The Synthesis of *gem*-Halonitro Sugars and Their Conversion into Epoxynitro Sugars[1]

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Halogenation of methyl 4,6-*O*-benzylidene-3-deoxy-3-nitrohexopyranosides having the α-D-*talo*, β-D-*galacto*, and α-D-*galacto* configurations, and of the 2,3-dideoxy-3-nitro β-D-*lyxo* and α-D-*lyxo* analogs, smoothly furnished 3-halo-3-deoxy-3-nitro derivatives. The glycosides were chlorinated in methanolic solution with aqueous sodium hypochlorite, and similarly brominated with either bromine in the presence of alkali or *N*-bromoacetamide in the presence of sodium acetate. The analogous nitro glycosides having the β-D-*arabino*, β-D-*manno*, α-D-*manno*, and β-D-*gluco* configurations and also the 2-acetates of the last three compounds were brominated likewise whereas the α-D-*gluco* isomer and its 2-acetate were resistant under the conditions examined. The preferred C-3 configuration in the halonitro products appeared to be that which has an equatorial nitro group and an axial halogen atom in the normal pyranose chair conformation ($^4C_1$). In most instances the halogenation was found to be highly stereoselective in that sense although in some cases the inverse C-3 epimer was formed in a minor proportion. Base treatment of some of the halohydrins led to 2,3-anhydro-3-nitro glycosides. Such epoxide formation may be associated with epimerization at C-2 and -3, for which a mechanism involving a retrograde Henry reaction is postulated.

L'halogénation des méthyl benzylidène-4,6-*O* déoxy-3 nitro-3 hexopyranosides ayant les configurations α-D-*talo*, β-D-*galacto*, et α-D-*galacto*; et des analogues dideoxy-2,3 nitro-3 β-D-*lyxo* et α-D-*lyxo*; conduit aux dérivés halo-3 deoxy-3 nitro-3 selon des réactions douces. Les glycosides ont été chlorés en solution méthanolique par l'hypochlorite de sodium aqueux et bromés de la même façon soit par le brome en présence d'alcalis soit par le *N*-bromo acétamide en présence d'acétate de sodium. Les glycosides analogues nitro ayant les configurations β-D-*arabino*, β-D-*manno*, α-D-*manno* et β-D-*gluco* de même que les acétates en 2 des trois derniers composés ont été bromés de la même façon tandis que l'isomère α-D-*gluco* et son acétate en 2 sont résistants dans les conditions étudiées. La configuration préférée sur le C-3 des produits halonitro apparait être celle qui possède un groupe nitro équatorial et un atome d'halogène axial, dans la conformation chaise normale du pyranose ($^4C_1$). Dans la plupart des exemples, l'halogénation est hautement stéréosélective bien que dans certains cas il se forme en proportion mineure, de l'épimère inverse sur le C-3. Le traitement basique de certains de ces halohydrines conduit aux anhydro-2,3 nitro-3 glycosides. Une telle formation d'époxyde peut être associée à l'épimérisation sur le C-2 et -3 pour laquelle un mécanisme faisant intervenir une réaction de "retro-Henry" a été postulé.

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Primary and secondary aliphatic nitro compounds are readily halogenated in the presence of base to afford geminal halonitro derivatives (2, 3). Even though this has long been known, such halogenations apparently have never been tried in nitro carbohydrates, and the few halogen derivatives so far prepared in this field were not of the geminally substituted type. Thus, 2,4,6-tri-*O*-acetyl-3-deoxy-3-nitro-α-D-glucopyranosyl bromide has been made (4) by one of the customary methods for acetobromo sugars from the corresponding α-tetraacetate, and vicinal iodonitro derivatives have been shown (5) to arise by the addition of nitryl iodide to unsaturated sugars. We now report the preparation of several 3-chloro- and 3-bromo-3-deoxy-3-nitrohexopyranosides and describe reactions which some of the products undergo, in particular, epimerization and epoxide formation controlled by stereochemical factors.

Chlorinations were performed by treating the 4,6-*O*-benzylidenated nitro glycosides in methanolic solution with aqueous, 5% sodium hypochlorite solution (or with "Javex" household bleach), normally at room temperature. Crystalline chloro derivatives were smoothly obtained in yields ranging from 75 to over 90%. For bromination, two methods were employed, usually with equal success. The first was similar to the chlorination just mentioned and consisted of generating the sugar nitronate by the provision of alkali at low temperature, which was then followed by bromine addition (Br_2 method).

[1]Part XXVIII in a series on reactions of nitro sugars. For Part XXVII see ref. 1.

In the second method *N*-bromoacetamide in the presence of sodium acetate was employed as the brominating agent (NBA method). The latter procedure was especially useful for compounds containing ester groups liable to cleavage under the alkaline conditions of the former procedure.

In many of the halogenations investigated, only one of the two possible C-3 epimeric products was encountered, and on account of the excellent yields it can be stated that the reactions were highly stereoselective. In some cases the second epimer was formed, too, but normally in a minor proportion. We assume that the favored epimer in all events is that which in the stable chair conformation bears the nitro group in equatorial and the halogen atom in axial orientation.

This assumption is based on the analogy to protonation of pyranoside 3-nitronates which invariably produces an equatorial nitro group (6, 7). N.m.r. data of the new products as well as certain chemical reactions were consistent therewith, and hence we have assigned formulas and configurational notations[2] on this premise. It must be admitted, however, that rigorous proof for the configuration of the halonitro carbon atom has not been advanced. In the account that follows, the chemistry of compounds having a *cis*-fused 4,6-benzylidene acetal ring will be treated first, and that of *trans*-fused acetals will be dealt with thereafter. A recent study (9) had revealed considerable differences in the ease of nitronate formation (*i.e.*, proton abstraction from C-3) in dependence of the over-all configuration of the molecule. Since the process of nitronate formation has to precede introduction of a halogen atom it could be expected that there would also be a strong influence of configuration upon the course of halogenation.

Reactions with cis-Fused Acetals

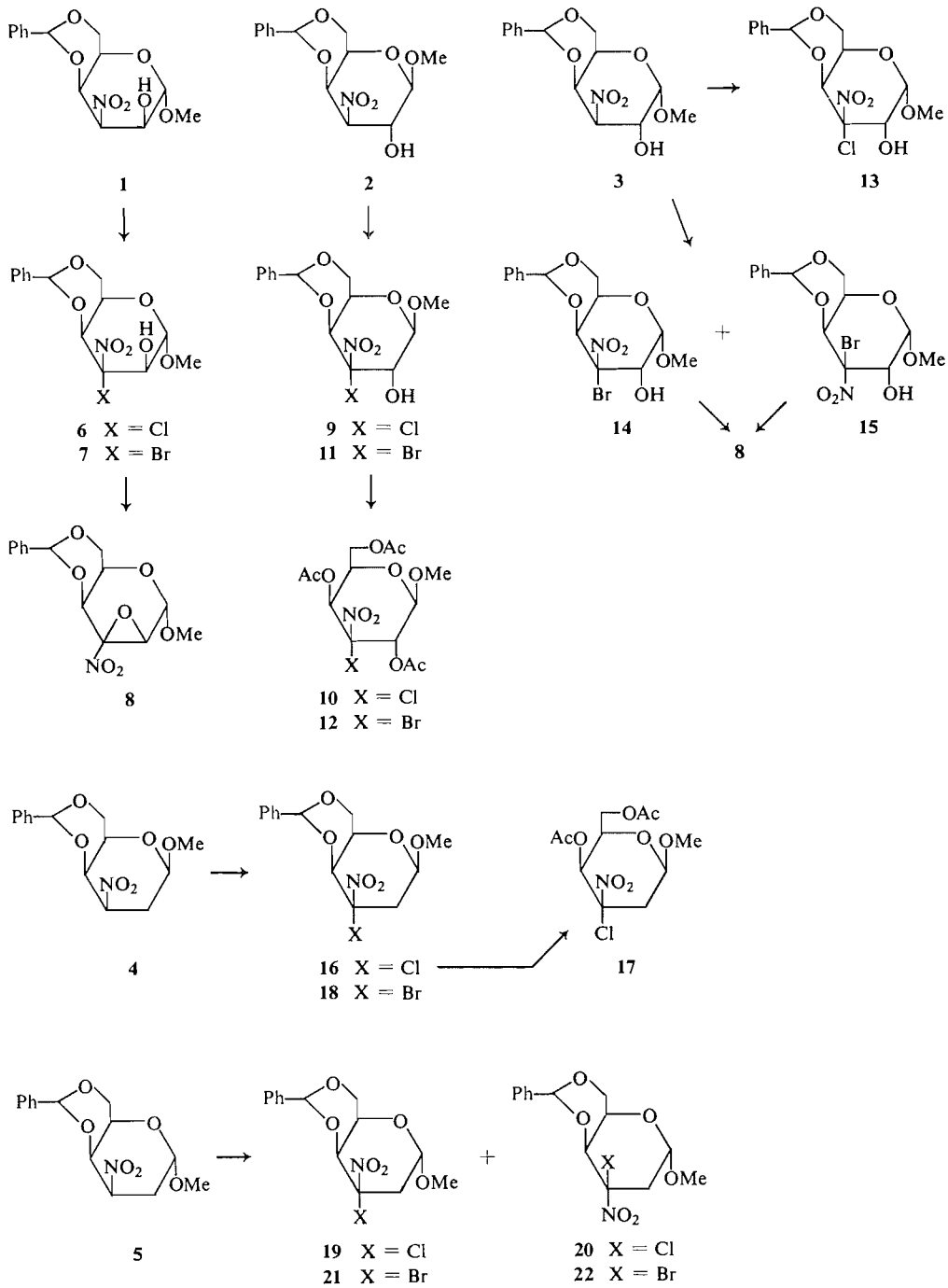
Consonant with the observed, facile formation of their nitronates (9), the methyl 4,6-*O*-benzylidene-3-deoxy-3-nitrohexopyranosides with the α-D-*talo* (**1**), β-D-*galacto* (**2**), and α-D-*galacto* (**3**) configurations, and the methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β- and α-D-*lyxo*-hexopyranosides (**4** and **5**) all furnished 3-halo derivatives smoothly in high yields.

