Conformational Preference and Configurational Equilibria of the Methyl 3-Deoxy-3-nitro-pentopyranosides and their Nitronates[1]

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The conformations of four methyl 3-deoxy-3-nitropentopyranosides and their sodium nitronates in aqueous solution were examined by n.m.r. spectroscopy, and the results are explained by calculation of free energies of non-bonded interactions. It is shown that protonation of glycoside nitronates is a kinetically controlled process. The β-epimerization of nitronates was investigated, and relative thermodynamic stabilities of epimers were determined and correlated with conformations. The non-bonded interaction between the nitronate grouping and an adjacent, equatorial hydroxyl group ($A^{(1,3)}$ effect) must be associated with a free energy in excess of 2 kcal/mol. The influence of this effect upon conformational and configurational equilibria in glycoside nitronates and upon nitromethylene acidity is emphasized. The compounds were found to differ in their behavior during early stages of the β-epimerization reaction, which was linked to differential nitromethylene acidities. Mechanisms for the reaction are discussed.

On a déterminé en solution aqueuse et par r.m.n., les conformations de quatre méthyl déoxy-3 nitro-3 pentopyranosides et de leurs nitronates de sodium; on explique les résultats obtenus à l'aide de calculs d'énergie libre d'intéractions non liées. On démontre que la protonation des nitronates de glycosides est un processus contrôlé cinétiquement. On a de plus étudié l'épimérisation β des nitronates; on a déterminé les stabilités thermodynamiques relatives des épimères et établi une corrélation avec les conformations. On doit considérer que l'intéraction non liée entre le groupe nitronate et un groupe hydroxyle équatorial voisin (effet $A^{(1,3)}$) amène une contribution de plus de 2 kcal/mol à l'énergie libre. On met en relief l'influence de cet effet sur l'équilibre conformationnel et configurationnel des nitronates de glycosides et sur l'acidité des groupes nitrométhylènes. On a trouvé que, suivant l'acidité des groupes nitrométhylènes, la réactivité des divers composés varie dans les stades préliminaires de la réaction d'épimérisation β. On discute des mécanismes de la réaction.

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Introduction

The nitromethane cyclization of L′-methoxydiglycolaldehyde (**1**) and its D′ enantiomer (**1***)[2] (1–3), and many further applications of this reaction which have recently been reviewed (4), have provided facile access to a large body of nitrogenous carbohydrates. In the course of these investigations a stereochemical rule has emerged that concerns the liberation of 3-deoxy-3-nitroaldopyranosides (and analogous 4-deoxy-4-nitro-ketopyranose derivatives) from their *aci* salts, in which process a new center of asymmetry is created. The configuration adopted, usually to the exclusion of the epimeric alternative, is that which possesses an equatorial nitro group in the favored chair conformation. Thus, for example, in methyl D-hexopyranosides with their innate preference for the C_1^4 chair, products having the D-*gluco*, D-*manno*, D-*galacto*, and D-*talo* configurations are obtained, whereas corresponding β-1,6-anhydro sugars locked in the C_4^1 conformation give rise to products having the D-*allo*, D-*altro*, D-*gulo*, and D-*ido* configurations (4). One puzzlement of long standing has been the seemingly exceptional behavior of methyl 3-deoxy-3-*aci*-nitro-β-D-*erythro*-pentopyranoside sodium (**2**), the main product in the nitromethane cyclization of **1**, which on acidification gave both 3-epimers, with methyl 3-deoxy-3-nitro-β-D-ribopyranoside (**6**) unexpectedly preponderating strongly over the β-D-*xylo* isomer **7** (2). Methyl 3-deoxy-3-*aci*-nitro-α-L-*threo*-pentopyranoside sodium (**3**) produced the α-L-arabinopyranoside **8**, whereas the β-D-*threo* nitronate **4** gave the β-D-arabinopyranoside **9**; in other words,

[1]Part XIX of a series on the reactions of nitro sugars. For part XVIII see ref. 22.

[2]Occasional reference is made herein to optical antipodes of some of the compounds depicted. They are indicated by starred numbers, and mirror image formulas are dispensed with. The conformational symbols used in this article are explained in ref. 23.

opposite configurations were engendered at C-3 in these two nitronates (3). The 3-epimers of **8** and **9**, *i.e.* the corresponding *lyxo* derivatives **10** and **11**, were not encountered.

In order to shed light on these stereochemical problems, and also to explore further the factors which govern epimeric product composition in the formation and base-catalyzed epimerization of sugar nitronates, we have now examined by n.m.r. spectroscopy the aforementioned methyl deoxynitropentosides and their sodium salts. For the purpose of this study the β-D-*xylo* isomer **7**, which had previously been shown to exist but had not been isolated, was prepared in crystalline form for the first time, as were also the β-L-*xylo* and β-L-*ribo* enantiomers **7*** and **6***.

Results and Discussion

Conformation of the Glycoside Nitronates

Contrary to earlier assumptions (2), which were based on the tenets of conformational analysis prevailing at a time when the importance of certain non-bonded interactions had not yet been realized and the benefits of n.m.r. spectroscopy were not widely available, we now have found that the β-D-*erythro* nitronate **2** does not prefer the C_1^4 chair conformation (**2***a*). All the coupling constants for the ring protons H-1, -2, and -4 are small (Table 1), indicating absence of vicinal, *trans*-diaxial orientations and therefore ruling out the C_1^4 form which would possess two pairs of protons so oriented. The spectral data are consistent with the inverted, C_4^1 chair conformation (**2***b*), which we believe describes best the molecule in its ground state even though three axial substituents are present.[3]

The α-L-*threo* isomer **3** possesses one pair of vicinal, *trans*-diaxial protons in either chair conformation (**3***a* and *b*). However, the n.m.r. spectrum shows only small couplings in the H-1, -2, and -4 proton signals (Table 1), thus ruling out both chair forms, and it therefore appears that we are dealing with one of the unusual cases where a skew conformation can be postulated for a monocyclic pyranoside. Inspection of models leaves little choice but the S_1^5 form (**3***c*), which is consistent with the spectrum.[4]

The spectrum of the β-D-*threo* isomer **4** also exhibits only small couplings in the H-1, -2, and -4 signals, indicating absence of vicinal *trans*-diaxial protons. While this feature eliminates conformation **4***a* from consideration, it is compatible with the inverted chair **4***b* but also with a skew form, S_1^5 (**4***c*).

