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Preliminary communication

Lactol ring-opening in the solvolysis of a glycoside. Neighboring-group participation by 2-*O*-(2-hydroxyethyl) and 2-*O*-(2-hydroxypropyl) substituents

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In examining ^{13}C-n.m.r. spectra of hydrolyzates of *O*-(2-hydroxypropyl)cellulose, as an extension of studies[1] on other cellulose ethers, it appeared possible to attribute some minor resonance-signals to acetals (*e.g.*, **1**) formed from residues of the polymer (*e.g.*, **2**) bearing a 2-*O*-(2-hydroxypropyl) substituent. Model studies performed in testing such a possibility have furnished definitive examples, described here, of a neighboring-group participation-reaction of this kind; they involved solvolysis of methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-hydroxypropyl)-α- and -β-D-glucofuranoside (**3** and **4**, respectively) and the corresponding 2-*O*-(2-hydroxyethyl) derivatives[2] (**5** and **6**, respectively).

Compounds **3** and **4** were synthesized from methyl 3,4,6-tri-*O*-benzyl-α- and -β-D-glucofuranoside[3] by reaction with 1-chloro-2,3-epoxypropane[4], to give **7** and **8**, respectively, followed by hydrogenolysis of the oxiranes with lithium aluminum hydride[5].

When dissolved in chloroform containing 0.1% of hydrogen chloride, glycoside **4** yielded at least four products during 8 h at room temperature. According to t.l.c., two compounds (**10** and **11**), migrating slightly faster than **4**, were formed early in the reaction, and then gradually disappeared as two less-polar compounds (**14** and **15**) made their appearance. By processing the reaction mixture at an appropriate stage, these four products were isolated as oils after column chromatography on silica gel.

The structural formulas proposed for **10**, **14**, and **15** are based on spectroscopic evidence; product **11** was never more than a trace component, and was not adequately characterized (however, see later). For example, the mass spectrum of **10** confirmed its molecular weight (M^+, 522) and the base peak (*m/z* 251), corresponding to release of the 1,4-dioxane portion as a fragment ion by cleavage of the C-3–C-4 bond, was consistent with the acyclic-aldose acetal depicted. From the number and characteristics of the signals in its ^{1}H- and ^{13}C-n.m.r. spectra, **10** was evidently a product of the rearrangement of **4**, in which a hydroxyl group was now located at C-4, and the methoxyl group was retained at C-1. The molecular weights of **14** and **15** were also confirmed by mass spectrometry (M^+, 490 for both), and close similarities between their fragmentation patterns indicated that the two products are diastereoisomers. This conclusion was supported, and additional information favoring bicyclic structures **14** and **15** was provided,

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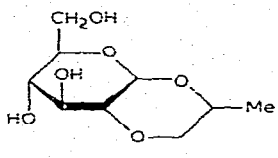
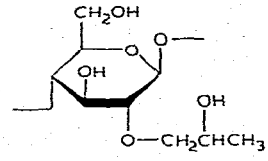
by the ^1H- and ^{13}C-n.m.r.-spectral data. Differing in configuration at C-8, these two products represent a resolution of the enantiomeric forms of the original 2-*O*-(2-hydroxypropyl) substituent of **4**. Based on $^1H-^1H$ coupling data, the configuration at C-8 of **14** is designated (*S*), and of **15**, (*R*). Presumably, the minor intermediate (**11**) was the diastereomer of **10**.



1



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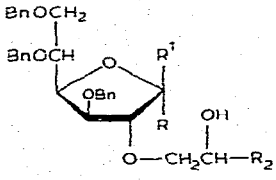
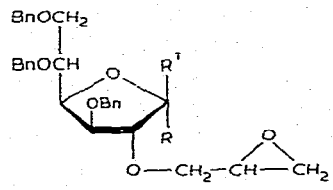
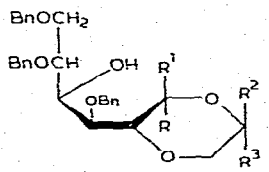


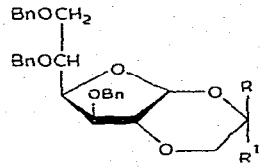
3 R = OMe, R^1 = H, R^2 = Me
4 R = H, R^1 = OMe, R^2 = Me
5 R = OMe, R^1 = R^2 = H
6 R = R^2 = H, R^1 = OMe



7 R = OMe, R^1 = H
8 R = H, R^1 = OMe



9 R^1 = R^3 = H, R = OMe, R^2 = Me
10 R^1 = OMe, R = R^3 = H, R^2 = Me
11 R^1 = OMe, R = R^2 = H, R^3 = Me
12 R = OMe, R^1 = R^2 = R^3 = H
13 R = R^2 = R^3 = H, R^1 = OMe

