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THE SYNTHESIS OF NEW DEOXYNITROINOSITOLS BY CYCLIZATION OF 6-DEOXY-3-*O*-METHYL-6-NITRO-D-ALLOSE AND -L-TALOSE*†

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ABSTRACT

6-Deoxy-3-*O*-methyl-6-nitro-D-allose (**5**) and -L-talose (**6**) were synthesized from 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-allofuranose (**1**) by the nitromethane method *via* their furanoid, 1,2-*O*-isopropylidene derivatives (**2** and **3**). The barium hydroxide-catalyzed cyclization of the free nitrohexoses (**5** and **6**) was investigated. Under conditions favoring kinetic control (pH ~8, 0°), **5** gave mainly 1D-5-deoxy-2-*O*-methyl-5-nitro-*allo*-inositol (**7**), with the 1L-*epi*-1 (**8**) and *epi*-6 (**9**) stereoisomers as minor products. Compound **6** afforded a high yield of the *myo*-5 isomer (**11**); the 1L-*allo*-5 (**13**) and 1D-*epi*-1 (**14**) isomers were formed in small proportions but not isolated. The thermodynamically controlled, mutual interconversion of the stereoisomeric products was studied, as was the formation of nitronate salts and the regeneration of free nitroinositols. Upon immediate acidification, the nitronate obtained from **11** gave **11** and the *neo*-2 epimer (**12**) in a ratio of 2:3. The nitronate produced by **7** underwent rapid β-epimerization. The five isolated deoxynitroinositol monomethyl ethers were further characterized as tetra-acetates (**7a**, **9a**, **11a**, and **12a**) and isopropylidene derivatives (**7b**, **8b**, and **9b**).

INTRODUCTION

The Grosheintz–Fischer synthesis[1] of deoxynitroinositols from 6-deoxy-6-nitrohexoses has recently become a subject of renewed interest focusing on its stereochemical course[2–5]. The 3-methyl[2–4] and 3-benzyl[5] ethers of 6-deoxy-6-nitro-D-glucose and -L-idose were used in our studies, mainly to facilitate product analysis but also to prepare partially blocked deoxynitroinositols as potential intermediates for future syntheses in the inosamine field‡. Much is now known about kinetic and thermodynamic control in the synthesis and cyclization of these nitrohexose

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†Cyclizations of Dialdehydes with Nitromethane: Part XVIII. For Part XVII, see Ref. 5. This work was supported by the National Research Council of Canada (Grant A1350 to H.H.B.).
‡Inosamines (aminodeoxyinositols) having the *scyllo*, *neo*-2, and 1D-*myo*-1 configurations are constituents of the antibiotics bluensomycin[6], hygromycin[7], and minosaminomycin[8], respectively.

derivatives and in the epimerization of the resulting inositols, particularly with regard to the influence of the pH of the reaction media. The method has been applied recently to the synthesis of nitrocycloheptanehexols[9], and Wolfrom's early adaptation to a synthesis[10] of streptamine has been reinvestigated and considerably extended[11].

Having previously described[2–4] the δ-*O*-methylated deoxynitroinositols that possess the *scyllo*, 1D- and 1L-*myo*-1, *muco*-3, and *epi*-3 configurations, we now report the synthesis and some epimeric interconversions of the stereoisomers having the 1D-*allo*-5, 1L-*epi*-1, *epi*-6, *myo*-5, and *neo*-2 configurations*.