Chlorination of **1** gave methyl 4,6-*O*-benzylidene-3-chloro-3-deoxy-3-nitro-α-D-idopyranoside (**6**) which could be isolated in 85% yield when the reaction was performed at 0°. When it was performed at room temperature, **6** could not be isolated but was converted into methyl 2,3-anhydro-4,6-*O*-benzylidene-3-nitro-α-D-talopyranoside (**8**) which crystallized in over 80% yield. This epoxide had previously been obtained in a different way (10). Bromination of **1** by either the Br_2 or the NBA method readily furnished the bromonitro analog **7**. Sodium borohydride reduction of **7** according to Iffland and Criner (11) regenerated **1**, demonstrating that bromination was not attended by any unexpected structural or configurational change. A short treatment of **7** with sodium hydroxide at 25° led to the epoxide **8** in 90% yield. The facile formation of **8** from **6** and **7** strongly supports the *trans*-diaxial halohydrin grouping in these compounds (12*a*).

Chlorination as well as bromination by either method, of the β-D-*galacto* isomer **2** similarly afforded halogen derivatives as single products in good yields. They were methyl 4,6-*O*-benzylidene-3-chloro-3-deoxy-3-nitro-β-D-gulopyranoside (**9**) and its bromo analog **11**. Both products were characterized further by acid-catalyzed debenzylidenation followed by acetylation, to give methyl 2,4,6-tri-*O*-acetyl-3-chloro-3-deoxy-3-nitro-β-D-gulopyranoside (**10**) and its bromo analog **12**, respectively. As in the aforementioned case of **7**, borohydride reduction of **11** regenerated the starting sugar **2** (90% yield). Unlike **7**, however, the bromohydrin **11** did not give an epoxide upon treatment with aqueous alkali. Instead, debromination producing **2** occurred in reversal of the bromination, with the abstraction of Br^+ ion being evidenced by a positive potassium iodide – starch test. When **11** was refluxed in 0.03 *N* methanolic sodium methoxide solution for 20 min it partly survived but largely decomposed with liberation of benzaldehyde.[3] The fact that no epoxynitro sugar was formed in any

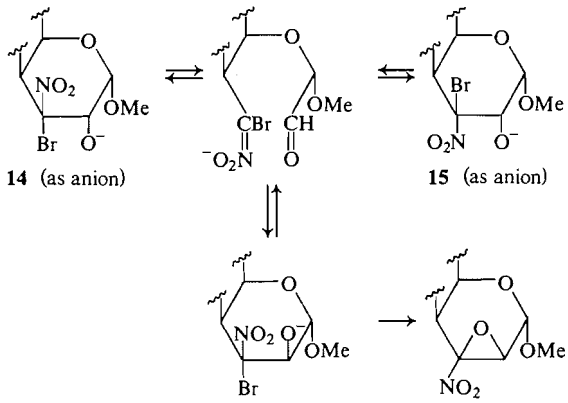
[2]Following a suggestion by Professor D. Horton, Columbus, Ohio, and pending the adoption of an official international nomenclature rule for the configuration of sugars that bear unequal geminal substituents on the ring we use the established configurational designations combined with the sequence rule of Cahn *et al.* (8). The substituent which according to this rule has the *higher* priority is thought of as replacing the *hydroxyl group* at the carbon concerned. Thus, for example, if H-3 in the formula of 3-deoxy-3-nitro-D-glucose is replaced by bromine or chlorine (both of which have priority over nitro), the resultant halonitro sugar is regarded as a derivative of D-allose with the halogen atom occupying the place of OH, and the NO_2 group, that of H.

[3]The benzylidene acetal ring in **2** is known to be quite labile towards base (7).



of these base treatments supported the *cis*-bromohydrin configuration.

Chlorination of the α-D-*galacto* isomer **3** afforded methyl 4,6-*O*-benzylidene-3-chloro-3-deoxy-3-nitro-α-D-gulopyranoside (**13**) in over 90% yield. Contrasting with the stereoselectivity of this reaction and all the halogenations of **1** and **2**, bromination of **3** resulted in mixtures of epimers. The Br_2 method gave a crude product (yield, 91%) which exhibited two spots on t.l.c. and showed two benzylidene methine proton resonances (τ 4.48 and 4.30) in an intensity ratio



SCHEME I

55:45. Upon chromatographic separation the pure crystalline epimers were isolated in yields of 49 and 33%. The preponderant product was considered to be that which has an equatorial nitro group, *i.e.*, methyl 4,6-*O*-benzylidene-3-bromo-3-deoxy-3-nitro-α-D-gulopyranoside (**14**), and the lesser product was assigned the α-D-*galacto* configuration (**15**). Bromination of **3** by the NBA method gave **14** and **15** in the ratio of 85:15. Reductive removal of the bromine reconverted both **14** and **15** into **3**, thus confirming the epimerism. Interesting observations were made when the products were treated with alkali. It might have been expected that at least one of them (**14**) would incur debromination, like its β-anomer **11**, to give the starting glycoside **3**. However, **14** remained unchanged for 20 h in a methanolic, 0.03 *N* sodium hydroxide solution at room temperature. In refluxing sodium methoxide solution it appeared to suffer far-reaching decomposition (like **11**) but a crystalline product could nevertheless be isolated in 25% yield. The same product arose slowly (10 h) in high yield (72%) from the epimer **15** by action of methanolic hydroxide even at room temperature. Surprisingly it proved identical with the epoxide **8** previously engendered from **1** (via **6** or **7**). These results clearly imply epimerization at C-2, a phenomenon not observed in the alkali treatments of the halonitro compounds having the α-D-*ido* or β-D-*gulo* configuration. The following explanation is offered.

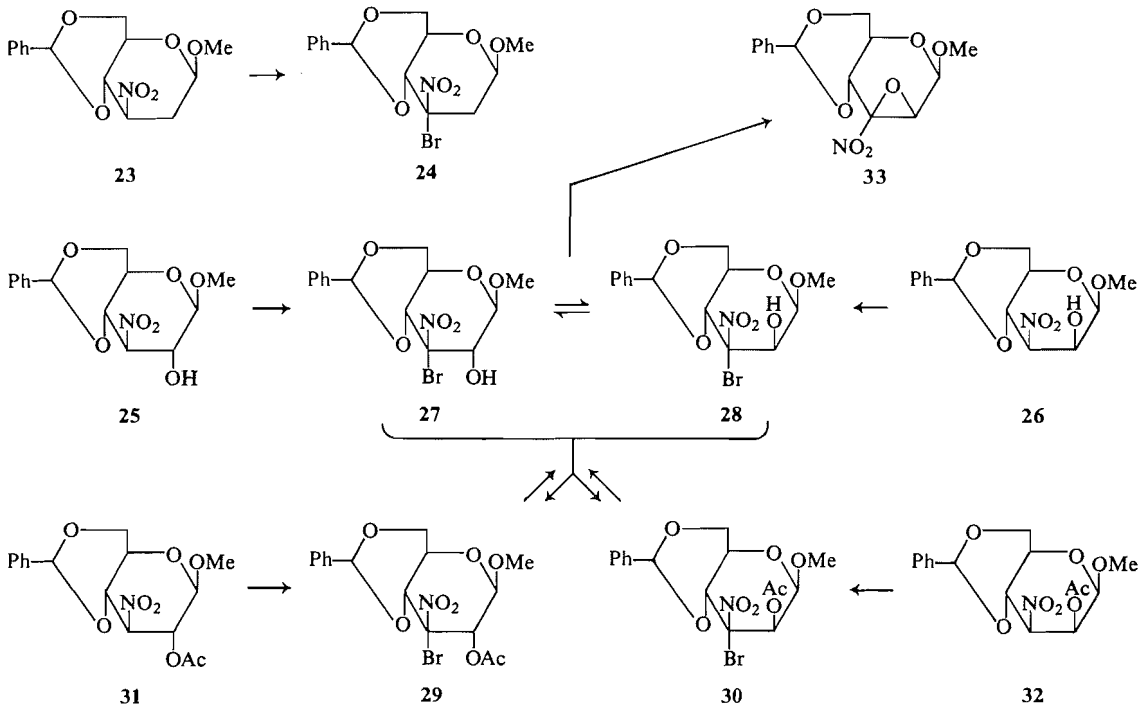
The three bromonitro α-D-glycosides (**7**, **14**, and **15**) have in common substantial strain due to non-bonded interaction of the axial, glycosidic methoxyl group and the axial substituent at C-3. Whereas the structure of **7** with a *trans*-diaxial halohydrin arrangement is conducive to rapid epoxide formation upon proton abstraction from OH-2, this is not the case for **14** and **15**. However, these two compounds may undergo (reversible) ring opening by way of a retrograde Henry reaction, are thus able to epimerize, and therefore they, too, eventually furnish the epoxide **8** (Scheme 1). It appears plausible that ring cleavage occurs more readily in **15** than **14** since an axial nitro group is associated with a higher conformational free energy than an axial bromine atom.[4] In the β-glycoside **11**, which lacks 1,3-diaxial strain, the driving force for a retrograde Henry reaction is diminished, and abstraction of Br^+ by base was observed instead.

The 2-deoxy glycosides **4** and **5** also reacted readily, giving high yields of halonitro derivatives. The β-anomer **4** gave single products, namely methyl 4,6-*O*-benzylidene-3-chloro-2,3-dideoxy-3-nitro-β-D-*xylo*-hexopyranoside (**16**) and its bromo analog **18**. Debenzylidenation of **16** followed by acetylation furnished the corresponding 4,6-diacetate **17**. By contrast, the α-anomer **5** gave mixtures of 3-epimeric halonitro compounds, both in chlorination (the α-D-*xylo* (**19**) and α-D-*lyxo* (**20**) epimers in the ratio 86:14) and in bromination by either method (the α-D-*xylo* (**21**) and α-D-*lyxo* (**22**) epimers in ratios of about 75:25). The epimers could be distinguished by the chemical shifts of their benzylidene methine protons and they were separated by column chromatography. The minor components (**20** and **22**) were characterized by physical data and not by elemental analysis, but spectroscopic evidence including mass spectra supported the structural assignments (see Experimental).