Relative Thermodynamic Stabilities of the Glycoside Nitronates

As had earlier been shown (3), mainly by polarimetry and chromatography, the three sodium nitronates **2**, **3**, and **4** spontaneously equilibrate, in aqueous solution, by epimerizing at C-2 and -4. At equilibrium, which is reached at room temperature within several hours, the β-D-*erythro* isomer **2** was found to predominate strongly over the *threo* isomers **3** and **4**. We have now confirmed this by n.m.r. spectroscopy, the chemical shifts and intensities of the methoxyl proton signals affording a convenient means of differentiating components, and of determining their ratios, in mixtures of the isomers. As the equilibration reaction progressed, starting from whichever nitronate, a fourth methoxyl signal appeared, at lowest field. We assign it to the fourth possible stereoisomer, the α-L-*erythro* nitronate **5**, which had hitherto escaped detection. A typical spectrum of an equilibrium mixture is depicted in Fig. 1, and the results of various experiments are recorded in Table 2. The differences in free energy calculated from the equilibrium constants show that **2** is more stable than its stereoisomers by approximately 0.8–1.0 kcal/mol. The differences between the three less stable compounds are slight, but **5** quite consistently appears to have the lowest stability.

[3]The chair may be assumed to be slightly flattened due to the sp^2 hybridization of C-3, which relieves somewhat the *syn*-diaxial hydroxyl interaction strain. The molecule could thus *approach* the half-chair form **2***c* (which would still agree with our n.m.r. data), but there is no reason for assuming a very great departure from the C_4^1 chair.

[4]A referee has suggested that the n.m.r. data of **3** may be interpreted in terms of "a rather strongly distorted chair form". Strong distortion so as to approach the half-chair HC_4^5 would in fact be consistent, and a definitive assignment is not implied. However, the half-chair would suffer from eclipsing of the C-2 and -3 bonds whereas rotation about the $C_{(2)}$–$C_{(3)}$ axis produces **3***c*, in which these bonds are staggered, without very much affecting the positions of the hydroxyl groups relative to the nitronate group. We therefore believe the skew form to be more likely (see also footnote 6) but, in the subsequent discussion, the only point that really matters is the fact that the compound obviously does not assume one of the normal chair forms.

TABLE 1. The n.m.r. data of sodium nitronates in D_2O

Compound	Chemical Shifts (τ)*						Couplings (Hz)			
	H-1	H-2	H-4	H-5	H-5′	OCH_3	$J_{1,2}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$
2	5.32	5.38	5.52	6.18	6.35	6.73	1.5	2	1.5	12
3	5.28	5.37	5.54	6.17	6.33	6.62	2	<1	<1	11
4	5.22	5.29	5.48	6.08	6.41	6.66	2.5	3	3	12.5
5						6.57				

*Measured with reference to acetone (τ = 7.91) as internal standard.

TABLE 2. Configurational equilibration of nitronates at room temperature, as determined by n.m.r. spectroscopy

Starting nitronate	Equilibrium mixture (percentage figures obtained from OCH_3 peak intensities)			
	2	**3**	**4**	**5**
2	65	14	14	7
	60	14	15	11
3	59	15	13.5	12.5
	57	17	15	11
4	64	14	11	11
Mean	61	14.8	13.7	10.5

$K_{2/3} = 4.12$, whence* $-\Delta G^\circ_{2/3} = 0.84$ kcal/mol
$K_{2/4} = 4.45$, $-\Delta G^\circ_{2/4} = 0.88$
$K_{2/5} = 5.80$, $-\Delta G^\circ_{2/5} = 1.04$

*From $-\Delta G^\circ = RT \ln K = 1.36 \log K$.

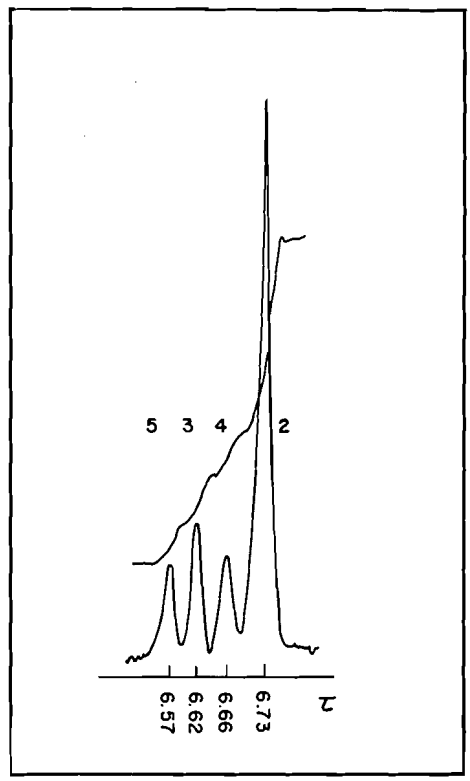


FIG. 1. The n.m.r. spectrum (60 MHz, with 100 Hz sweep width) of the methoxyl signal region of sodium nitronates at epimeric equilibrium in D_2O.

With this information on hand, the conformational preferences displayed by the nitronates may be discussed in terms of free energies of non-bonded interactions. Experimental values recorded for conformational free energies of substituents on six-membered rings show considerable scattering (5*a*, 6), and some arbitrariness is therefore inherent in the choice of certain parameters for calculations. Nevertheless, a reasonable picture has been presented of the conformational preferences in cyclitols, hexopyranosides, and pentopyranosides (5*b*, *c*). We are using the same approach and are adopting recent improvements which have been described in great detail by Angyal (7). Accordingly, we employ the following values (in kcal/mol) for non-bonded interactions: between an axial hydroxyl or methoxyl group and one *syn*-axial hydrogen, 0.45; between two *syn*-axial hydroxyl groups, 1.5; between adjacent, diequatorial hydroxyl (or methoxyl) groups, 0.35; for the anomeric effect of the methoxyl group in aqueous solution, 1.05; increment to the anomeric effect if 2-OH is axial, 0.45 (Δ2 effect). Unknown at the outset was the magnitude of the interaction between the nitronate grouping and an adjacent hydroxyl. When the latter is axial, its dihedral angle with the C=N bond is about 120°, and interaction can be assumed to be negligible; but when it is equatorial, the dihedral angle is close to 0°, and substantial strain will exist. This condition is an example of the more general $A^{(1,3)}$ effect (8), and an energy term (*A*) must be added whenever it occurs. Table 3 contains the calculated, total interaction energies for the two chair forms of each of the four nitronates, and by

TABLE 3. Calculated energies of non-bonded interaction in nitronates

Compound (Configuration)	Conformation	kcal/mol
2 (β-D-*erythro*)	**2***a*	1.4+2*A*
	b	1.95
3 (α-L-*threo*)	**3***a*	1.85+*A*
	b	0.9+*A*
4 (β-D-*threo*)	**4***a*	2.30+*A*
	b	1.25+*A*
5 (α-L-*erythro*)	**5***a*	3.35
	b	0.8+2*A*

relating these data with our experimental findings it became possible to derive at least a minimum estimate for the *A* term and to demonstrate the importance of the $A^{(1,3)}$ effect in the stereochemical behavior of nitro glycosides.