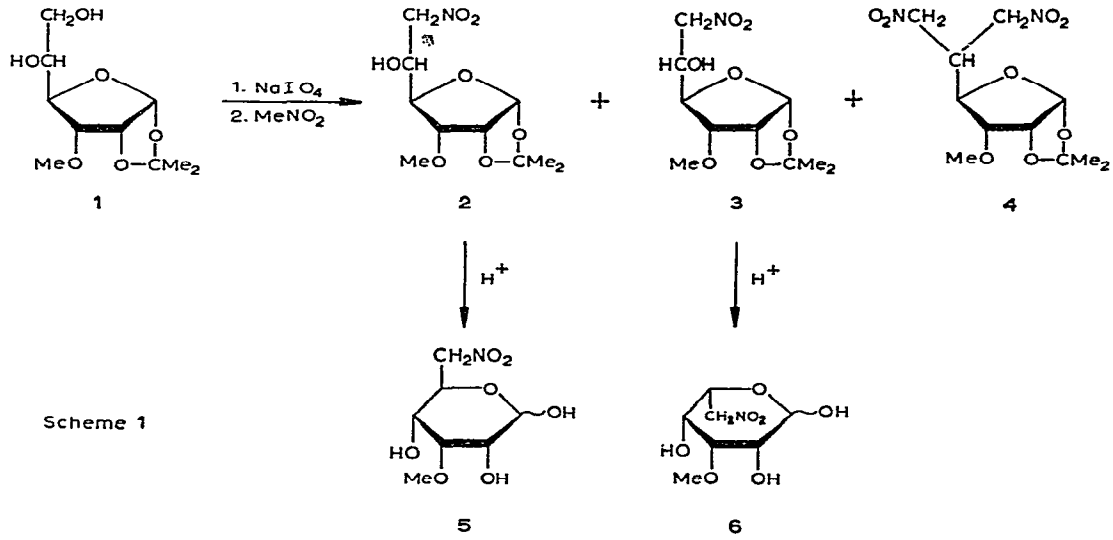
RESULTS AND DISCUSSION

Synthesis of the 6-deoxy-6-nitrohexoses

6-Deoxy-3-*O*-methyl-6-nitro-D-allose (**5**) and -L-talose (**6**) were synthesized according to Scheme 1. Known 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-allofuranose (**1**) was oxidized with sodium metaperiodate, by use of minor modifications of the published procedure[13]. The resulting, crude α-D-*ribo*-pentodialdo-1,4-furanose derivative was allowed to react with nitromethane in the presence of sodium methoxide. The reaction time (18 h) and temperature (25°) were chosen to effect some degree of thermodynamic control[5]. Column chromatography of the crude product furnished crystalline 6-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-6-nitro-α-D-allofuranose (**2**, 17%) and -β-L-talofuranose (**3**, 22%), as well as crystalline mixtures of the two in an over-all ratio 2:3 (30%; yields based on **1**). In addition, there was obtained a small yield (1.5%) of a by-product whose n.m.r. spectrum and elemental analysis accorded with the branched-chain, dinitro structure **4**. Presumably, this compound arose from **2** and (or) **3** by β-elimination of the hydroxyl group, followed by Michael addition of nitromethane to an intermediate nitro-olefin. The configurations of the 5-epimeric main products were readily allocated on the basis of the Cotton effect, which was negative in **2** and positive in **3**, revealing C-5 to have *R* and *S* stereochemistry, respectively[2,14,15]. The compounds gave very similar n.m.r. spectra; the ring-proton coupling constants were close to those found[16] in computer-analyzed spectra of 1,2:5,6-di-*O*-isopropylidene-α-D-allose and -β-L-talose, which indicates that **2** and **3** adopt a furanoid ring conformation similar to that established[16] for these analogs.

Deacetonation of **2** and **3** by trifluoroacetic acid at room temperature gave syrupy **5** and **6**, respectively. These sensitive, free sugars were characterized by their optical rotations and g.l.c. patterns only. The g.l.c. of either (trimethylsilylated) product showed two major peaks which presumably were due to the pyranoid anomers. Compound **6** gave an additional major peak, and both compounds gave minor peaks (intensity 1–3%), which probably originated from furanoid and, possibly, open-chain forms. None of these peaks coincided with those of the inositols

*In short-form expressions such as these, the appended numeral denotes the position of the deoxynitro function in the molecule. Full names are given following the IUPAC-IUB 1973 Recommendations for Cyclitols[12].