Reactions with trans-Fused Acetals

In nitro glycosides possessing a *trans*-fused 4,6-*O*-benzylidene ring we have so far investigated brominations only. Methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-*arabino*-hexopyranoside (**23**) gave with NBA an amorphous bromo derivative (yield, 87%) which appeared uniform according to its n.m.r. spectrum and

[4]For substituted cyclohexanes, values of approximately 0.5 and 1.05 kcal/mol are given for the bromo (12*b*) and nitro (13) substituents, respectively. In 3-deoxy-3-nitro pyranosides an even higher value for the nitro group must be postulated from the results of recent studies in this laboratory (6).



t.l.c. It was assigned the β-D-*ribo* configuration (**24**).

Considerably more complicated were the reactions performed with D-*gluco* and D-*manno* derivatives. It must be recalled in this connection that in the presence of alkali these nitro glycosides form nitronate much less readily than their D-*galacto* and D-*talo* isomers, and moreover that the D-*manno* derivatives are liable to incur rapid epimerization at C-2 (9).

Bromination of the β-D-mannoside **26** at 0° by the Br_2 method did not go to completion. It afforded a mixture which according to integration of signals (τ 4.23, 4.32, 4.42, and 4.48) contained four products in the ratio 5:10:35:50. The compounds present to the extent of 10 and 50% were shown by chromatographic isolation to be unreacted **26** (τ 4.32) and the β-D-glucoside **25** (τ 4.48), respectively. The latter obviously arose by epimerization and failed to be brominated. The two remaining products, together 40% of the mixture, were bromonitro compounds as was first suggested by a shift of the asymmetric nitro vibration from 1550 to 1565 cm^{-1} (14). Although they could be separated chromatographically from the non-brominated material, they could not be separated from each other and were never isolated individually; nevertheless, they were assigned, on the basis of subsequently described experiments, the structures of methyl 4,6-*O*-benzylidene-3-bromo-3-deoxy-3-nitro-β-D-allopyranoside (**27**) (major product, τ 4.42) and -altropyranoside (**28**) (minor product, τ 4.23). The NBA method proved more effective, **26** yielding almost quantitatively a mixture of **27** and **28** in a ratio of 4:1. The near identity of the mixtures of bromo derivatives obtained by the two methods was established by comparison of their i.r. and n.m.r. spectra and optical rotations.[5] It is most noteworthy that either bromination caused extensive epimerization at C-2; whereas for the Br_2 method this could be expected in the light of previous results concerning the action of alkali upon **26** (9), it is remarkable that the sodium acetate present in the NBA method apparently suffices to give the same result.

Bromination of the β-D-glucoside **25** by NBA also produced **27** and **28**, again in a similar ratio (75:15), with some **25** (10%) remaining unre-

[5]A similar mixture of **27** and **28** was produced, also in high yield, by substituting *N*-bromo-succinimide for NBA. Cleavage of the benzylidene ring with concomitant introduction of bromine at C-6 was not observed under our reaction conditions which differ from those of Hanessian's NBS reaction (15).

acted. The *manno* isomer **26** was not detected in the product whose n.m.r. spectrum was practically identical with those of the previously obtained mixtures of **27** and **28**, except for weak signals due to remnant **25**. This result was also borne out by close similarities in i.r. spectra and optical rotations. The Br_2 method proved ineffective for bromination of **25**.

Acetylation of a mixture of **27** and **28** by the mild procedure using acetyl chloride in the presence of triethylamine (4, 16) furnished separable 2-acetates **29** and **30** which were isolated in pure form in yields of 70 and 15%. The same acetates were obtained, each in 95% yield and evidently as single products, upon NBA bromination of the 2-*O*-acetyl derivatives **31** and **32** (of **25** and **26**, respectively). Clearly, with the 2-OH group being blocked by acetylation, no epimerization took place on C-2 and the configurations of **27** and **28** at this site have thus been established. In accord therewith were the $J_{1,2}$ coupling constants of **29** (8 Hz) and **30** (0 Hz).

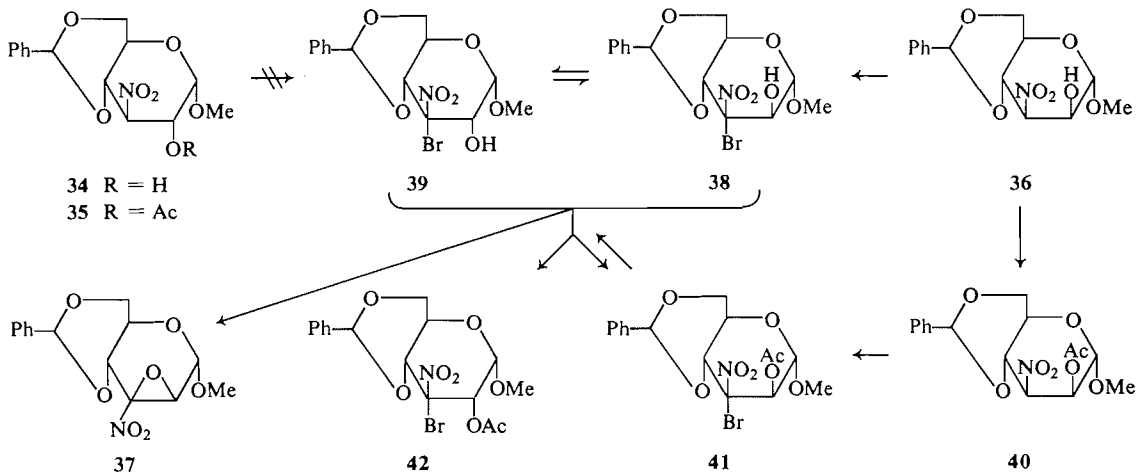
Treatment of the β-D-*altro* bromonitro acetate **30** with 0.04 *N* sodium methoxide in methanol at 0° or at room temperature led to deacetylation followed by 2-epimerization, to give mixtures of **27** and **28**, with the β-D-*allo* derivative (**27**) preponderating four- to five-fold. That is to say, base treatment of **30** at low temperatures produced the same bromonitro compounds, and in virtually the same proportions, as did bromination of **25** or **26**. Reacetylation of a mixture originating from **30** led to isolation of the epimeric, β-D-*allo* acetate **29** in a yield of 65%. The conclusion to be drawn from all these results is that the bromonitro glycosides **27** and **28** (but not their acetates) are readily interconvertible by base, and that a thermodynamic equilibrium tends to be established between them. The epimerization observed in the course of bromination of the β-D-glucoside **25** must exclusively take place on this stage (*i.e.* in **27**) since **25** itself does not epimerize to **26**. The epimerization occurring in the bromination of the β-D-mannoside **26**, shown above to be possible at the stage of **28**, may also take place in **26** itself as can be inferred from previous work,[6] so that perhaps both pathways are utilized in this instance.

Compound **28**, which possesses a *trans*-diaxial bromohydrin structure, was expected to give quite readily an epoxide when treated with base. As previously mentioned, the liberation of **28** from its acetate by methoxide at low temperature was succeeded by partial 2-epimerization; there was no evidence for epoxide formation. However, when mixtures of **27** and **28** were *refluxed* in methoxide-containing methanol for 30 min, epoxide formation did occur. Thus methyl 2,3-anhydro-4,6-*O*-benzylidene-3-nitro-β-D-mannopyranoside (**33**) was isolated in yields of 78 and 84% upon such treatment of the closely similar isomer mixtures originating from brominations of **25** and **26**, respectively. Yields were smaller (41 and 37%) when the acetates **29** and **30** were treated *directly* with boiling methoxide solution, instead of being first saponified (and allowed to epimerize) in the cold; a certain degree of degradation was noticed in these cases.[7] At any rate, the amount of epoxide **33** formed in each instance far exceeded the supply of **28**. This was true even for the alkali treatment of **30** since epimerization following its deacetylation was faster than epoxide formation. The bulk of **33** must therefore be provided by **27** through a mobile, epimeric equilibrium. The epimerization is thought to proceed by reversible ring opening as discussed for **14** and **15**, above.

In the α-anomers of this configurational series, brominations proceeded more sluggishly if at all. Thus, methyl 4,6-*O*-benzylidene-3-deoxy-3-nitro-α-D-glucopyranoside (**34**) failed to react in the Br_2 procedure, and it did not react with NBA in methanol and sodium acetate even when heated under reflux for as long as 10 h. Its 2-acetate **35**, too, was completely inert towards NBA under conditions which had led to nearly quantitative bromination of the β-anomer **31** (3 h at 25°). The α-D-*manno* isomer **36** was only partially brominated by the NBA method although the β-anomer (**26**) had been brominated completely. The mixture obtained was judged on the basis of t.l.c. and n.m.r. evidence (see

[6]Compound **26** was completely (that is, within the limits of detectability by t.l.c.) converted into **25** under conditions of alkalinity comparable to those prevailing in the Br_2 method of bromination (9).

[7]Liberation of benzaldehyde was observed, which is indicative of base-catalyzed β-elimination of the C-4 acetal linkage and implies carbanion formation at C-3. One can only surmise that, at elevated temperature, abstraction of bromine from C-3 becomes markedly competitive with deacetylation. Nitronate so generated would no longer be able to produce epoxide but would undergo other transformations. Compare the behavior of **11** in alkaline media.