From the fact that compound **2** preponderantly exists in the conformation **2***b* one may deduce for **2***a* a relative energy excess of at least 1 kcal/mol, whence $1.4 + 2A \geqq 1.95 + 1$, or $A \geqq 0.8$ kcal/mol. More revealing is the observation that the free energy of **3** is 0.84 kcal/mol higher than that of **2** (Table 2). From this difference an interaction energy of 2.8 kcal/mol is computed for **3**, based on the value 1.95 for **2** in its prevailing form, **2***b*. Hence if **3** existed as an equilibrium mixture of conformers **3***b* and *a*, and the free energy of such a mixture were given[5] by the expression $(0.8 + A)$ kcal/mol, *A* would equal 2.0 kcal/mol. However, the n.m.r. spectrum showed that **3** does not in fact occupy the chair forms, and therefore one has to conclude that *A* is even larger, perhaps 2.5 kcal/mol or more, causing the energy of **3***b* to exceed markedly that of the skew form **3***c* into which the molecule seems to escape on account of this strain. For although skew forms are not normally adopted by pyranosides, **3***c* is free from $A^{(1,3)}$ strain, thus offering an attractive choice for a molecule which would be severely hindered in either chair form.[6] A similar calculation for the isomer **4**, using the experimentally determined energy difference *vs.* **2** (0.9 kcal/mol, see Table 2) and assuming an equilibrium of conformers **4***b* and *a* in the ratio 86:14 (calculated from Table 3), would result in an *A* value of 1.70 kcal/mol. However a higher value, demanded by the conformational behavior of **3** as just discussed, should apply here too, on the premise that the $A^{(1,3)}$ effects are equal in the chair conformations of both isomers. Since any higher *A* value will make **4***b* (and *a*) less stable than the compound has actually been found to be, in relation to **2**, one is led to postulate that **4***b*, although allowed by the n.m.r. data, is not the preferred conformation but that a skew form, **4***c*, is adopted to a large extent.

These results can be viewed in yet another way. Considering that the calculated energy difference between the most favored chair forms **3***b* and **4***b* is 0.35 kcal/mol, one would expect the isomers to be present, at the epimeric equilibrium, in a ratio of about 2:1 if indeed the chair conformations prevailed. The ratio actually found is different (close to 1:1), suggesting that other conformations are involved.

Finally, the epimeric equilibrium between **2** and what is presumed to be the α-L-*erythro* isomer **5** (Table 2) corresponds to a free energy difference of 1.04 kcal/mol. The preferred conformation of **5** is not known, but in view of the magnitude of the $A^{(1,3)}$ effect it is safe to say that it should be **5***a* even though all the other steric factors work in favor of **5***b* (see Table 3). The difference in interaction energies calculated for the system **2***b* ⇌ **5***a* (1.4 kcal/mol, Table 3) is somewhat higher than the experimental value,[7] but calculation based on **5***b*, using any *A*- value consistent with the other findings, would give much too high a figure.

In summary, the studies have revealed that the $A^{(1,3)}$ effect is the most powerful factor determining preferred conformations and equilibria of epimerization in glycoside nitronates, the interaction energy associated with it certainly exceeding 2 kcal/mol. The order of thermodynamic stabilities, **2** > **3** > **4** > **5**, is as previously

[5]The difference (0.95 kcal/mol) in interaction energies calculated for **3***b* and *a* (Table 3) corresponds to an equilibrium ratio 83:17 for these conformers. By taking into account the entropy of mixing, one finds $0.8 + A$ as the calculated energy value for an equilibrium mixture **3***b* ⇌ **3***a*.

[6]In cyclohexanone, the energy difference between chair and flexible forms is only about one-half that in cyclohexane, allowing skew forms in substituted cyclohexanones to play a significant role (5*d*). A similar situation should pertain in our nitronates.

[7]Agreement would of course be achievable by taking the anomeric effect to contribute 0.35 kcal/mol less energy. Such arbitrary measure, when applied to the isomers **3** and **4**, would affect the results of the previous calculations somewhat but not significantly, in the direction of a higher *A* value.

TABLE 4. The n.m.r. data of nitro glycosides in D_2O

	Chemical Shifts (τ)*							Couplings (Hz)					
Compound	H-1	H-2	H-3	H-4	H-5	H-5′	OCH_3	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$
6	5.14	5.52	5.13	5.68	6.14	6.21	6.67	3	3	3	1.5	1.5	12
7	5.70	5.98	5.45	6.26	6.54	6.68	6.58	9	11	8	1.5	10	9
8	5.75	5.90	5.27†	5.63	6.18	6.25	6.56	7.8	9.5	3.7	2	1.5	12
9	5.22	5.60	5.23	5.62	6.24	6.33	6.72	3.5	10.5	3.5	1.5	1.5	12.5

*Measured with reference to acetone (τ = 7.91) as internal standard.
†The H-3 signal is a quartet whose peaks are slightly broadened presumably because of the small shift between H-1 and -2 giving rise to virtual coupling.

suggested but must be interpreted in the light of this interaction. Whether the effect is primarily of steric or dipolar nature remains open.

Conformation of the Free Nitro Glycosides

Methyl 3-deoxy-3-nitro-β-D-ribopyranoside (**6**) and its β-D-*xylo* (**7**), α-L-*arabino* (**8**), and β-D-*arabino* (**9**) isomers were all found to prefer, in aqueous solution, that chair conformation in which the nitro substituent occupies the equatorial position. This is the C_1^4 conformation for the β-D-*xylo* compound (**7***a*), but the C_4^1 conformation for the others (**6***a*, **8***a*, **9***a*). The ring proton resonances leading to these conclusions are listed in Table 4. In agreement herewith, the signals given by the axial methoxyl groups in **6***a* and **9***a* occur at higher field than those of the equatorial methoxyl groups in **7***a* and **8***a*.