Scheme 1

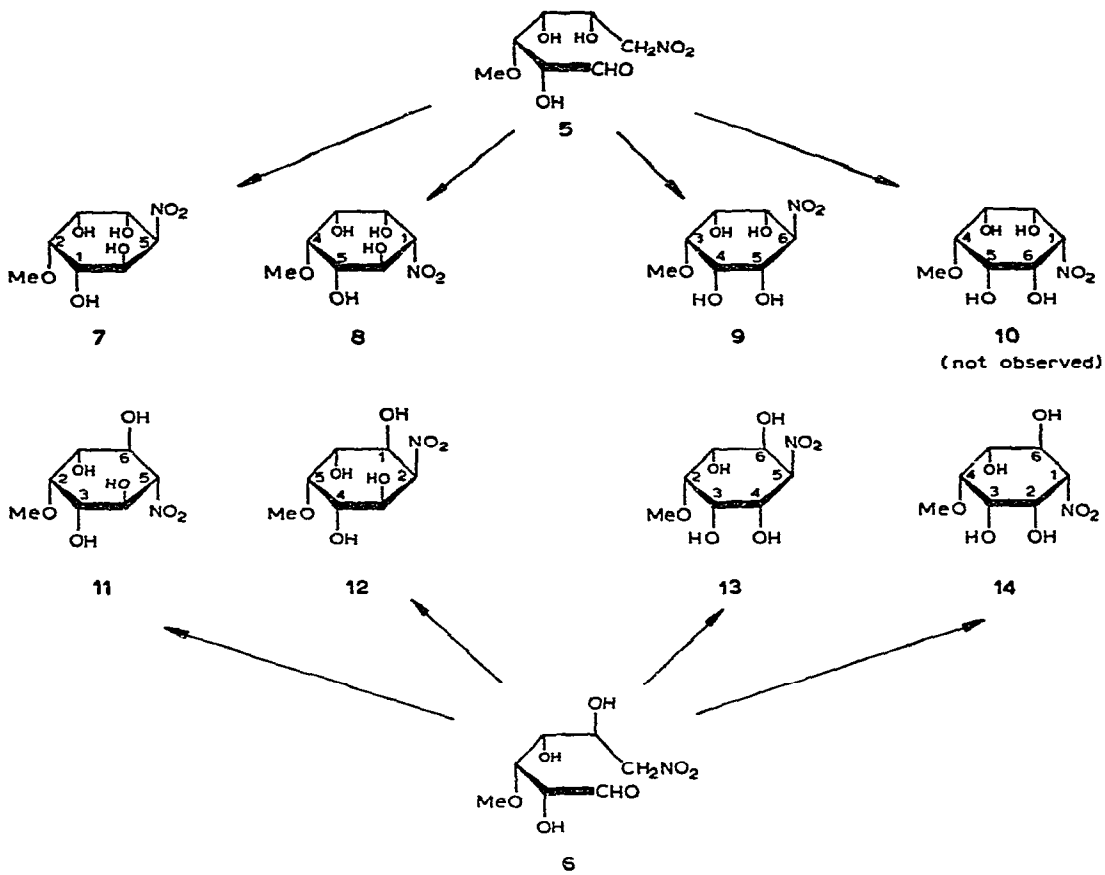
derived from the sugars (see later), and all of them disappeared upon cyclization. However, some samples of **5** and **6** also gave small peaks (intensity 2–4%) that represented inositol derivatives. Cyclization, which occurs with remarkable ease above pH 7, appears to proceed slowly even in neutral to slightly acidic medium during processing and storage of the free sugars*. Therefore, no attempts at purification were made and crude **5** and **6** were used without delay.

Cyclizations

When a given 6-deoxy-6-nitrohexose cyclizes by internal nitroalkane–aldehyde addition, two new chiral centers are generated, at C-1 and C-6 of the hexose, and four stereoisomeric products are theoretically possible. This statement presupposes that C-5 of the original hexose (or the corresponding carbon atom in any of the products) does not suffer epimerization, a proviso which may be expected to hold when the reaction is kinetically controlled. The nitroinositols **7–10** and **11–14** so deriving from the D-*allo* (**5**) and L-*talo* (**6**) sugars, respectively, are depicted in Scheme 2. It is seen that **9–12** have achiral *meso* structures, whereas the remaining four isomers are chiral. If thermodynamic equilibration intervenes, all eight isomers may be formed from either hexose, with the enantiomeric pairs **7/13** and **8/14** emerging as racemates. Some of the products may, of course, be disfavored for steric reasons, so that the number observable or isolable may be reduced.

In the account that follows, the results of cyclization experiments will be described first, and proof for the configurations assigned to the products will be given in a subsequent section. Component ratios in reaction mixtures could be determined

*This is reminiscent of the marked instability of L-*ido* analogs, which tend to cyclize spontaneously in the absence of alkali[5,11,17].