Experimental) to contain some starting material **36**, about 25% of the 2-epimer **34**, and approximately 30% of each of two new products. No attempt was made to separate the products but the presence of two bromonitro derivatives was confirmed by base treatment which afforded the known (10) epoxide, methyl 2,3-anhydro-4,6-*O*-benzylidene-3-nitro-α-D-mannopyranoside (**37**). The latter was isolated in a yield of 51%, which implies that both bromonitro sugars present must have contributed to its formation. Undoubtedly, one of them was methyl 4,6-*O*-benzylidene-3-bromo-3-deoxy-3-nitro-α-D-altropyranoside (**38**) and the other, most likely its α-D-*allo* isomer **39**, in analogy to the β-series. Bromination of the 2-acetate **40** of the α-D-mannoside **36** gave in high yield the 2-acetate **41** of **38** as a crystalline but rather sensitive compound. Deacetylation of **41** at room temperature produced what according to the n.m.r. spectrum was a 2:3 mixture of the same bromonitro sugars that arose in the bromination of **36** (*i.e.* presumably **38** and **39**), and treatment of the deacetylated mixture (or of **41** directly) with refluxing methanolic methoxide again gave the epoxide **37** (yields, 76–82%). Reacetylation of the mixture gave acetates in an approximate ratio of 2:3, and although these could not be separated either, the n.m.r. spectrum suggested that the lesser component was **41**. The major component, then, must have been the acetate of **39**, *i.e.*, presumably the α-D-*allo* derivative **42**. In summary, then, the experiments in this anomeric series have shown that α-D-*manno*, but not α-D-*gluco*, derivatives are effectively brominated by NBA, that epimerizations occur if 2-OH is unprotected, and that the bromonitro derivatives are readily converted into an epoxide.

Stereochemical Considerations

In all the halogenations studied, the preferred configuration arising at C-3 was that which places the nitro group equatorially when the pyranoside ring occupies the normal chair conformation. In a majority of instances a single halonitro derivative was obtained in a high yield, and in certain cases where two products arose these were epimeric at C-2 but stereochemically identical at C-3. However, in some instances C-3 epimers having an axial nitro group were formed as minor products. An explanation for these observations is now to be attempted.

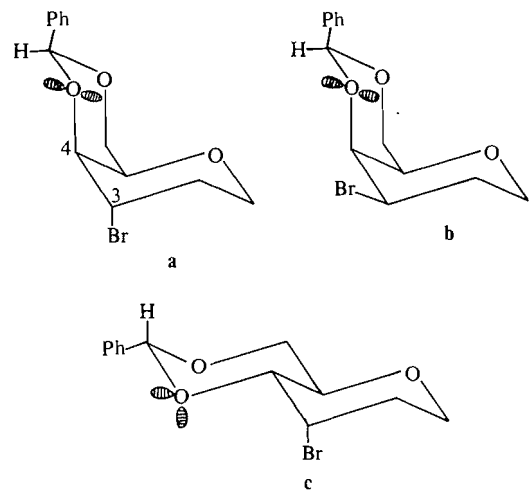
One possibility to be considered is steric control of the approaching, halogen-transferring agent. In principle, the carbanionic site (C-3) in all the nitronates should be freely accessible for attack from the lower side of the glycoside ring while attack from the upper side should be sterically hindered by the axial hydrogen atoms and (or) oxygen functions situated at C-2 and -4. This factor would generally favor axial placement of the incoming halogen and consequently, equatorial placement of the nitro group, and would requi re no qualification for the β-glycosides all of which were indeed halogenated in a stereochemically uniform way. In α-glycosides the axial but more remote methoxyl group presumably reduces somewhat the accessibility of the lower pyranoside face, thereby tending to diminish the degree of stereoselectivity. This was seen in the halogenations of the α-D-*galacto*

and α-D-*lyxo* glycosides (**3** and **5**), and bromination seemed to be affected more so than chlorination. In the α-D-*talo* compound (**1**) this effect was not evident, probably because it is small relative to the especially severe hindrance afforded by the two axial oxygen functions on the upper side of the ring. If this line of reasoning is valid one should have expected the α-D-*manno* acetate **40** to give, in addition to the bromo derivative **41** that was produced, at least a small proportion of the corresponding 3-epimer. However, no evidence for formation of the latter has so far been obtained. A similar expectation does not necessarily apply to bromination of the non-acetylated α-D-*manno* compound **36**, since an epimer with axial nitro group, if it is formed as a primary product, may well be too unstable for observation and may suffer rapid epimerization to **38** and (or) **39**.

A further point of interest is the complete inertness of α-D-*gluco* derivatives (**34** and **35**) towards bromination even by the NBA method. It would be hard to visualize that they constitute a category apart as far as the facility of approach of the halogenating agent is concerned. Rather, we are inclined to believe that they failed to form the requisite nitronate salt in the weakly basic reaction medium. The particularly low nitromethylene acidity in 3-deoxy-3-nitro pyranosides having a 2,3,4-triequatorial substituent arrangement has been observed and explained previously (6, 9, 17, 18), but the present finding of an apparent difference in degree between α- and β-anomers is remarkable. Possibly it is a manifestation of a polar effect by which the methoxyl group, through the direction of its dipole in α-glycosides, opposes the development of carbanionic character at C-3.

Spectroscopic Evidence in Support of Configurational Assignments

In earlier work (18) the chemical shift of the benzylidene methine proton signal in n.m.r. spectra of 4,6-*O*-benzylidene-3-deoxy-3-nitrohexopyranosides has proved of diagnostic value for differentiating stereoisomers. Regularities in such shifts observed in the present work tend to support the C-3 configurations of the halonitro derivatives as assigned on the basis of chemical considerations. Table 1 shows that introduction of a halogen atom at C-3 has in some cases little or no effect upon the τ-value of the methine signal whereas in other cases a small but distinct downfield shift (0.1–0.2 p.p.m.) is observed. Virtually unaffected are the signals in those halogen derivatives which possess a *cis*-fused acetal structure and arise either as single (**6**, **7**, **9**, **11**, **13**, **16**, **18**) or as predominant epimers (**14**, **19**, **21**). The group characterized by the downfield shift comprises the minor epimers (**15**, **20**, **22**) in the *cis*-acetal series and all of the products having a *trans*-fused acetal ring. These observations are best explained by assuming that the methine proton experiences a change in shielding when the C_3-halogen bond is *gauche* to the C_4-oxygen bond (*i.e.*, parallel to one of the nonbonding orbitals of O-4) while no such effect is associated with an *anti* orientation of these bonds. When the pyranoside rings are depicted in the $^4C_1$ conformation in agreement with coupling constants found for H-1 and -4, the chemical shift data are thus consistent with the C-3 configurations as allocated. (See the partial formulas **a**–**c**).



Also in accord with configurations assigned to C-3 are the chemical shifts of the anomeric proton signals insofar as these signals are discernible. In halonitro derivatives presumed to have the "normal" C-3 configuration (impyling axial halogen), the signal of an equatorial H-1 (in α-glycosides) is either virtually unaffected or shifted slightly downfield, and the signal of an axial H-1 (in β-glycosides) is markedly shifted downfield. By contrast, the "abnormal" compounds **15**, **20**, and **22** exhibit a moderate upfield shift of their H-1 signal. At the same time the anomeric methoxyl signals of these three compounds occur about 0.1 p.p.m. upfield from

TABLE 1. Chemical shifts (τ) of n.m.r. signals of halonitro sugars and precursors (100 MHz, in $CDCl_3$)

Compound	$PhCHO_2$	OCH_3	$OCOCH_3$	H-1	H-2	H-4
cis-Acetals						
1	4.41	6.59		5.02	5.37	
6	4.39	6.57		4.95	5.61	5.22
7	4.39	6.57		4.95	5.52	5.12
2	4.48	6.40				
9	4.50	6.43		5.48	5.26	5.45
11	4.51	6.44		~5.45	~5.50	5.30
3	4.51	6.56		5.03	5.28	5.28
13	4.48	6.56		5.01	5.01	5.38
14	4.48	6.55		4.99	~5.20	~5.20
15	4.30	6.64		5.09	~5.7	5.17
4	4.46	6.51				
16	4.44	6.48		5.31	7.20, 7.50	5.53
18	4.44	6.48		5.28	7.22, 7.43	5.43
5	4.43	6.66		4.99	7.40, 7.80	5.27
19	4.42	6.64		4.92	7.00, 7.44	5.47
20	4.28	6.76		5.14	6.96, 7.39	5.32
21	4.41	6.63		4.89	6.94, 7.37	5.33
22	4.28	6.78		5.21	~6.85, 7.30	5.30
trans-Acetals						
23	4.43	6.53		5.48	7.45, 7.77	
24	4.33	6.50		5.21	~7.25	
25	4.49	6.46				
26	4.32	6.44				
27	4.42	6.44				
28	4.23	6.44				
31	4.47	6.52	7.95	5.52	4.61	
29	4.39	6.51	7.93	5.37	4.47	
32*	4.33	6.50	7.89	5.48	4.13	6.05
30	4.21	6.48	7.95	4.96	4.12	
34	4.49	6.55		5.17		
35	4.48	6.61	7.95	4.95	4.73	
36	4.34	6.61		5.28		
40	4.32	6.62	7.94	5.26	4.47	
38	4.24	6.61				
39	4.43	6.55				
41	4.20	6.61	7.99	5.28	4.34	

*See ref. 16.

those of their precursors whereas in all other cases the influence of halogenation upon these signals appears insignificant.

Table 1 shows, furthermore, that the chemical shift of the benzylidene methine proton in non-halogenated glycosides incurs no significant change upon acetylation of the compound in position 2; compare **25**, **26**, **34**, and **36** with their respective 2-acetates **31**, **32**, **35**, and **40**. Assuming that the same holds true for the corresponding bromonitro glycosides one can correlate the 2-acetates **29** and **30** (which were isolated) with the non-acetylated bromination products that show τ 4.42 and 4.23, respectively, and that could not be separated but were designated on this basis as **27** and **28**. By a similar argument one can attribute formulas **38** and **39** to the components showing τ 4.24 and 4.43, of the mixtures resulting from bromination of **36** or deacetylation of **41**.

Experimental

For general preparative instrumental techniques see preceding articles of this series (*e.g.*, refs. 1, 10, 18). Optical rotations were measured at room temperature in chloroform solutions (*c*, 0.5–1) unless otherwise indicated. I.r. spectra were obtained from Nujol mulls on a Beckman IR-20 instrument. The n.m.r. data given for the characterization of compounds (Table 1 and elsewhere)

were obtained with a Varian HA-100 spectrometer; a T-60 spectrometer was used for monitoring reactions. The data refer to $CDCl_3$ solutions with TMS as internal standard. The following solvent systems (v/v) were employed for t.l.c. and column chromatography on silica gel: A, carbon tetrachloride – ethyl acetate (7:3); B, the same (4:3); C, petroleum ether (b.p. 30–60°) – ethyl acetate (2:3); D, the same (3:2).