These findings remove the basis for regarding the formation of the β-D-riboside **6** from the β-D-*erythro* salt **2** as a peculiar exception to the general rule of equatorial placement of the nitro group, and this rule is now recognized to hold for the acidification of all known 3-deoxy-3-nitro-aldopyranosides and structurally analogous keto-pyranosides and sugar anhydrides. The conformations **7***a*, **8***a*, and **9***a* come as no surprise as they are the same as those preferred by the corresponding, non-nitro parent glycosides, but the case of **6***a* is worthy of special note. β-D-Ribopyranose favors the C_1^4 chair (9), although the inverted chair is populated to a considerable degree (7). Methyl β-D-ribopyranoside had long been assumed to exist in the C_1^4 chair form (10), but recent n.m.r. data indicate that the two chair forms have about equal stability (7), and this is ascribed to a somewhat greater anomeric effect of the methoxyl group compared to that of the hydroxyl group. An analogous situation pertains in β-D-ribopyranose tetraacetate in acetone solution (11). Only further enhancement of the anomeric effect, as experienced by tri-*O*-acetyl-β-D-ribopyranosyl halides in chloroform, causes strong predominance of the C_4^1 form (12). Substitution by a nitro group of the axial hydroxyl on C-3 in methyl β-D-ribopyranoside (in the C_1^4 form) evidently compels chair inversion with similar strength.[8] The conformational free energy of the nitro group in the nitrocyclohexane system has been determined (6) to be 1 kcal/mol, but this value (which refers to a nonaqueous medium) barely exceeds the 0.9 kcal/mol associated here with an axial hydroxyl, in opposition to two axial hydrogens, and would be unable to account for the observed effect.[9] An appreciably higher value must apply in our nitro glycosides in water, which could be due to increased bulk owing to hydration, or to dipolar interaction with the ring oxygen.

Stereochemistry of Acidification of Nitronates

At this point it is interesting to discuss, in the light of the preceding considerations, the stereochemical course of the acidification of the nitronates **2**, **3**, and **4**. Let us compare the relative, thermodynamic stabilities calculated for the two 3-epimeric nitro glycosides that can theoretically arise from each nitronate. The interaction energies for the favored conformers (*i.e.* those having an equatorial nitro group) are listed in Table 5.

[8]The n.m.r. spectra of **6** in D_2O (Table 4) and in $CDCl_3$ exhibited virtually identical splitting patterns, indicating that the predominant conformation (**6***a*) was, within observable limits, no less populated in the former solvent than in the latter. The extra stabilization that **6***a* may be afforded in a nonpolar solvent due to an increased anomeric effect and the possibility of intramolecular hydrogen bonding between the *syn*-axial hydroxyl groups is, therefore, not required for its preponderance.

[9]In fact, by equating the interaction of an axial nitro group and two opposing hydrogen atoms with 1 kcal/mol, one would obtain equal energies for the two chair forms of **6**, assuming that the *gauche*, nitro–hydroxyl interactions are the same.

TABLE 5. Calculated, partial* energies of non-bonded interaction in conformers having an equatorial nitro group

Compound (Configuration)	kcal/mol
6*a* (β-D-*ribo*)	2.4
7*a* (β-D-*xylo*)	1.75
8*a* (α-L-*arabino*)	2.20
10*a* (α-L-*lyxo*)	1.35
9*a* (β-D-*arabino*)	1.70
11*a* (β-D-*lyxo*)	2.65

*Less *gauche* nitro-hydroxyl interactions; see text.

Where applicable in these computations, the anomeric effect was assigned a value of 1.4 kcal/mol (rather than 1.05 kcal/mol as in Table 3), the higher value applying to methanolic solutions (5*e*).[10] The figures do not include the contributions by *gauche* interactions of the nitro group with its neighboring hydroxyls; the energy associated therewith is unknown but may be disregarded as it should be equal in any two 3-epimers and will therefore cancel in their free energy difference. Now it is seen that the β-D-riboside (**6***a*), the major product obtained from **2**, is considerably less stable than the β-D-xyloside (**7***a*) which was obtained as a minor product only. Similarly the α-L-arabinoside (**8***a*), which arose from the salt **3**, is less stable according to these calculations than its 3-epimer, the α-L-lyxoside (**10***a*), which has not been detected as a product. It is therefore concluded that the acidification of **2** and **3** is kinetically controlled. The same is presumably true for the acidification of **4**, although in this case the product, namely the β-D-arabinoside (**9***a*), represents the more stable epimer. Angyal and Luttrell have recently reported (14) that, in the analogous acidification of 2-*aci*-nitrocyclohexan-1,3-diol, kinetic control is not achievable because epimerization at the nitro carbon is too rapid. Obviously this does not apply to the nitro sugars, and as far as **6** and **7** are concerned we have noticed no mutual interconversion of these epimers in aqueous solution, neutral or acidic.

Evidently, the predominant path for protonation of the salt **2** is approach from the less hindered, upper side of the favored conformer **2***b*. Protonation of **2***b* from the opposite side, to give the minor product **7**, is disfavored for one or both of two reasons, namely, hindrance from the hydroxyl groups and resistance of the nitro group against being placed axially. Protonation of the conformer **2***a* should lead to **7** more readily, but since **2***a* can be present only in small proportion, **7** is relegated to the role of a by-product. As for the *threo* salts **3** and **4**, inspection of molecular models of the likely conformations **3***c* and **4***c* suggests that steric impediments to proton approach are not much different on either side, but it reveals that the direction which leads to the respective *arabino* configuration is that which avoids transitional placement of the nitro group in the unfavorable, axial position. One may thus infer, from the observed stereoselectivity in these protonations, that the structure of the transition state resembles the product and not the nitronate; for if it resembled the latter, appreciable selectivity would not be expected.[11]

Mechanism of β-*Epimerization*

To explain epimerizations at carbon atoms adjacent to the nitromethylene group, as well as some other base-catalyzed reactions involving those β-carbons, intermediate α-nitroalkene structures have been postulated, and the role of such intermediates has been substantiated by experimental evidence in several instances (16–20). Accordingly it is thought that $\Delta^{2,3}$- and $\Delta^{3,4}$-unsaturated nitro glycosides are intermediates in the epimerizations **2** ⇌ **3** ⇌ **4** ⇌ **5**. We have been able to isolate a small amount of an unsaturated material by column chromatography of the mixture of **6*** and **7*** that was obtained upon deionization of the β-L-*erythro* nitronate **2*** (see footnote 2). The i.r. spectrum of the syrupy material showed a strong peak at 1528 cm^{-1} indicating a nitroalkene grouping. The n.m.r.