Scheme 2. **7**, 1D-5-deoxy-2-*O*-methyl-5-nitro-*allo*-inositol; **8**, 1L-1-deoxy-4-*O*-methyl-1-nitro-*epi*-inositol; **9**, 6-deoxy-3-*O*-methyl-6-nitro-*epi*-inositol; **10**, 1-deoxy-4-*O*-methyl-1-nitro-*cis*-inositol; **11**, 5-deoxy-2-*O*-methyl-5-nitro-*myo*-inositol; **12**, 2-deoxy-5-*O*-methyl-2-nitro-*neo*-inositol; **13**, 1L-5-deoxy-2-*O*-methyl-5-nitro-*allo*-inositol; **14**, 1D-1-deoxy-4-*O*-methyl-1-nitro-*epi*-inositol.

with an accuracy of ±1% by g.l.c., the trimethylsilylated products being well-separated, except for **8** and **9** which have identical retention times.

The course of the cyclization of **5** at 0° in aqueous solution at pH 7–8 is shown in Table I. A strong increase in dextrorotation occurred during the first 5 h and then levelled off. Although 5% of **5** still remained after 23 h, the reaction at that point was interrupted by acidification in order to minimize secondary interconversions. (Previous work[3–5] had shown that these are conditions appropriate to achieving kinetic control.) The main product (~72% of the inositols formed) was the 1D-*allo*-5 isomer (**7**), and the *epi* isomers **8** and **9** together constituted ~26% of the inositols. In addition, a small proportion (2%) of an unidentified component was present. It had the relative retention time of **11**, and may indeed have been **11** originating from a small amount of **6** contaminating **5** or, less likely under the conditions, from

TABLE I

CYCLIZATION OF 6-DEOXY-3-*O*-METHYL-6-NITRO-D-ALLOSE BY $Ba(OH)_2$ AT pH 7–8 AND 0°

Time (h)	$[\alpha]_{436}^{23}$ *(degrees)*[a]	*Composition (%) by g.l.c.*[a]				
		Hexose	**7**	**8+9**	**11**	**12**
0[b]	+1	99	—	~1	—	—
5 min	+11	73	20	7	—	—
0.5	+21	66	26	8	trace	—
1	+30	58	33	9	trace	—
2	+53	42	43	14	1	—
3	+67	30	54	15	1	—
4	+79	20	61	18	1	—
5	+92	13	69	17	1	—
23	+97	5	68	25	2	—

[a]After acidification and processing; see Experimental. [b]Prior to the addition of base.

epimerization of **8**. However, it cannot be ruled out that it was the *cis* isomer **10**. The latter could arise from **5**, but its existence among the products could not be demonstrated. Crystallization of the reaction mixture easily afforded **7** (36%), and **8** (5%) with some difficulty. Conventional acetonation of the mother liquor, using cupric sulfate catalysis, gave **9** as its di-*O*-isopropylidene derivative **9b** (3%) and permitted recovery of starting hexose **5** as its 1,2-*O*-isopropylidene derivative **2** (3.5%). Continued acetonation under forcing conditions, using 2,2-dimethoxypropane or acetone and triethyl orthoformate, yielded another 7% of **7** as a mono-*O*-isopropylidene derivative (**7b**) and another 1% of **8** as the di-*O*-isopropylidene derivative (**8b**).

TABLE II

CYCLIZATION OF 6-DEOXY-3-*O*-METHYL-6-NITRO-L-TALOSE BY $Ba(OH)_2$ AT 7.9–8.7 AND 0°

Time[a] *(h)*	$[\alpha]_{365}^{23}$ *(degrees)*[b]	*Composition (%) by g.l.c.*[b]				
		Hexose	**11**	**12**	**13(+7)**	**14(+8 & 9)**
0[c]	+134	92	4	~3	1	—
5 min	+134	85	10	1	4	—
0.5	+130	76	18	2	4	—
1	+115	72	22	2	4	—
1.6	+93	33	57	2	7	1
2	+70	15	74	2	8	1
2.6	+52	6	83	3	7	1
3.5	+45	6	81	4	7	2
4.5	+42	3	85	3	7	2
5.4	+41	1	86	4	7	2
23.5	+37	1	87	3	7	2

[a]After the 1-h test sample had been withdrawn, the pH of the reaction solution was adjusted from 7.9 to 8.7 (see Experimental). [b]After acidification and processing; see Experimental. [c]Prior to the addition of base.