Materials

The nitro glycosides to be halogenated were obtained according to the references given in parentheses: **1** (18), **2** (18, 19), **3** (18), **4** (1), **5** (1), **23** (1, 21*a*), **25** (18, 20, 21*b*), **26** (18, 19), **31** (20, 21*b*, 22), **32** (16), **34** (18, 19), **35** (23), **36** (18). The hitherto unknown *methyl 2-O-acetyl-4,6-O-benzylidene-3-deoxy-3-nitro-α-D-mannopyranoside* (**40**) was prepared by acetylation of **36** with acetyl chloride and triethylamine in methylene chloride as described (16) for the acetylation of **32** (see also the preparation of **29** from **27** + **28**). It was obtained as an amorphous powder in 86% yield; $[\alpha]_D$ +4.5°; ν_{max} 1745 and 1560 cm^{-1} ($OCOCH_3$ and NO_2). N.m.r. (in $CDCl_3$): τ 2.66 (m, 5H, phenyl), 5.03 (q, 1H, H-3), and Table 1; $J_{1,2}$ = 1.5, $J_{2,3}$ = 3.5, $J_{3,4}$ = 11 Hz.

Anal. Calcd. for $C_{16}H_{19}NO_8$ (353.3): C, 54.40; H, 5.42; N, 3.97. Found: C, 54.56; H, 5.29; N, 3.97.

Preparation of Halonitro Glycosides: General

Chlorinations were performed using a reagent grade, 5% aqueous sodium hypochlorite solution, or with equal success, commercial household bleach *Javex*, a product of Bristol-Myers Canada Limited, containing 6% sodium hypochlorite. Brominations were carried out with bromine in alkaline medium (Br_2 method) or with *N*-bromoacetamide in the presence of sodium acetate (NBA method). The procedures are detailed for compounds **6** and **7**. The remaining halonitro derivatives were obtained in the same general way, with occasional modifications as specified. Reactions were routinely monitored by t.l.c.

Upon completion of the halogenations, the products were isolated in one of two ways depending upon their solubility. In each case, the methanolic reaction solution was diluted with water, and part of the methanol was removed by evaporation under reduced pressure (bath temperature, 35°). Frequently the halogenated product separated thereby in crystalline and nearly pure form in large quantity. It was collected by filtration, washed with cold water, and dried in a desiccator before being recrystallized as necessary and specified. This *precipitative procedure* is referred to as work-up (P). When precipitation was unsatisfactory, the solution was concentrated further until most of the methanol was removed, and the remaining aqueous solution was then extracted three times with chloroform. The combined extract was washed twice with water, dried over anhydrous sodium sulfate, and evaporated to afford the product usually in nearly pure form. This *extractive procedure* is referred to as work-up (E).

Methyl 4,6-O-Benzylidene-3-chloro-3-deoxy-3-nitro-α-D-idopyranoside (6)

To an *ice cold* solution of **1** (124 mg) in methanol (30 ml) was added hypochlorite solution (1.2 ml). Inspection by t.l.c. (solvent B) after 5 and 15 min showed absence of **1** and presence of a single, faster moving spot. The solution was neutralized at 0° with 2 *N* acetic acid and worked-up (P). The crude product was recrystallized from ethanol–water to furnish **6** (117 mg, 85%); m.p. 104–105°, $[\alpha]_D$ +48.3°, ν_{max} 3480 and 1570 cm^{-1} (OH and NO_2).

Anal. Calcd. for $C_{14}H_{16}ClNO_7$ (345.7): C, 48.70; H, 4.65; Cl, 10.27. Found: C, 48.80; H, 4.86; Cl, 10.40.

Methyl 4,6-O-Benzylidene-3-bromo-3-deoxy-3-nitro-α-D-idopyranoside (7)

(a) Br_2 Method

To an ice-cold solution of **1** (103 mg) in methanol (15 ml) was added aqueous, 0.1 *N* sodium hydroxide (3.7 ml). The mixture was stirred for 5 min after which bromine was added in small drops until the color of the solution remained slightly yellow. Stirring was then continued for another 5 min and followed by work-up (E). The white product (104 mg) was recrystallized from chloroform–pentane to give **7** (96 mg, 74%); m.p. 126–128°, raised to 129–130° by a second recrystallization. The product had $[\alpha]_D$ +45.5° and ν_{max} 3550, 3490 (OH) and 1565 cm^{-1} (NO_2).

Anal. Calcd. for $C_{14}H_{16}BrNO_7$ (390.3): C, 43.14; H, 4.13; Br, 20.46. Found: C, 43.26; H, 4.17; Br, 20.83.

(b) NBA Method

To a solution of **1** (200 mg) in methanol (20 ml) was added NBA (100 mg) and a saturated, aqueous solution of sodium acetate (2 ml). The reaction mixture was agitated for 30 min at room temperature. Work-up (E) afforded **7** (235 mg, 94%), m.p. 127–129° and undepressed upon admixture of **7** from the Br_2 method. The i.r. spectra of the two products were identical.

Methyl 4,6-O-Benzylidene-3-chloro-3-deoxy-nitro-β-D-gulopyranoside (9)

Chlorination of **2** (62 mg) was carried out at room temperature. According to t.l.c. (solvent C) no **2** was left after 10 min, and a single, faster moving spot was seen. The reaction mixture was allowed to stand for another 15 min, and work-up (E) then gave crude **9** (72 mg) which was recrystallized from ethyl acetate – petroleum ether to give pure **9** (58 mg, 76%); m.p. 166–167°; $[\alpha]_D$ +35.1°, ν_{max} 3480 and 1570 cm^{-1} (OH and NO_2).

Anal. Calcd. for $C_{14}H_{16}ClNO_7$ (345.7): C, 48.70; H, 4.65; Cl, 10.27. Found: C, 48.62; H, 4.78; Cl, 10.26.

Methyl 2,4,6-Tri-O-acetyl-3-chloro-3-deoxy-3-nitro-β-D-gulopyranoside (10)

Compound **9** (200 mg) was debenzylidenated by treatment (24) with 90% trifluoroacetic acid (5 ml) for 20 min at room temperature. The syrupy product obtained upon evaporation failed to crystallize and was therefore acetylated by the boron trifluoride method (22), a reaction time of 20 min being allowed. The acetylation mixture was poured into and stirred with ice water, and the oily product which separated was extracted into chloroform (3 × 30 ml). The extract was washed twice with 5 ml of cold, saturated sodium bicarbonate solution and twice with 5 ml of water. Drying (Na_2SO_4) and evaporation of the solvent gave **10** as a syrup which could be crystallized from chloroform–pentane. The product showed m.p. 91–92°, $[\alpha]_D$ −6.3°, ν_{max} 1765, 1745 ($OCOCH_3$), and 1575 cm^{-1} (NO_2).

Anal. Calcd. for $C_{13}H_{18}ClNO_{10}$ (383.8): C, 40.72; H, 4.73; Cl, 9.25. Found: C, 40.77; H, 4.71; Cl, 9.48.

Methyl 4,6-O-Benzylidene-3-bromo-3-deoxy-3-nitro-β-D-gulopyranoside (11)

(a) Br_2 Method

To an ice-cooled suspension of **2** (311 mg) in methanol (40 ml) was added aqueous 0.1 *N* sodium hydroxide (11 ml). After stirring for 4 min a clear solution resulted to which bromine was added dropwise until a light yellow color persisted. Stirring at 0° was continued for 15 min and then followed by work-up (P). The product **11** (281 mg, 72%) showed m.p. 75–78°, $[\alpha]_D$ +31.6°, ν_{max} 3450 (OH) and 1565 cm^{-1} (NO_2).

Anal. Calcd. for $C_{14}H_{16}BrNO_7$ (390.2): C, 43.14; H, 4.13; Br, 20.46; N, 3.59. Found: C, 43.03; H, 4.24; Br, 20.38; N, 3.80.

(b) NBA Method

The reaction mixture was heated at reflux temperature for 1 h and then worked-up (P) to furnish **11**, m.p. 77–79°, in a yield of 69%. The i.r. spectrum was identical with that of **11** from (*a*).

Methyl 2,4,6-Tri-O-acetyl-3-bromo-3-deoxy-3-nitro-β-D-gulopyranoside (12)

Compound **11** (140 mg) was debenzylidenated, and the syrupy product acetylated, as described for the preparation of **10** from **9**. Prolonged trituration of the acetylation mixture with ice water gave the triacetate **12** as a solid (103 mg after drying; m.p. 107–108°) which was recrystallized from ethyl acetate – petroleum ether; m.p. 112–113°, $[\alpha]_D$ +25°, ν_{max} 1765, 1740 ($OCOCH_3$) and 1570 cm^{-1} (NO_2).

Anal. Calcd. for $C_{13}H_{18}BrNO_{10}$ (428.2): C, 36.48; H, 4.24; Br, 18.67; N, 3.27. Found: C, 36.60; H, 4.31; Br, 18.69; N, 3.32.

Methyl 4,6-O-Benzylidene-3-chloro-3-deoxy-3-nitro-α-D-gulopyranoside (13)

The glycoside **3** (120 mg) in methanol (15 ml) was treated with hypochlorite solution (1 ml) for 1 h at room temperature. Formation of a uniform product moving faster than **3** was indicated by t.l.c. (solvent D). Work-up (E) furnished crystalline **13** (123 mg, 92%) which upon recrystallization from ethanol–water melted at 121–122°; $[\alpha]_D$ +144°, ν_{max} 3540 and 1570 cm^{-1} (OH and NO_2).

Anal. Calcd. for $C_{14}H_{16}ClNO_7$ (345.7): C, 48.70; H, 4.65; Cl, 10.27. Found: C, 48.53; H, 4.77; Cl, 10.13.