[10]For preparative purposes the liberation of the nitro glycosides from their *aci* salts has been performed in this work and earlier (3, 13) by the action of a cation exchange resin in methanol, which superseded the original procedure (2) of acidification with potassium bisulfate in the dry state.

[11]During this writing there appeared extensive studies by Bordwell and Yee (15), presenting evidence for product-like transition states in the protonation of cycloalkanenitronates.

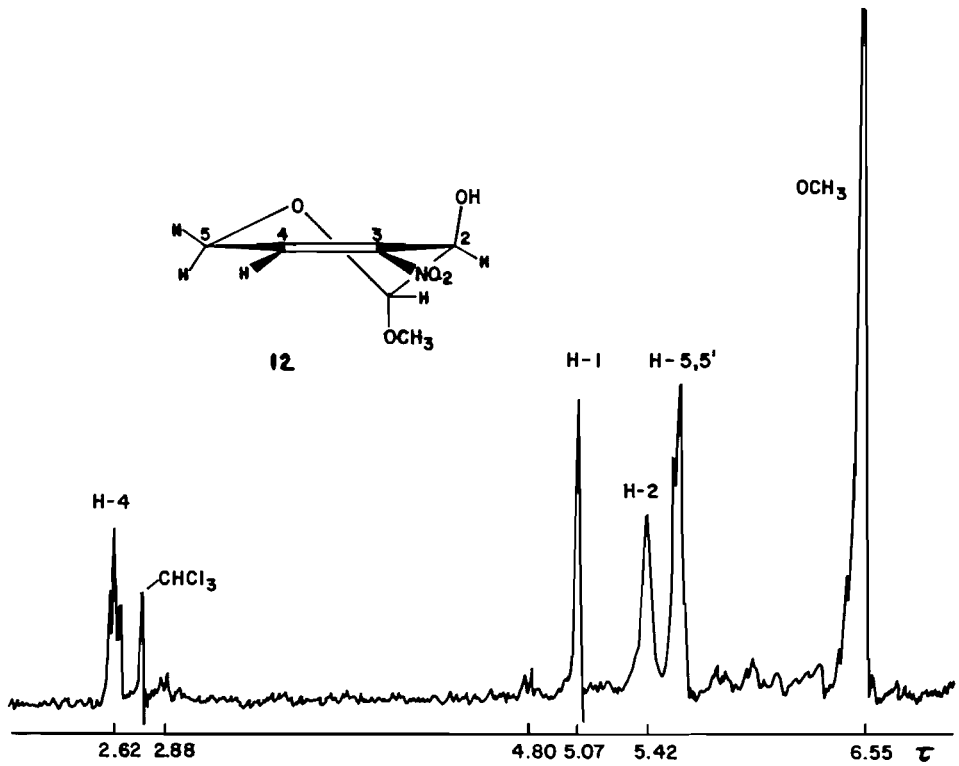


FIG. 2. The n.m.r. spectrum (100 MHz in $CDCl_3$) of nitro olefin **12**.

spectrum (Fig. 2) revealed that the product was not entirely uniform. The major component was characterized by a low-field triplet attributable to an olefinic proton which was coupled with two vicinal protons and must, therefore, be situated on C-4. The two one-proton signals assigned to H-1 and -2, respectively, appeared as singlets due to very small vicinal coupling. The spectrum fits the structure of methyl 3,4-dideoxy-3-nitro-β-L-*glycero*-pent-3-enopyranoside (**12**) in the conformation depicted. The weak doublets observed at τ 4.80 and 2.88 are probably due to the olefinic and anomeric protons of the corresponding, $\Delta^{2,3}$-unsaturated isomer. The minor component amounted to about 15% of the product.

The nitro olefins so obtained arose by acid-catalyzed dehydration of **6*** and(or) **7***, and it does not necessarily follow that they are involved in the epimerizations which occur in weakly basic medium. However, the fact that dehydration can take place under mild conditions, albeit to a limited extent, seems significant. It was shown, moreover, that **12** meets at least one requirement for being an intermediate in the epimerization. When placed in aqueous alkali (1 equiv), the olefin instantly added base to give nitronate, and the addition was found to be faster than the epimeric nitronate equilibration. An n.m.r. spectrum scanned from 1–5 min after the start of the reaction indicated that the olefin had already disappeared, giving mainly **2*** along with some **4*** (the latter presumably originating from the minor component in the olefin). There was only a trace of **3*** at this point, but its proportion increased with time as the proportion of **2*** decreased. These observations may be interpreted in terms of a rapid setting-up of a mobile equilibrium **2*** $\rightleftharpoons$ **12** in which **2*** preponderates vastly (so that **12** is not seen in the spectrum), and through which **3*** is formed in a relatively slow reaction.

Whereas the findings just described lend support to the mechanism of reversible dehydration

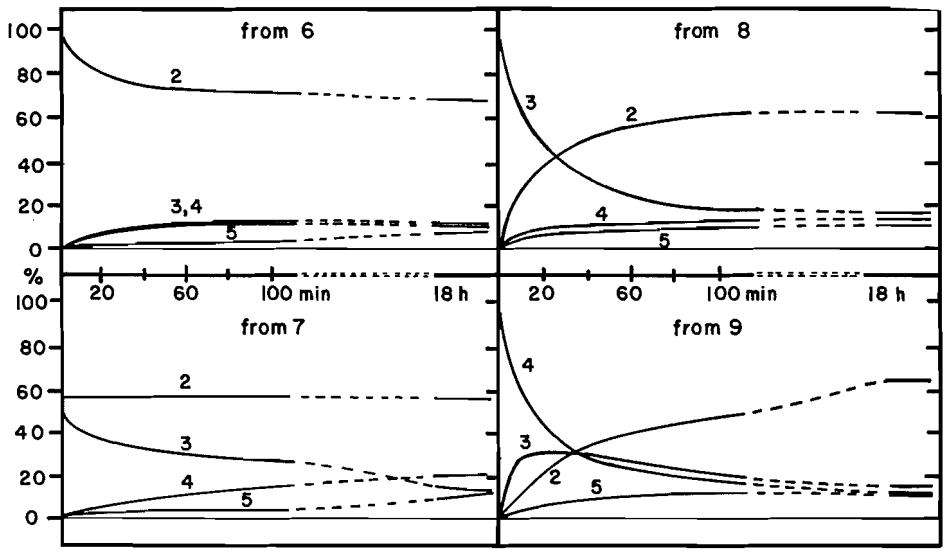


FIG. 3. Time-dependent change in composition of glycoside mixtures during alkaline epimerization.