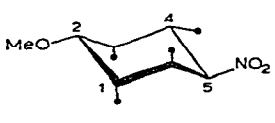
The cyclization of **6** under similar conditions (Table II) was accompanied by a decrease in dextrorotation, but optical activity was still present when, after 5 h, the sugar had been consumed almost completely. Little change in product composition took place thereafter. The main product was the optically inactive *myo*-5 isomer **11** (87%), which was isolated crystalline in high yield and purified *via* its tetra-acetate **11a**. G.l.c. of the reaction mixture showed three additional peaks with intensities of 3, 7, and 2%. Although none of the minor products could be isolated, it was possible to assign the first-listed peak to the *neo*-2 isomer **12** (also optically inactive), as **12** became available for comparison in another way (see below). The second and third peaks had the same relative retention times as **7** and **8** (obtained from **5**), so that they could be attributed to the enantiomers of these, namely **13** and **14**, which are expected to arise from **6**. However, their specific rotations ($[\alpha]_{365}$ $-53°$ and $+125°$, respectively, deduced from the values found for the isolated antipodes) require a 7:2 mixture to show levorotation, and since the final reaction mixture was dextrorotatory, it is evident that the actual proportion of levorotatory **13** was less than the g.l.c. peak intensity suggested. It is therefore probable that the peak, in part, represented racemic **7**/**13**. Although such a racemate might arise through secondary epimerization, it would also be produced if the starting sugar **6** contained some **5**. Indeed, when samples of less-pure **6** were used in similar experiments, a larger proportion of **7** than **13** was formed and some **7** could be isolated.

In summary, it has been shown that kinetically controlled cyclization of **5** gives at least three, and cyclization of **6** apparently gives all four, of the expected inositol isomers, with one in each case strongly preponderating. The preponderant products (**7** and **11**) are easily obtained on a preparative scale, whereas **8** and **9** can be prepared in small yields *via* acetone derivatives.

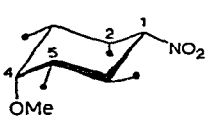
When a 1:3 mixture of **5** and **6** was treated for 1 day at 25° with 1 equiv. of sodium methoxide in methanol–nitromethane and then processed by acetylation and acetonation, derivatives of **9** and **11** corresponding to an ~25% yield of each could be elaborated. Also present, but not separated, were *allo*-5 and *epi*-1 isomers (presumably as racemates), but **12** was absent. Although this variant[2] of the cyclization procedure has not yet been studied in detail, it appears to hold promise as the best approach to **9**.

We then examined the cyclization in a more strongly alkaline (pH > 12) solution of barium hydroxide at 25°. These conditions favor thermodynamic control[1–4] and therefore should produce similar equilibrium mixtures of stereoisomers, irrespective of the use of **5** or **6** as starting material. It was convenient to employ a mixture of **5** and **6**. Predictably, the reaction proceeded faster than in the previous experiments; the starting sugars were consumed within 1 h and the optical activity disappeared within 1 day. From the g.l.c. pattern of the nitroinositols obtained after acidification, it appeared that the alkaline reaction solution contained 68% of the product as the nitronate which is common to **11** and **12**, the rest being the nitronate common to **9** and **10** and the racemic nitronate common to **7**, **8**, **13**, and **14**. Acidification followed by isolation of products proved disappointing from a prepara-

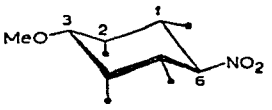
tive point of view, inasmuch as the yield of crystalline material, a 2:3 mixture of **11** and **12**, was only 26%. These products were then separated through their crystalline tetra-acetates **11a** and **12a**. The mother liquor was acetonated to give small amounts (2–5%) of **9b** and racemic **7b/13b** and **8b/14b**. The chief interest in these results is the preponderance of the *neo*-5 isomer (**12**), which permitted its isolation and is to receive further comment below.