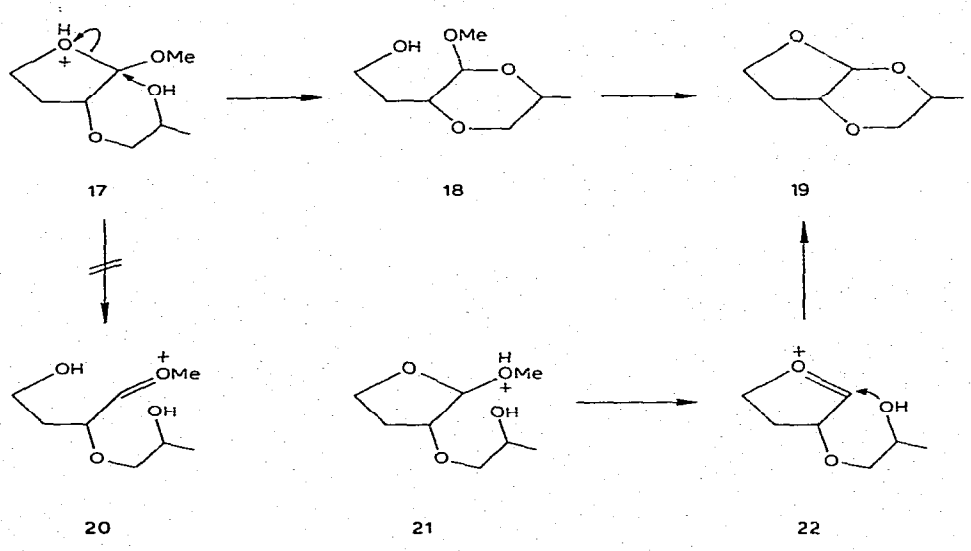


14 R = Me, R^1 = H
15 R = H, R^1 = Me
16 R = R^1 = H

In accord with these findings, the solvolysis of the α anomer **3** gave results paralleling those for **4**. That is, a major, transient product had chromatographic and spectroscopic properties closely similar to those of **10**, leading to its formulation as the anomer of the latter, *i.e.*, **9**. Also detected was a minor product corresponding chromatographically to **11**. As would be expected, the end products of the reaction were **14** and **15**, although their rates of formation were lower than in the solvolysis of the β-glycoside. Results closely analogous to these were obtained with the 2-*O*-(2-hydroxyethyl) derivatives (**5** and **6**). That is, only *one* monocyclic product was found early in each reaction (probably, **12** from the α anomer, and **13** from the β), and only

one final product (**16**) was obtained from both anomers. Furthermore, the ^{1}H- and ^{13}C-n.m.r. spectra of **12**, **13**, and **16** were virtually the same as those of **9**, **10**, and **14**, respectively, allowance being made for minor differences attributable to the absence of a methyl group from the 2-substituent of **5** and **6**.

It appears that each of these solvolysis reactions proceeds by an initial, lactol-ring opening, in concert with a nucleophilic attack on C-1 by the hydroxyl group of the 2-substituent, *e.g.*, **17** → **18**. This could account for the formation of a *single* anomeric form of **18** from each glycoside (which was demonstrated most clearly with glycosides **5** and **6**), whereas, if an acyclic carbonium ion (**20**) were formed initially, two anomeric products could be expected. Hence, although the aldoside moiety undergoes ring opening, the reaction mechanism may not be "acyclic" in the conventional sense[6—9], because of the high probability that a concerted, neighboring-group participation-step is involved. That is, the transition state would possess more SN2 than SN1 character. It is noteworthy, therefore, that conjugate acid **17** meets the requirements of the bimolecular (A-2) mechanism proposed[10] for some solvolysis reactions of glycofuranosides*. In the present instance, the solvolytic attack on C-1 by the hydroxylic component is *intra*-molecular, giving rise to a novel type of sugar acetal (**18**) that incorporates a 1,4-dioxane moiety. The anomeric methoxyl group of **18** is then subsequently displaced by OH-4, to give a more stable, bicyclic product (**19**) which is probably *cis*-fused. Another possible source of **19** is its direct formation from the glycoside *via* protonated species **21** and carbonium ion **22**, corresponding to the A-1 mechanism[12] associated[8,9] with many solvolysis reactions of glycosides, especially pyranosides. Obviously, however, this route can be of only minor importance here.



*However, this mechanism may not apply to all acid-catalyzed hydrolyses of glycofuranosides[11].

As already noted, when the 2-substituent of a glycoside is a 2-hydroxypropyl group, diastereomeric products are obtained that differ in configuration at C-8. This carbon atom becomes incorporated into the fused, 1,4-dioxane ring of **14** and **15**, and the methyl group (C-9) attached to it must introduce nonbonded interactions that, according to n.m.r. evidence, impose different conformations on both the five- and six-membered rings of **14** and **15**.

Finally, glycoside **4** and acetal **14**, after the removal of *O*-benzyl protecting groups, were converted in acidic media into bicyclic *pyranose* derivatives corresponding to **1**. In accord with what has been presented here, **4** yielded a 1 : 1 mixture of diastereoisomers, whereas **14** gave only one of these products.

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