Methyl 4,6-O-Benzylidene-3-bromo-3-deoxy-3-nitro-α-D-gulopyranoside (14) and -α-D-galactopyranoside (15)

(a) Br_2 Method

The glycoside **3** (311 mg) in methanol (40 ml) was treated with 0.1 *N* sodium hydroxide solution (11 ml) for 5 min at 0° and then brominated during 15 min. Work-up (P) afforded a white solid material (355 mg) which according to the t.l.c. (solvent B) was free from starting material but contained two products in similar proportions. An n.m.r. spectrum of the material exhibited two sharp singlets at τ 4.30 and 4.48 with an intensity ratio of 45:55 (benzylidene methine protons). The mixture was chromatographed on a column of silica gel (20 g) which was eluted with solvent C. A clean separation was achieved. The faster moving fraction gave the α-D-*galacto* isomer **15** (130 mg, 33%), m.p. 66°, $[\alpha]_D$ +160.3°, ν_{max} 3540 and 1560 cm^{-1}. The slower fraction gave the α-D-*gulo* isomer **14** (190 mg, 49%), m.p. 118–120°, $[\alpha]_D$ +108°, ν_{max} 3510 and 1560 cm^{-1}.

Anal. Calcd. for $C_{14}H_{16}BrNO_7$ (390.2): C, 43.14; H, 4.13; Br, 20.46. Found for **14**: C, 42.85; H, 4.22; Br, 20.45. Found for **15**: C, 43.27; H, 4.15; Br, 20.72.

(b) NBA Method

The glycoside **3** (93 mg) was completely brominated after 30 min at room temperature. The solid product obtained upon work-up (P) exhibited n.m.r. signals at τ 4.30 and 4.48 in an intensity ratio of 15:85. Column chromatography as described under (*a*) furnished **15** (12.6 mg, 11%) melting at 65–67° and **14** (82 mg, 71%) melting at 119–120°. Identity of the products with those obtained under (*a*) was confirmed by their i.r. spectra.

Methyl 4,6-O-Benzylidene-3-chloro-2,3-dideoxy-3-nitro-β-D-xylo-hexopyranoside (16)

The nitro glycoside **4** (177 mg) was chlorinated in methanol (45 ml) with hypochlorite solution (1.8 ml) at room temperature for 20 min. According to t.l.c. (solvent D) the reaction appeared complete after 10 min. Work-up (E) gave a syrup which was converted into a solid (182 mg, 92%) by dissolution in ethanol and careful addition of water; m.p. 48–49°, $[\alpha]_D$ +18.2°, ν_{max} 1565 cm^{-1} (NO_2).

Anal. Calcd. for $C_{14}H_{16}ClNO_6$ (329.7): C, 51.10; H, 4.89; Cl, 10.77. Found: C, 51.06; H, 4.80; Cl, 10.82.

Methyl 4,6-Di-O-acetyl-3-chloro-2,3-dideoxy-3-nitro-β-D-xylo-hexopyranoside (17)

Debenzylidenation (reaction time 1 h) and subsequent acetylation of **16** (330 mg) was performed as described for the conversion **9** → **10**. The syrupy product was crystallized from cyclohexane to give **17** (192 mg, 65%), m.p. 90–91°, $[\alpha]_D$ +27.5°, ν_{max} 1745 (shoulder at 1760) and 1570 cm^{-1} ($OCOCH_3$ and NO_2).

Anal. Calcd. for $C_{11}H_{16}ClNO_8$ (325.7): C, 40.60; H, 4.95; Cl, 10.86. Found: C, 40.76; H, 5.05; Cl, 10.81.

Methyl 4,6-O-Benzylidene-3-bromo-2,3-dideoxy-3-nitro-β-D-xylo-hexopyranoside (18)

The glycoside **4** (60 mg) was brominated by the NBA method at room temperature. The reaction was complete (t.l.c.) after 15 min and work-up (P) gave **18** (65 mg, 96%) as a white, amorphous powder; $[\alpha]_D$ +22°, ν_{max} 1565 cm^{-1}.

Anal. Calcd. for $C_{14}H_{16}BrNO_6$ (374.2): C, 45.05; H, 4.31; Br, 21.35. Found: C, 45.03; H, 4.12; Br, 21.35.

Methyl 4,6-O-Benzylidene-3-chloro-2,3-dideoxy-3-nitro-α-D-xylo-hexopyranoside (19) and -α-D-lyxo-hexopyranoside (20)

A solution of the glycoside **5** (250 mg) in methanol (30 ml) was treated with hypochlorite solution (2 ml) at room temperature for 2 h. The t.l.c. (solvent D) indicated formation of a major product and a faster moving, minor product. Work-up (E) furnished a syrup (240 mg, 85.5%) whose n.m.r. spectrum displayed two methine proton signals, τ 4.28 and 4.42, with an intensity ratio 14:86. The two products were separated by passage through a column of silica gel (20 g) using solvent D as eluant.

The faster moving fraction gave the α-D-*lyxo* isomer **20** (35 mg, 12.5%) which crystallized from ethanol–water; m.p. 122–123°, $[\alpha]_D$ +126°, ν_{max} 1570 cm^{-1}. The mass spectrum of **20** (mol. wt. 329.74) exhibited an intense molecular ion peak at *m/e* 329. An isotopic distribution pattern conforming to a chloro derivative was observed, A strong peak at *m/e* 298 likely resulted from loss of

OCH_3, and less prominent peaks at *m/e* 223 and 192 were attributed to loss of C_6H_5CHO from the molecular ion and the aforementioned fragment. Another strong peak was at *m/e* 180.

The slower chromatographic fraction furnished the α-D-*xylo* isomer **19** (188 mg, 67%) which was also crystallized from ethanol–water; m.p. 101–102°, $[\alpha]_D$ +128°, ν_{max} 1565 cm^{-1}. Its mass spectrum also showed a molecular ion peak at *m/e* 329, and the fragmentation pattern was quite similar to that of **20** except for a medium intense peak at *m/e* 177 which was practically absent in the latter.

Anal. Calcd. for $C_{14}H_{16}ClNO_6$ (329.7): C, 51.10; H, 4.89; Cl, 10.77. Found: C, 51.04; H, 4.83; Cl, 10.79.

*Methyl 4,6-O-Benzylidene-3-bromo-2,3-dideoxy-3-nitro-α-D-xylo-hexopyranoside (**21**) and -α-D-lyxo-hexopyranoside (**22**)*

(a) Br_2 Method

The glycoside **5** (200 mg) in methanol (30 ml) was treated for 5 min with aqueous 0.1 *N* sodium hydroxide (6.8 ml). Bromine was then added dropwise in slight excess, and the reaction was allowed to proceed for another 10 min. Work-up (P) gave a crude solid (220 mg, 98%) which showed two spots, both faster than **5**, on t.l.c. with solvent A. The n.m.r. spectrum exhibited methine proton signals at τ 4.28 and 4.41 with an intensity ratio 25:75. The products were separated on a silica gel column (20 g) by elution with solvent A.

The faster moving product obtained from the column was the α-D-*lyxo* isomer **22** (41 mg, 21%), m.p. 105–106°, $[\alpha]_D$ +140.5° (*c*, 0.3), ν_{max} 1565 cm^{-1}. The mass spectrum showed intense molecular ion peaks at *m/e* 373 and 375 in accord with the composition $C_{14}H_{16}BrNO_6$. Less intense peaks were present at *m/e* M − 31, probably due to loss of OCH_3. A single peak of medium intensity was observed at *m/e* 262 and may have resulted from loss of HBr and OCH_3.

The second product eluted from the column was the α-D-*xylo* isomer **21** (156 mg, 69%); m.p. 103–104°, $[\alpha]_D$ +112.5°, ν_{max} 1565 cm^{-1}. Its mass spectrum was very similar to that of isomer **22** but showed an intense peak at *m/e* 221 which was not given by the latter.

Anal. Calcd. for $C_{14}H_{16}BrNO_6$ (374.2); C, 45.05; H, 4.31; Br, 21.35. Found: C, 45.02; H, 4.14; Br, 21.63.

(b) NBA Method

A 60-mg sample of **5** was brominated by NBA. The crude material obtained upon work-up (P) was identical to that obtained under (*a*) according to t.l.c. (solvent A) and n.m.r. spectroscopy, the spectrum showing an intensity ratio 22:78 for the τ 4.28 and 4.41 signals and being otherwise identical with that of the previous product mixture.

*Methyl 4,6-O-Benzylidene-3-bromo-2,3-dideoxy-3-nitro-β-D-ribo-hexopyranoside (**24**)*

The glycoside **23** (200 mg) was brominated by the NBA method at reflux temperature for 1 h. Work-up (P) afforded **24** (222 mg, 87%) as a white amorphous powder; $[\alpha]_D$ −26.2°, ν_{max} 1560 cm^{-1}.

Anal. Calcd. for $C_{14}H_{16}BrNO_6$ (374.2): C, 45.05; H, 4.31; Br, 21.35. Found: C, 45.19; H, 4.23; Br, 21.31.

*Bromination of Methyl 4,6-O-Benzylidene-3-deoxy-3-nitro-β-D-mannopyranoside (**26**)*

(a) Br_2 Method

A mixture of the glycoside **26** (311 mg) in methanol (25 ml) and aqueous 0.1 *N* sodium hydroxide (12.5 ml) was stirred in an ice water bath for 10 min. Bromine was added as in previous examples, and stirring at 0° was continued for 10 min. Work-up (P) gave a white solid material (319 mg) which exhibited four n.m.r. signals in the methine proton region (τ 4.23, 4.32, 4.42, and 4.49; intensity ratios 5:10:35:50). The t.l.c. (solvent A) showed one major spot having the same mobility as the nitro glucoside **25**, one slightly faster moving spot representing new product(s), and a weak, slow-moving spot having the mobility of starting material **26**. The mixture was chromatographed on silica gel (20 g) with the solvent A. All fractions were examined by t.l.c. and pooled appropriately. The fast-moving material (120 mg, $[\alpha]_D$ −39.8°, ν_{max} 1565 cm^{-1}) that was eluted first appeared homogeneous on t.l.c. but was revealed to be a mixture by its n.m.r. spectrum (methine proton signals at τ 4.42 and 4.23 in the ratio 85:15). The major component was assumed to be *methyl 4,6-O-benzylidene-3-bromo-3-deoxy-3-nitro-β-D-allopyranoside* (**27**), and the minor component, its β-D-*altro* isomer **28**.

