.02:1.00. By reference to the results obtained and described under the heading of methyl 2-*O*-[2-(diethylamino)ethyl]-3-*O*-methyl-β-D-glucopyranoside, it is evident that **2** having a 2-(diethylamino)ethyl substituent in the 2-*O*-position is eluted at

21.5 min and, it is concluded, that it is the isomer having the substituent in the 4-*O*-position that is eluted at 14.7 min.

*Identification of the 2-*O*-, 3-*O*-, 4-*O*-, and 6-*O*-[2-(diethylamino)ethyl]-substituted* D-*glucopyranosides.* — The 3-*O*- and 4-*O*-[2-(diethylamino)ethyl]-derivatives of **1** were identified by comparison of retention times and peak enhancements of authentic, known derivatives on g.l.c. The 6-*O*-derivative was identified by the process of elimination, since only the 3-*O*-, 4-*O*-, and 6-*O*-derivatives were possibilities.

The 2-*O*-[2-(diethylamino)ethyl] derivative of **2** was identified by retention times and peak enhancements with the authentic compound on g.l.c. The absence of the 4-*O*-isomer in the products of reaction of *N*,*N*-diethylaziridinium chloride with **2** was demonstrated by the elution of the authentic 4-*O*-derivative on g.l.c. where there was no peak from the reaction product. Again, the 6-*O*-derivative was identified by the process of elimination, since the 2-*O*- and 4-*O*-derivatives were known and the 6-*O*-derivative was the only remaining possibility.

In the case of the mono-*O*-[2-(diethylamino)ethyl]- derivatives of **1** and **2**, the order of elution of the isomers on g.l.c. with the OV-1 column was 4-*O*-, 3-*O*-, 6-*O*- for **1**, and 2-*O*-, 6-*O*- for **2**. The order of elution of mono-*O*-[2-(diethylamino)ethyl]-derivatives of **3** was[5] 4-*O*-, 3-*O*-, 2-*O*-, 6-*O*-; this was shown by hydrolytic removal of the glucosidic group and chromatographic identification of the mono-*O*-[2-(diethylamino)ethyl]-D-glucopyranoses[20]. In addition to the foregoing derivatives, a variety of other monosubstituted D-glucopyranoses provide confirmation for the same order of elution; these derivatives include *O*-(2-hydroxyethyl)[16], *O*-(2-aminoethyl)[16], *O*-[(*N*-methyl-*N*-2-hydroxyethylamino)ethyl][21], and *O*-methylsulfonylethyl[22]. Thus, in all cases, the general and reliable order of elution has been 4-*O*-, 3-*O*-, 2-*O*-, 6-*O*-.

*Analysis for 2-*O*-, 3-*O*-, 4-*O*-, and 6-*O*-(2-diethylamino)ethyl-substituted* D-*glucopyranosides.* — The distribution of diethylaminoethyl groups among the 2-*O*- and 6-*O*-positions in **1** was determined on the freeze-dried residue (*p*-dioxane extraction) by g.l.c. on an Aerograph model 1520* instrument. The column was a 1/8-in. outside-diameter stainless-steel tube, 10 ft. long. It was packed with 5% OV-1 on Chromosorb W (80–100 mesh). The column was operated isothermally at 210°. The distribution of diethylaminoethyl groups in **2** was determined by the same procedure as described for **1** except that in this case the column was operated isothermally at 190°. All samples were trimethylsilylated by the method of Sweeley, *et al.*[23] before chromatographic analysis. The area of each peak was determined by triangulation, and the d.s. of each isomer was calculated.

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*It is not the policy of the Department to recommend the product of one company over those of any others engaged in the same business.

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