for the β-epimerization of **2** (and hence, **6**), an unexpected behavior exhibited by the nitro xyloside **7** in alkaline solution requires that a second mechanism be assumed to operate, at least in part, in the epimerization of this compound. Even though the reaction eventually leads to the expected equilibrium mixture of nitronates, it differs in early stages from the alkaline epimerization of the nitro riboside **6**. Upon addition of an equivalent amount of alkali, **6** is rapidly converted into its salt **2**, and no other product is visible in the n.m.r. spectrum for several minutes until the epimeric salts slowly emerge (Fig. 3). Since the salt **2** is common to the 3-epimers **6** and **7**, it might have seemed obvious to expect precisely the same sequence of events to occur with **7**. Contrary to expectations, addition of alkali to **7** produced the salt **2** *and* the salt **3** practically simultaneously (*i.e.*, within the 2 min needed for recording a spectrum), in a ratio of about 1:1. Thereafter followed slow equilibration, with formation of the remaining nitronate epimers and with a final ratio of about 4:1 in respect of **2** and **3** (Fig. 3; compare also Fig. 1). The change in optical rotation during this reaction also was in agreement with an "initial" formation, not of **2** alone but of **2** and **3** in about equal amounts (Fig. 4). Clearly, the large proportion of **3** observed near the start of the reaction must be due to a fast epimerization that occurs in **7**

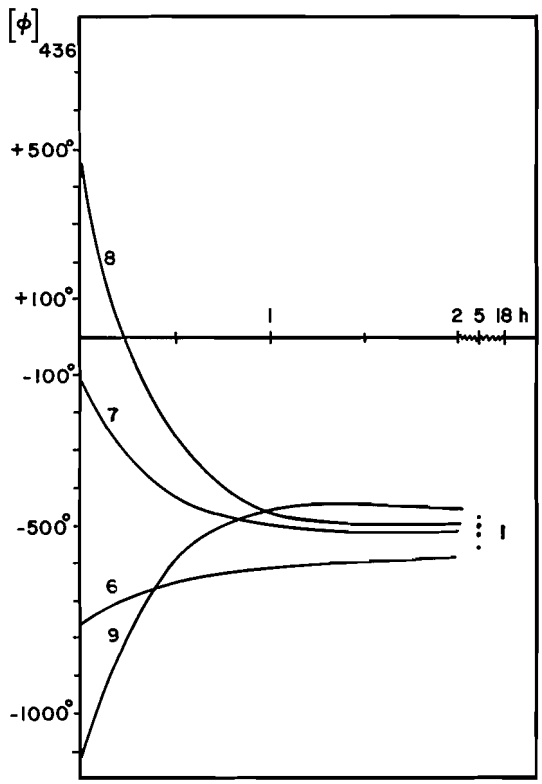
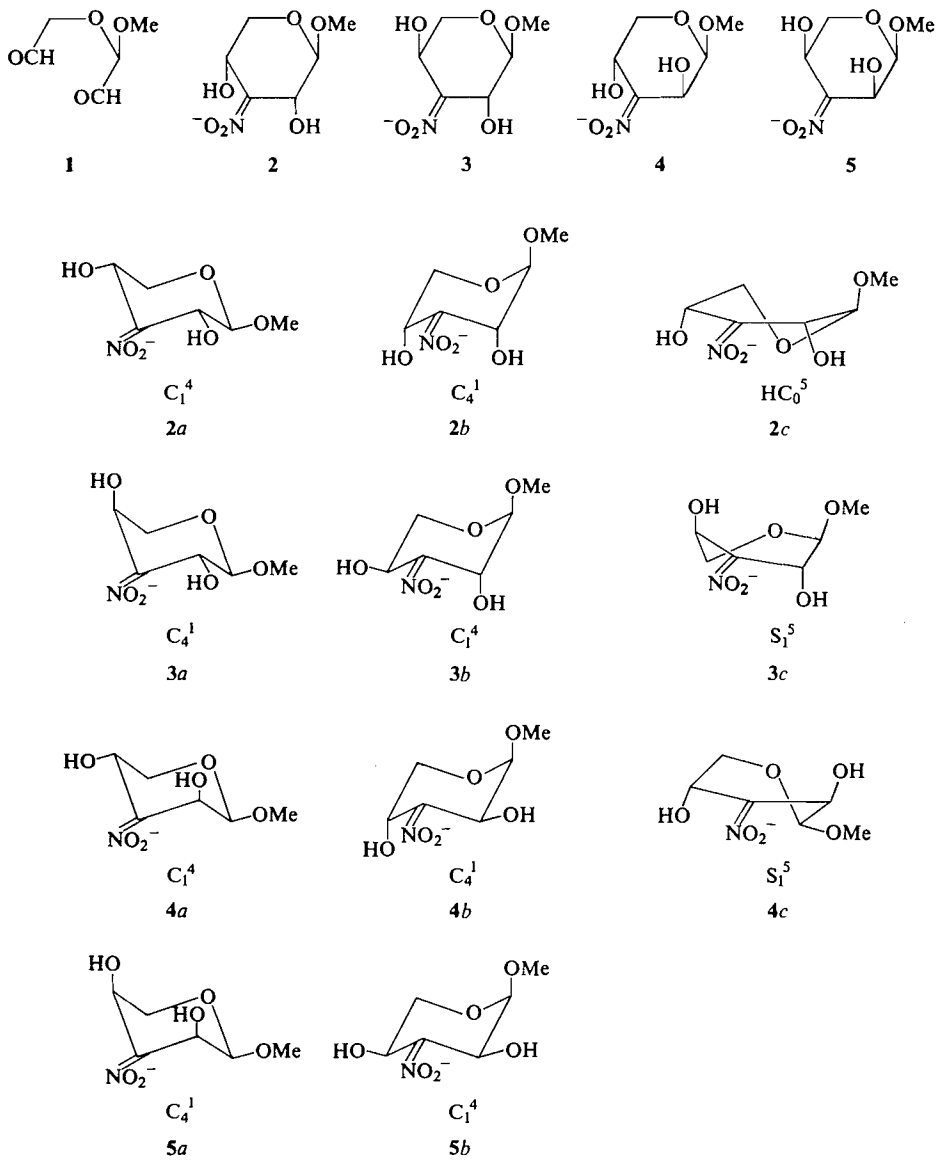
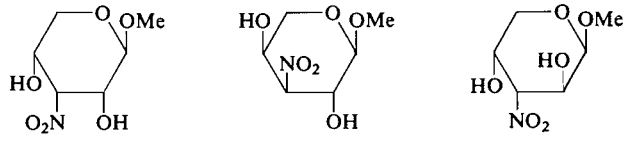


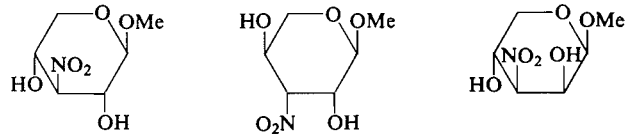
FIG. 4. Change of molecular rotations $[\Phi]_{436}$ of nitro glycosides in alkaline medium.