Continued elution gave some mixed fractions which were discarded, and then a fraction containing pure **25** (93 mg) which was identified with an authentic sample by comparison of n.m.r. and i.r. spectra, t.l.c. and an undepressed mixture m.p. of 180–181°. A subsequent chromatographically uniform fraction gave starting material (**26**) which was identified similarly (mixed m.p. 194–196°, undepressed).

(b) NBA Method

The glycoside **26** (415 mg) was brominated for 1 h in refluxing methanol (40 ml) with NBA (200 mg) in the presence of sodium acetate (4 ml of a saturated aqueous solution). Work-up (P) gave a white solid (507 mg, $[\alpha]_D$ −35.5°) that appeared uniform on t.l.c. (various solvents) but showed two methine proton signals, at τ 4.42 and 4.23 in the intensity ratio 80:20. The i.r. spectrum was identical with that of the chromatographically purified mixture of **27** and **28** described under (*a*). A similar mixture was obtained by reaction with NBA for 5 h at room temperature.

(c) With N-Bromosuccinimide

Substitution of this reagent (71 mg) for NBA in the above reaction gave a product (106 mg, from 103 mg of **26**) whose n.m.r. spectrum was superimposable on that of the aforementioned mixture of **27** and **28**.

*Bromination of Methyl 4,6-O-Benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (**25**)*

Compound **25** (415 mg) was brominated with NBA as just described for **26**. After 1 h a small amount of **25** remained and a strong, faster moving product spot was observed on t.l.c. (solvent A). This picture did not change upon continued refluxing of the mixture for another 5 h. Work-up (P) gave a crude material (457 mg, $[\alpha]_D$ −41.2°) whose n.m.r. spectrum exhibited three methine proton signals, τ 4.22, 4.41, and 4.48, in the ratio 15:75:10. Except for some minor signals the spectrum was closely similar to that of the mixture of **27** and **28** obtained from

26, and the same was true for the i.r. spectrum. In view of these similarities and of the similar $[\alpha]_D$-value and t.l.c. pattern it was concluded that the product consisted of **27** and **28** (contaminated by some starting material).

Application of the Br_2 method as described for **26** gave no product after a reaction time of 15 min at 0°; a minute trace of product seemed to appear after 30 min at 25° (t.l.c. with solvent A). Unchanged **25**, m.p. 180°, was isolated in high yield.

Methyl 2-O-Acetyl-4,6-O-benzylidene-3-bromo-3-deoxy-3-nitro-β-D-allopyranoside (29)

(a) From the 2-Acetate 31

Compound **31** (200 mg) was brominated by the NBA method with a reaction time of 3 h at room temperature. Work-up (P) afforded 234 mg (95.5%) of a solid that was uniform in t.l.c. (solvent G) and upon recrystallization from ethyl acetate – petroleum ether afforded pure **29** (197 mg); m.p. 223–225°, $[\alpha]_D$ −69°, ν_{max} 1755 and 1570 cm^{-1} ($OCOCH_3$ and NO_2).

Anal. Calcd. for $C_{16}H_{18}BrNO_8$ (432.3): C, 44.50; H, 4.20; N, 3.24; Br, 18.45. Found: C, 44.58; H, 4.28; N, 3.09; Br, 18.70.

(b) From the Mixture of 27 and 28

A mixture (150 mg) of **27** and **28** originating from bromination of **26** (see earlier) was dissolved in methylene chloride (6 ml) and chilled (0°). To a cold solution of triethylamine (1.93 ml) in dry ether (30 ml) was added acetyl chloride (1.04 ml). The reagent, from which triethylammonium chloride precipitated copiously, was magnetically stirred at 0° for 5 min before the glycoside solution was added. The mixture was stirred for 30 min at 0° and then agitated briefly with cold water. Upon phase separation the aqueous layer was extracted twice with ether. The combined organic layer and extract was washed with three portions of water, dried over Na_2SO_4, and evaporated. The residue gave two spots on t.l.c. (solvent A), the faster spot being much stronger than the slower one. The n.m.r. spectrum showed signals in the region of τ 4.30–4.50 (methine proton and H-2 of **29**) and in the region of 4.10–4.20 (methine proton and H-2 of **30**) in an intensity ratio 80:20. Column chromatography of the mixture on 20 g of silica gel with solvent A led to isolation of the fast-moving component (117 mg, 70.5%) which according to its i.r. spectrum and m.p. 222–224° was identical with **29** described under (*a*). The slower component eluted from the column proved to be the isomer **30** (see the subsequent section).

Methyl 2-O-Acetyl-4,6-O-benzylidene-3-bromo-3-deoxy-3-nitro-β-D-altropyranoside (30)

(a) From the 2-Acetate 32

Compound **32** (150 mg) was brominated with NBA for 1 h at room temperature. Work-up (P) gave crude **30** (174 mg, 95%), m.p. 140–142°, $[\alpha]_D$ −76.2°. Upon recrystallization from ethanol–water the data were m.p 152–153°, $[\alpha]_D$ −80.8°, ν_{max} 1775 and 1565 cm^{-1}.

Anal. Calcd. for $C_{16}H_{18}BrNO_8$ (432.3): C, 44.50; H, 4.20; Br, 18.45. Found: C, 44.43; H, 4.30; Br, 18.64.

(b) From the Mixture of 27 and 28

The slow-moving product obtained from the column (see the preceding section) weighed 24.5 mg (15%), melted at 149–151°, and gave an i.r. spectrum identical with that of **30** from (*a*).

Attempted Bromination of α-D-Glucosides 34 and 35

Compound **34** (311 mg) and NBA (150 mg) were refluxed for 10 h in a mixture of methanol (30 ml) and saturated sodium acetate solution (3 ml). The t.l.c. gave no evidence for product formation, and work-up (P) led to recovery of **34** (242 mg, 78%), m.p. 166–167°, which was identified by its n.m.r. spectrum.

The 2-acetate **35** (100 mg) was similarly treated, with proportionate amounts of reagents, for a period of 3.5 h at room temperature. Upon work-up, 96 mg of unchanged **35**, m.p. 196–197°, was recovered.

Application of the Br_2 method to **34** (as described for **26**) gave no evidence for product formation (t.l.c. with solvent A) after 15 min at 0°, nor after 30 min at 25°. Unchanged **34**, m.p. 166–167°, was recovered.

Bromination of Methyl 4,6-O-benzylidene-3-deoxy-3-nitro-α-D-mannopyranoside (36)

The glycoside **36** (200 mg) was treated with an excess of NBA (400 mg) in refluxing methanol. Inspection by t.l.c. (solvent C) indicated that reaction had taken place but remained incomplete after 3 h; the pattern was essentially unchanged after 4 h. Work-up (P) then gave a white solid (213 mg) which t.l.c. showed to be not uniform but to contain at least one spot that moved faster than the starting material. Some of the latter appeared to be present also. The i.r. band attributable to the asymmetric stretching vibration of the nitro group was split, with one peak being at 1565 and the other at 1550 cm^{-1}. This suggested the presence of bromonitro and nitro sugars in the mixture. The n.m.r. spectrum of the material exhibited four methine proton signals at τ 4.24, 4.34, 4.43, and 4.48. By integration the first signal was seen to constitute 33%, and the last signal, 25% of the total intensity. The two intermediate signals integrated together (42%); however, the one at τ 4.43 could visually be judged to make the greater contribution by far. The signals at τ 4.34 and 4.48 were assigned to residual starting compound **36** and its α-D-*gluco* isomer **34**, respectively. The signals at τ 4.24 and 4.43 were tentatively attributed to *methyl 4,6-O-benzylidene-3-bromo-3-deoxy-3-nitro-α-D-altropyranoside* (**38**) and its α-D-*allo* isomer (**39**). No attempt was made to separate the products, but the presence of bromonitro sugars to an extent of over 50% was shown by the generation of an epoxide as will be described later on.

Methyl 2-O-Acetyl-4,6-O-benzylidene-3-bromo-3-deoxy-3-nitro-α-D-altropyranoside (41)

The 2-acetate **40** (100 mg) was brominated with NBA at room temperature for 2 h. Work-up (P) produced a crystalline material (103 mg, 85%); m.p. 152–153°, $[\alpha]_D$ +12.3°, ν_{max} 1760 and 1570 cm^{-1}. The n.m.r. data in Table 1 together with further observations ($J_{1,2} \sim 0$ Hz; disappearance of the H-3 quartet of **40**) were in accord with structure **41**. The microanalysis was not wholly satisfactory although it did indicate the presence of 93% of the expected amount of bromine in the sample. Instability of the compound resulting in loss of bromine during preparation and storage of the analytical sample might be an explanation.

Anal. Calcd. for $C_{16}H_{18}BrNO_8$ (432.3): C, 44.50; H, 4.20; Br, 18.45. Found: C, 45.97; H, 4.57; Br, 17.12.

Reactions of Halonitro Glycosides

Borohydride Reductions

For reductive debromination (11), sodium borohydride was added to the ethanolic solution of the bromonitro sugar at room temperature unless specified otherwise. Amounts of reagents and reaction times are given below. For work-up the reaction mixture was slightly acidified with *N* acetic acid, diluted with water, and partially evaporated under reduced pressure to remove most of the ethanol. The product began to separate in crystalline form during this operation; it was collected, washed with water, and dried, and it normally proved pure after one recrystallization from ethanol–water or as specified.

*(a) **1** from **7**.* Compound **7** (200 mg) and $NaBH_4$ (80 mg) in ethanol (40 ml) were allowed to react for 5 min in an ice-water bath. The product (128 mg, 80%), m.p. 174–175°, proved identical with an authentic sample of **1** (lit. m.p. 175° (23), 177–178° (18)) by its i.r. spectrum and on t.l.c. (solvent B). The t.l.c. also suggested the presence of a trace of epoxide **8**.

*(b) **2** from **11**.* Compound **11** (100 mg) and $NaBH_4$ (50 mg) in ethanol (20 ml) were allowed to react for 30 min at 25°. Identity of the product **2** (71 mg, 90%) with an authentic sample was established by comparison of i.r. spectra and an undepressed mixture melting point of 232° (lit. m.p. 230–231° dec. (19), 232° (21)).

