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Note

Azidolysis of methyl 2,3-anhydro-4,6-*O*-benzylidene-D-glycosides

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Although the opening of oxirane derivatives of carbohydrates is widely used in synthesis[1,2], there has been little systematic study We now describe an initial approach to studying this problem We had at our disposal the complete stereochemical series of methyl 2,3-anhydro-4,6-*O*-benzylidene-D-glycosides (α and β, *allo*, *gulo*, *manno*, and *talo*), and their opening with azide ion under standard conditions was investigated T l c was used to determine the time of complete disappearance of each oxirane Although this is a crude form of kinetic study, the 72-fold difference in rate between the fastest and slowest compounds makes the approach usable The times (h) so determined were as follows·

	allo	*manno*	*gulo*	*talo*
α	2	8 5	18	2
β	6 75	1	16	0 25

Nucleophilic ring-opening of epoxides is known[1,2] to give exclusively *trans*-products, and where the oxirane ring is attached to a six-membered ring it normally opens according to the Furst–Plattner rule[3] to give the diaxial product This is clearly a kinetic effect, the diaxial transition-state being more favoured than the alternative[4,5]. Where *trans*-diequatorial products are formed, the oxirane ring may react *via* a genuinely diequatorial intermediate, or there may be changes in conformation prior to, and after, reaction 2,3-Anhydropyranosides can exist only in the half-chair conformations **1** and **2**, and those of the 4,6-*O*-benzylidene-alloside and -mannoside series are further restricted to the $^{O}H_{5}$ form Thus, the α-alloside **3**, on azidolysis, would be expected to undergo diaxial attack (at C-2) to give methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside, whereas the mannoside **4** would similarly be expected to undergo attack at C-3 to give the 3-azidoaltroside. The situation is complicated, however, by the electronic differences between positions 2 and 3. Nucleophilic ring-opening reactions occur preferentially[5,6] by attack at the centre

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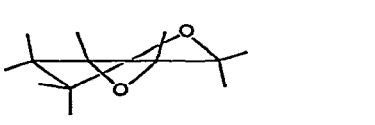
which can more readily sustain a positive charge (*i e*, the reaction has some S_N1 character) For 2,3-anhydropyranosides, C-2 is therefore deactivated by electron-withdrawing groups attached to C-1 This deactivation reinforces the stereochemical effect in the reaction of the mannoside **4** and so, on azidolysis, only the 3-azido-altroside is obtained[7]. A similar result was obtained[8] with the β-mannoside **5**, except that the reaction of the α-mannoside **4** required 8 5 times as long for completion The anomeric methoxyl-group of the α compound **4** is in a pseudo-axial orientation and therefore sterically hinders attack by the incoming nucleophile at C-3 This effect, which is absent in the β-anomer **5**, may account for the difference in reactivity of the anomers



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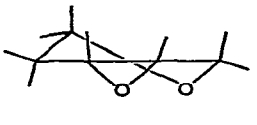

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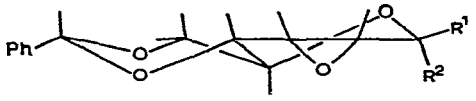
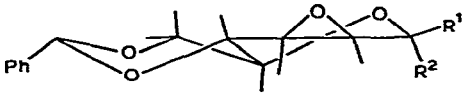


3 $R^1 = H, R^2 = OMe$
5 $R^1 = OMe, R^2 = H$

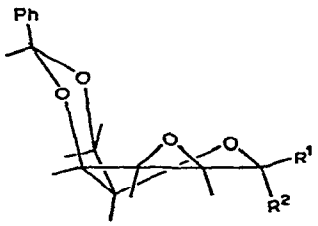


4 $R^1 = H, R^2 = OMe$
6 $R^1 = OMe, R^2 = H$

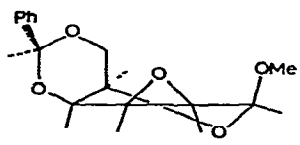
In the azidolysis reaction of the allosides, the electronic and stereochemical effects are opposed The stereochemical effect predominates for the reactions of both the α and β anomers azidolysis of the α-anhydroalloside **3** gave[7] the 2-azidoaltroside in 75% yield and methyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-glucopyranoside (from diequatorial opening) in only 5% yield, from the similar reaction of the β anomer **6**, a 40% yield of the diaxial product (from attack at C-2) and a 7% yield of the diequatorial product were obtained[8] Under standard conditions, reaction of the α compound **3** was complete after 2 h, whereas the β anomer **6** required 6 75 h for complete reaction Again, it was the compound (β anomer) having MeO-1 *cis* to the incoming nucleophile which reacted the more slowly, however, this group is pseudo-equatorial and is not expected to interfere sterically with the incoming group It is possible that polar interaction between the attacking ion and the lone pairs of electrons of the anomeric oxygen atom was responsible for inhibition of the attack This inhibitory effect on attack at C-2 of the β compound also accounts for the relatively large proportion of glucoside produced in the reaction Attack at C-3 of the allosides probably involves genuine diequatorial attack on the molecule in the ground-state conformation