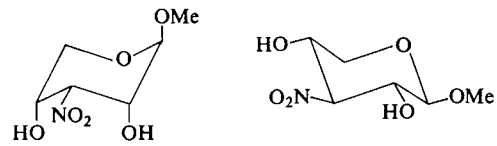
and does not proceed via **2**. Another phenomenon apparently related herewith was observed in the alkaline epimerization of the β-D-arabinoside **9**. In an early stage of this reaction, too, the nitronate **3** was produced in an amount larger than corresponded to the final equilibrium proportion. Its initial rate of formation was greater than that of **2** concurrently formed, but the rates then reversed, and that part of **3** which constituted a temporary excess over the equilibrium disappeared slowly (Fig. 3). It has thus become understandable that **9**, in the presence of alkali, displays a *complex* "mutarotation", a fact which had been recorded but not commented upon earlier (3). The results suggest that a mechanism other than the reversible dehydration to nitroalkene is involved at least in part of the over-all epimerization. For if only the dehydration mechanism were available, all **3** engendered from **9** (or its salt **4**) would of necessity have to arise via **2** (or via **5**), which evidently is not the case. A clue to an understanding of the epimerizations



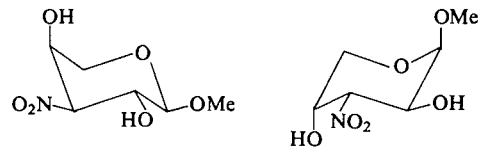
6 8 9



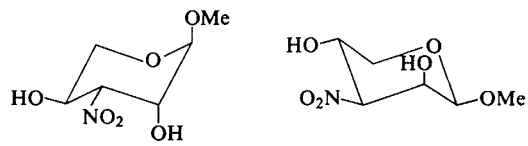
7 (10) (11)



6*a* 7*a*



8*a* 9*a*



(10*a*) (11*a*)

came forth when the pK_a values of the nitro glycosides were compared. Table 6 shows p*H* values measured (at zero time) upon half-titration, and while some of these data may be apparent rather than true pK_a values,[12] they nevertheless reflect differential tendencies of nitronate formation. Most conspicuously, the xyloside **7** is a markedly weaker acid than the riboside **6**. This result is in harmony with the conformational free energies of **7***a*, **6***a*, and their common anion **2***b* which, on the basis of the preceding discussions, is expected to arise more readily from the latter than from the former. Now we suggest that **7***a*, having for stereochemical reasons a diminished nitromethylene acidity, is prone to competitive proton abstraction from its hydroxyl groups. Alkoxide formation at position 4 would initiate

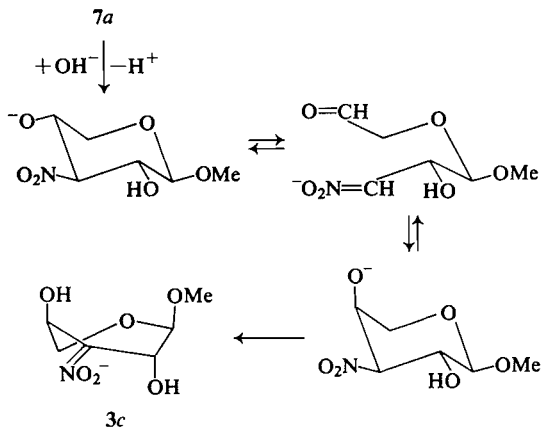
TABLE 6. Acidities of nitro glycosides (by half-titration with NaOH in water)

Compound	p*H**
6	8.40
7	10.15
8	9.20
9	10.00

*Measured at room temperature with a glass electrode immediately after adding 1/2 equiv of base. Changes with time were insignificant within 15 min.

[12] A true value would be expected only if there existed, at the time of measurement, an equilibrium between the given nitro compound and the corresponding *aci* form, unadulterated by the presence of substantial amounts of epimers. This condition seems to be largely fulfilled for **6** and **8**, perhaps less so for **9**, but certainly not for **7**.

ring opening between C-4 and -3 (reverse Henry reaction), and subsequent recyclization would account for the formation of the epimeric nitronate **3** (Scheme 1). A similar if more complicated



SCHEME 1

sequence could be written to explain the formation of **3** from the relatively weak acid **9** without intermediacy of **2** (Scheme 2). Although reversible ring opening was invoked by Grosheintz and Fischer (21) to explain epimerization in deoxynitroinositols, those investigators did not consider alternative pathways via nitroolefins, nor did they advance proof for the mechanism. The nitroolefin route is certainly available as long as the nitromethylene group, rather than a vicinal carbinol group, is the site of base-induced ionization. This condition can ordinarily be presumed to apply.[13] However, when steric factors reduce the nitromethylene acidity, as they do in **7**, the compound approaches in character a *tertiary*-nitro β-carbinol.[14] Such carbinols, in contrast to those having a primary or secondary nitro group, are known to undergo reverse Henry reaction with facility.

In the light of the results presented in this article, many observations regarding epimerizations and relative thermodynamic stabilities in the hexose analogs (4) become understandable. An example is the predominance of the α-D-*talo* configuration after nitronate equilibration followed by acidification. A comprehensive treatment of the hexose series is under way.

[13]The formation of $\Delta^{4,5}$-unsaturated 3-nitronate (18) is compelling evidence for the presence of $\Delta^{3,4}$-olefins in equilibrium with 3-nitronates.

[14]Other instances of steric diminution of nitromethylene acidity have been discovered by W. Rank in this laboratory and will be dealt with elsewhere.