*(c) **3** from **14**.* Compound **14** (170 mg) and $NaBH_4$ (80 mg) in ethanol (35 ml) were allowed to react for 10 min at 25°. Upon recrystallization from ethyl acetate – petroleum ether the product **3** (131 mg, 97%) was identical with an authentic sample according to i.r. and n.m.r. spectra; m.p. 165–167° (lit. m.p. 166–167° (18)).

*(d) **3** from **15**.* Compound **15** (20 mg) upon similar debromination gave **3** (12 mg, 75%) that was identified by its i.r. spectrum; m.p. 165–167°.

Alkaline Debromination and Epoxide Formation

*Methyl 2,3-anhydro-4,6-O-benzylidene-3-nitro-α-D-talopyranoside (**8**)*

*(a) From **1** via **6**.* The epoxide **8** was produced when the chlorination of **1** (see the preparation of **6**, above) was carried out at room temperature rather than at 0°. Thus, when **1** (62 mg) in methanol (15 ml) was treated with hypochlorite solution (0.6 ml), t.l.c. (solvent B) showed a single, faster moving spot (presumably **6**) after a reaction time of 15 min, and this spot was replaced by a slower spot corresponding to **8** after 35 min. Work-up (P) including recrystallization from ethanol–water gave **8** (50 mg, 81%), m.p. 215–216°. Its identity with known **8** was established by comparison of i.r. and n.m.r. spectra; lit. (10), m.p. 215–216°.

*(b) From **7**.* To a solution of **7** (35 mg) in methanol (2 ml) were added a few drops of aqueous *N* sodium hydroxide, and the mixture was stirred at 25° for 15 min during which time a white solid separated. Dilution with water and partial evaporation of the mixture afforded 25 mg (90%) of crystalline **8**, m.p. 214–215°.

*(c) From **15**.* Compound **15** (95 mg) was dissolved in methanol (30 ml) to which 1 ml of alcoholic, *N* sodium hydroxide was added. The slow generation of a product having the mobility of **8** was noticed on t.l.c. (solvent D) after a few hours, and the reaction appeared nearly complete after 10 h. The reaction mixture was diluted with water, and methanol was removed by evaporation whereby crystalline if slightly impure **8** (54 mg, 72%) was produced; m.p. 208–210°, $[\alpha]_D$ +89.0°; lit. $[\alpha]_D$ +91.8° (10).

*(d) From **14**.* When **14** was treated with base as under (*c*) it was recovered unchanged even after a prolonged time of exposure (20 h). However, when a sample (30 mg) in methanol (5 ml) together with 0.1 *N* sodium methoxide (1 ml) was heated to reflux for 20 min, reaction did take place to give a major, unidentified product of very low mobility (t.l.c. with solvent C) along with a minor product moving like **8**. Work-up as under (*c*) furnished crystalline **8** (6 mg, 25%), m.p. 213–215°, that was identified also by its i.r. spectrum. The unidentified material remained in the aqueous mother liquor.

*Debromination of **11***

A solution of **11** (50 mg) in ethanol (2 ml) was treated with 0.3 ml of aqueous *N* potassium hydroxide at room temperature. After 30 min all **11** had disappeared and a product having the mobility of **2** was formed (t.l.c. with solvent D). The reaction mixture was diluted with ethanol (10 ml), rapidly deionized by cation exchange, and immediately tested with potassium iodide – starch which produced a blue color. Evaporation of the solution and recrystallization of the residue from ethanol–water gave **2** (24 mg, 62%), m.p. and mixed m.p. 230–232°.

To a solution of **11** (80 mg) in methanol (5 ml) was added 0.1 *N* sodium methoxide in methanol (2 ml). After being refluxed for 20 min the reaction mixture was revealed by t.l.c. (solvent D) to contain a major, very slow-moving product beside some starting material. Dilution of the mixture with water caused **11** (16 mg) to separate; it was identified by its i.r. spectrum. The major reaction product could not be identified, but since a smell of benzaldehyde was noticed it likely was a degradation product. There was no chromatographic evidence for epoxide formation. (2,3-Anhydro glycosides of this type generally move faster than the corresponding 2-hydroxy derivatives.)

*Methyl 2,3-anhydro-4,6-O-benzylidene-3-nitro-β-D-mannopyranoside (**33**)*

*(a) From **30**.* Compound **30** (64.8 mg) was refluxed for 30 min in 0.035 *N* methanolic sodium methoxide solution (8 ml). The cooled solution was deionized with a cation exchange resin, diluted with water, and partially evaporated to remove methanol. A smell of benzaldehyde was noted. White crystals of **33** separated and were washed with water and dried (17 mg, 37%). The melting point, 179–180°, was raised to 182–183° by recrystallization from ethyl acetate – petroleum ether; $[\alpha]_D$ −68.4°. Microanalytical and spectral characterization of the product has been recorded (10).

*(b) From **29**.* Compound **29** (52 mg) gave **33** (15 mg, 40%) in the manner described under (*a*); m.p. 178–180°. The products were identical according to t.l.c., i.r., and n.m.r. spectra.

*(c) From mixtures of **27** and **28***

A mixture of **27** and **28** (60 mg; obtained from bromination of **26**) in methanol (5 ml) was refluxed for 30 min after addition of 0.1 *N* sodium methoxide solution (1.5 ml). Work-up as under (*a*) gave **33** (40 mg, 84%), m.p. 181–182°, identified also by its i.r. spectrum. A similar experiment using a mixture of **27** + **28** originating from

bromination of **25** gave **33**, m.p. 181–182°, in a yield of 78%.

Methyl 2,3-anhydro-4,6-O-benzylidene-3-nitro-α-D-mannopyranoside (37)

*(a) From **41**.* Compound **41** (65 mg) was refluxed for 30 min in 0.035 *N* methanolic sodium methoxide solution (8 ml). Upon cooling and dilution with water the reaction mixture deposited a voluminous precipitate of **37** which was collected, washed with water, and dried (38 mg, 82%). It melted at 173–174° and its i.r. spectrum was identical with that of **37** prepared by an independent method; lit. m.p. 173–174° (10).

*(b) From mixtures of **38** and **39**.* Eighty milligrams of the mixture of products obtained in the bromination of **36** and presumed to contain **38** and **39** was boiled for 20 min in 7 ml of 0.03 *N* sodium methoxide solution. The product obtained upon work-up and two recrystallizations from ethanol weighed 32.5 mg and proved identical with authentic **37** by an undepressed mixture m.p. 171–173°, and by its i.r. spectrum.

Similarly, a sample (60 mg) of the product of low-temperature deacetylation of **41** (see below) was heated in refluxing methanol (5 ml) and 0.1 *N* sodium methoxide solution (1.5 ml) for 30 min. Cooling and dilution with water gave a precipitate of **37** (36 mg, 76%), m.p. 172–173° (undepressed upon admixture of an authentic sample).

Deacetylation Accompanied by Epimerization

*(a) Reaction of **30**.*

To a solution of the β-D-*altro* acetate **30** (65 mg, 0.15 mmol) in methanol (5 ml) was added 0.30 mmol of sodium methoxide (3 ml of a 0.1 *N* solution). The mixture was allowed to stand at room temperature for 30 min after which time t.l.c. (solvent C) revealed absence of **30** and showed a single, slower spot. Deionization by cation exchange resin, dilution with water, and partial evaporation furnished a white solid (48 mg, 82%) showing $[\alpha]_D$ −38.2°. An n.m.r. spectrum exhibited two methine proton signals at τ 4.41 and 4.22, intensity ratio 80:20. The spectrum was virtually superimposable on those of the mixtures of **27** and **28** obtained in various brominations of **26** (see earlier). Since separation of the products was not possible, the mixture was acetylated by the acetyl chloride – triethylamine method (see the preparation of **29** from **27** + **28**). The solid mixture of acetates obtained was recrystallized twice from ethyl acetate – petroleum ether to give pure β-D-*allo* isomer **29** (34.5 mg, 65%), m.p. 223–225°. The identity of the product with **29** was confirmed by comparison of n.m.r. and i.r. spectra and by t.l.c. (solvent A).

When the above experiment was repeated with the use of only 0.15 mmol of $NaOCH_3$ and a reaction time of 1 h at 0°, the isolated product (52 mg) contained a small amount of unreacted **30** which could be removed by chromatography on silica gel (solvent C) and identified (m.p. 149–151°; i.r. spectrum). The main material eluted from the column (37 mg) was practically identical with previously obtained mixtures of **27** and **28** (product ratio, 85:15).

*(b) Reaction of **41***

To a solution of acetate **41** (86.4 mg, 0.2 mmol) in methanol (10 ml) was added 0.4 mmol of $NaOCH_3$ (4 ml of a 0.1 *N* solution). After 1 h at room temperature a seemingly uniform, more slowly moving product was formed (t.l.c., solvent A). Work-up (P) after 3 h gave a white solid (71 mg, 91%) which according to its i.r. spectrum (ν_{max} 3380 and 1560 cm^{-1}, OH and NO_2) was free from acetyl. The n.m.r. spectrum showed methine proton signals at τ 4.24 and 4.43, and corresponding OCH_3 signals at τ 6.61 and 6.55, tentatively assigned to **38** and **39**, respectively (ratio 4:6). Attempts to separate the products failed. The mixture (150 mg, from repeat experiments) was then acetylated with acetyl chloride and triethylamine in methylene chloride. (See the preparation of **29** from **27** + **28**.) Work-up afforded a solid material (153 mg) which appeared homogeneous on t.l.c. (various systems), having the same mobility as **41**. However, the n.m.r. spectrum revealed the product to be a mixture. The benzylidene methine signals overlapped with H-2 signals and therefore could not be analyzed, but there were two distinct singlets for *O*-acetyl protons, at τ 7.97 and 7.88 (intensity ratio 35:65; total intensity, 3H) which were tentatively attributed to **41** and its α-D-*allo* isomer **42**. Attempts to separate the mixture were unsuccessful.

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