Consideration of the reactions of the gulosides and talosides is complicated by the less-rigid geometry of the molecules, which allows the pyranoside ring to assume either half-chair conformation. The α-taloside appeared (from n m r data[9]) to be

mainly in the $^{0}H_{5}$ conformation **7** at normal temperatures, and reacted in this conformation to give methyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-idopyranoside, as the only isolated product[10], by diaxial opening This reaction was considerably more rapid than that of the corresponding mannoside **4** The α-taloside and α-mannoside differ only in the orientation of the substituent at C-4, and it thus appears that the pseudo-equatorial O-4 of the mannoside **4** hindered attack by azide at C-3, *cf* the effect of MeO-1 on the attack of the β-alloside **6**



7 $R^1 = H, R^2 = OMe$
8 $R^1 = OMe, R^2 = H$



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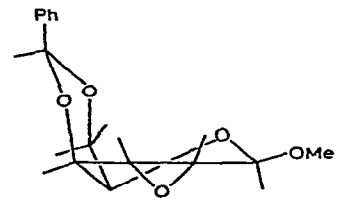

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There is no substituent *cis* to a nucleophile attacking at C-3 in the β-taloside, and the azidolysis proceeded even more rapidly to give predominantly the 3-azidoidoside In view of the ease of attack at C-3, it was surprising to find that a by-product, believed to be methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-β-D-galactopyranoside[11], was produced in the reaction The 3-azidoidoside presumably resulted from diaxial opening of the oxirane in the $^{0}H_{5}$ conformation (**8**) For 2-azidogalactoside to have been formed, by electronically less-favourable attack at C-2, some of the oxirane must have reacted in the alternative $^{5}H_{0}$ conformation (**9**).

The reactions of the α- and β-anhydrogulosides proceeded at approximately equal rates, and more slowly than the reactions of the anhydroallosides, to give the diaxial products[11] The low reactivity, relative to the allosides, is accounted for by the 1,3-diaxial interaction between the incoming nucleophile and the pseudo-axial group present at C-4 in the gulosides when in the $^{0}H_{5}$ conformation (*e g* , **10**), but absent from the allosides Reaction at C-2 of the β-guloside should be further hindered by the anomeric *cis* (pseudo-equatorial) substituent, and it is therefore surprising that this compound did not react more slowly than the α anomer (*cf* the α- and β-allosides) In contrast to the allosides, the gulosides did not undergo attack at C-3, despite their possible conformational mobility Attack in this way was probably inhibited by the adjacent *cis* substituent in the gulosides (pseudo-axial in the $^{0}H_{5}$ form, pseudo-equatorial in the $^{5}H_{0}$ form), and in the β-guloside by interaction with the pseudo-axial MeO-1 of the $^{5}H_{0}$ form

From the above results, it therefore appears that, in addition to the factors already known to influence the ring-opening reactions of oxiranes, the orientation of the groups adjacent to the reaction centre is also important Inhibition of the reaction appears to be caused by pseudo-axial groups that are cis to the incoming nucleophile

when they are adjacent (for diequatorial opening) or in the β-position (for diaxial opening) to the reaction centre, and (for diaxial opening) by adjacent pseudo-equatorial groups that are cis to the incoming nucleophile This last interaction is postulated as a polar one and it would be interesting, for this reason, to compare the reactions of charged and uncharged nucleophiles on these oxirane systems

EXPERIMENTAL

Azidolysis of epoxides under standard conditions — In a typical experiment, a solution of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (**3**) (250 mg), ammonium chloride (250 mg), and sodium azide (500 mg) in 2-methoxyethanol (25 ml, water content, 0 1% by g l c) was boiled under reflux Samples were removed at intervals for examination by t l c (methanol–toluene, 1 9), starting material was detectable after 1 5 h, but only a trace was visible after 2 h

Similar experiments were carried out on the other methyl 2,3-anhydro-4,6-*O*-benzylidene-D-hexopyranosides shown below (weight of starting material, t l c solvent system, and time required for disappearance of starting material are given), the quantities of reagent and solvent used were proportional to the weight of starting material β-alloside **5**, 50 mg, methanol–chloroform 1 19, 6 75 h, α-mannoside **4**, 250 mg, methanol–toluene 1 19, 8 5 h, β-mannoside **6**, 7 mg, methanol–toluene 1·19, 1 h, α-guloside, 50 mg, methanol–toluene 1 19, 18 h, β-guloside **10**, 100 mg, methanol–toluene 1 19, 16 h, α-taloside **7**, 510 mg, chloroform, 2 h, β-taloside **8**, chloroform–benzene 1 1, 15 min

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REFERENCES

1 R D GUTHRIE, in W PIGMAN AND D HORTON (Eds), *The Carbohydrates*, Vol I A, Academic Press, New York, 1972, p 423
2 N. R WILLIAMS, *Advan Carbohyd Chem Biochem* , 25 (1970) 109
3 J A MILLS, cited by F H NEWTH AND R F HOMER, *J Chem Soc* , (1953) 989
4 S J ANGYAL, *Chem Ind (London)*, (1954) 1230
5 R C COOKSON, *Chem Ind (London)*, (1954) 223, 1512.
6 R E PARKER AND N S ISAACS, *Chem Rev* , 59 (1959) 737
7 R D GUTHRIE AND D MURPHY, *J Chem Soc* , (1963) 5288
8 R D GUTHRIE, A M PRIOR, AND S E CREASEY, *J Chem Soc* , (1970) 1961
9 J A LIEBMANN, D PHIL Thesis, University of Sussex, 1971
10 S HANESSIAN AND T H HASKELL, *J Org Chem* , 30 (1965) 1080
11 R D GUTHRIE AND J A LIEBMANN, *J Chem Soc , Perkin I*, in press