Experimental

Nuclear Magnetic Resonance Spectra

The spectral data of Table 4 and Fig. 2 were measured on a Varian HA 100 instrument, and those of Tables 1 and 2 and of Figs. 1 and 3 were obtained on a Varian T60 instrument. The values for the nitronates **2**, **3**, and **4** in Table 1 were recorded within 2–3 min of adding an equivalent amount of sodium deuteroxide to solutions of the corresponding nitro glycosides **6**, **8**, and **9** in deuterium oxide. The spectra from which the points of Fig. 3 were derived by measuring methoxyl signal intensities were taken in similar fashion. Epimeric nitronate distributions at equilibrium (Table 2) were calculated from spectra that were taken 18–22 h after the start of the reaction; Fig. 1 is representative.

Optical Rotations

Optical rotations refer to aqueous solutions (*c* approximately 0.5 unless specified otherwise) at room temperature. They were determined in 1-dm tubes in a Perkin–Elmer automatic polarimeter, model 141. The specific rotations at various wavelengths of the free nitro glycosides are shown in Table **7**.

The molecular rotation curves of Fig. 4 were obtained from solutions which were made up by adding equal volumes of 0.02 *N* NaOH to 0.01 *M* solutions of the nitro glycosides. Hence the solutions were 0.05 *M* in nitronate (*c* approximately 0.1) and contained 1 equiv of excess NaOH. The wavelength 436 nm was chosen because large absolute rotations and optimal light intensity resulted in more accurate readings than at other wavelengths.

Materials

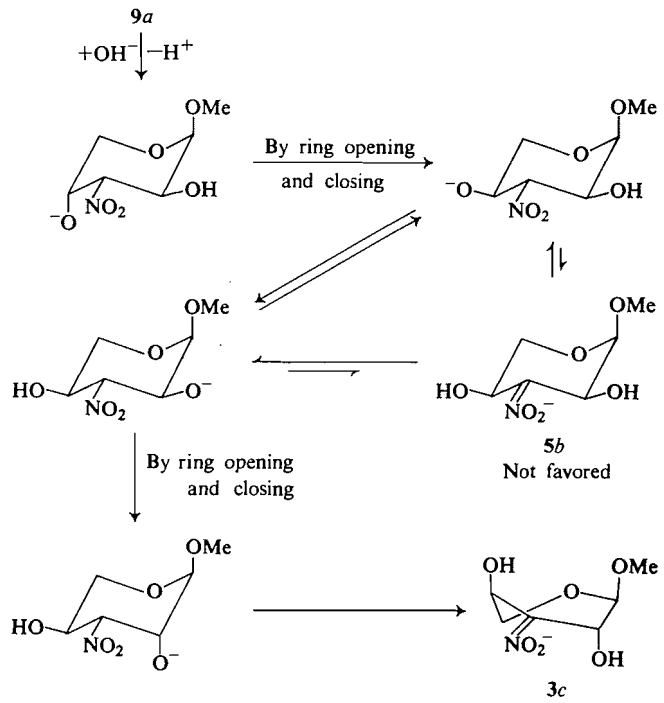
The sodium nitronates **2** and **2*** and the nitro glycosides **8** and **9** were prepared as previously described (refs. 2 and 3, respectively).

The nitronate **2** (0.62 g) was suspended in a mixture of methanol (36 ml) and nitromethane (4 ml), and the suspension was shaken for 5 min with 6 ml of methanol-washed Amberlite IR-120 (H^+), whereby the salt went in solution. Filtration and evaporation of the filtrate furnished a residue which was crystallized from ethyl acetate – petroleum ether (b.p. 30–60°) to give 0.27 g (48%) of *methyl 3-deoxy-3-nitro*-β-D-*ribopyranoside* (**6**), melting as reported (2) at 90–92°. The amorphous residue (0.31 g) obtained by evaporation of the mother liquor was chromatographed on 15 g of silica gel (Merck, 70–325 mesh) with carbon tetrachloride to which increasing amounts of ethyl acetate were added. At an eluent composition 2:1, a crystalline mixture of glycosides was obtained. Recrystallization from ethyl acetate – petroleum ether gave *methyl 3-deoxy-3-nitro*-β-D-*xylopyranoside* (**7**) as shiny needles, m.p. 186–187°, in a yield of 70 mg (13%).

Anal. Calcd. for $C_6H_{11}O_6N$ (193.2): C, 37.31; H, 5.74; N, 7.25. Found: C, 37.21; H, 5.62; N, 7.12.

An additional 17 mg (3%) of **6**, m.p. 92–94°, was obtained from the mother liquor.

In order to identify the product **7**, a sample (21 mg)



SCHEME 2

TABLE 7. Specific rotations of the free nitro glycosides

Compound	λ (nm)				
	589	578	546	436	365
6	−113.5	−118	−134	−226	−375
6*	+116	+120	+133	+227	+373
7	−46.7	−49.6	−57.0	−92.0	−124.3
7*	+48.0	+50.0	+55.5	+91.2	+123
8	+86	+87	+100	+155	+117
9	−273	−285	−323	−578	−635

was catalytically hydrogenated in 11 ml of 0.01 *N* hydrochloric acid in the presence of PtO_2 (30 mg), at 28° and ordinary pressure. Hydrogen consumption was 15 ml (required, 13.5 ml) after 2 h. The solution was then passed through a small column containing 0.5 ml of Dowex 1X2 (OH^-) resin, and was evaporated to give 16 mg of spontaneously crystallizing methyl 3-amino-3-deoxy-β-D-xylopyranoside. It melted at 195–197° after recrystallization from ethanol, undepressed upon admixture of a freshly recrystallized, authentic specimen (2).

The enantiomeric nitronate **2*** was deionized as described above for **2**. Work-up including column chromatography gave *methyl 3-deoxy-3-nitro-β-L-ribopyranoside* (**6***) as soft, granular crystals, m.p. 92–93°, and *methyl 3-deoxy-3-nitro-β-L-xylopyranoside* (**7***) as either feather-like crystals or hard prisms. Both kinds of crystals melted at 186–187°. A chromatographic fraction immediately preceding the fraction of **6*** and **7*** furnished a colorless oil which failed to crystallize although it showed a single spot on t.l.c. (CCl_4–EtOAc, 1:1). It had $[\alpha]_D$ +214, $[\alpha]_{578}$ +224, $[\alpha]_{546}$ +255, $[\alpha]_{436}$ +451° (*c*, 0.4 in water); ν_{max} in chloroform, 3200 (OH) and 1528 cm^{-1} (nitroalkene). The n.m.r. spectrum (Fig. 2) was in agreement with the structure of *methyl 3,4-dideoxy-3-nitro-β-L-glycero-pent-3-enopyranoside* (**12**).

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