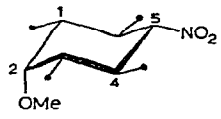
7, 7a



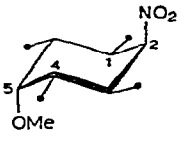
8, 8a



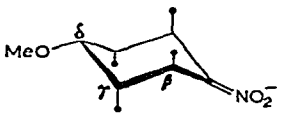
9, 9a



11, 11a

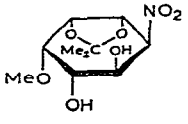


12, 12a

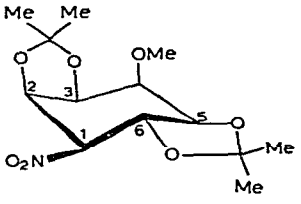


11/12-nitronate

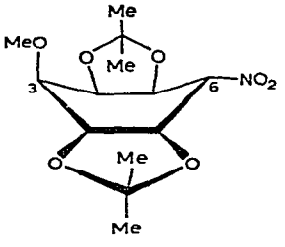
7–12, ↑ = OH
7a–12a, ↑ = OAc



7b



8b



9b

Epimerization experiments relevant to the mechanism of the cyclization

It has been discussed previously[3,4] that the distribution of stereoisomeric products in cyclizations of this kind strongly depends on reaction conditions and is governed by a complex interplay of kinetic and thermodynamic factors. In a given family of stereoisomeric, six-membered, cyclic nitropolyols (nitroinositols or nitropyranosides), the order of relative thermodynamic stabilities of the free nitro compounds differs greatly from that for the nitronate salts, as the change in hybridization alters the molecular geometry[4,18]. Consequently, if some degree of thermodynamic control obtains, the ratios of isomeric products will depend on the positions of the nitro ⇄ nitronate equilibria, which in turn are pH-dependent. At sufficiently high alkalinity (pH $\geqq$ 12), the products exist practically completely in the nitronate form,

as can be verified by u.v. and n.m.r. spectroscopy. Now, protonation of carbohydrate nitronates is subject to kinetic control[18], and the aforementioned production of a 2:3 ratio of **11** and **12** upon acidification of the strongly alkaline cyclization mixture is a consequence of this. In accord therewith, **11** and **12** were regenerated in the same ratio (and separated through their tetra-acetates) when a solution of either **11** or **12** was strongly basified and reacidified immediately. That protonation favors **12** kinetically, but not thermodynamically, agrees with conformational energy calculations[19] which indicate **11** to be more stable, and this was proved as follows. Separately dissolved in aqueous sodium hydrogen carbonate at pH 8.2 and 25°, the compounds gave virtually identical mixtures of epimers, with a 30:1 ratio of **11** and **12** (Table III, a and b). Very slowly, small proportions of other isomers were also formed in these thermodynamic equilibrations of the free nitro compounds. Interestingly, the 30:1 ratio is the same as that of **11** and **12** obtained in the cyclization of **6** at low pH (Table II), and it might therefore be argued that the latter process also involves thermodynamic control. However, we contend that this is not necessarily the case and that the equality of ratios observed was probably a coincidence. Convincing support for this contention was provided by analogous experiments with the 1D-*allo*-5 isomer **7**.

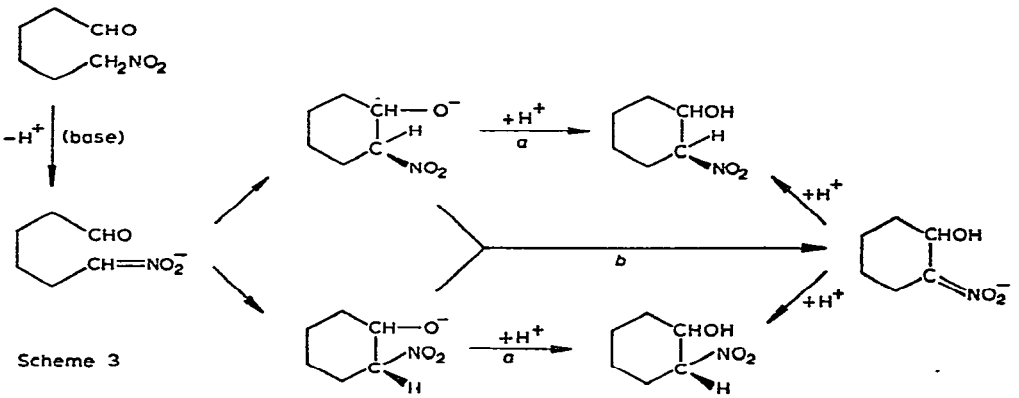
TABLE III

EPIMERIZATION OF DEOXYNITROINOSITOLS IN AQUEOUS SODIUM HYDROGEN CARBONATE SOLUTION AT pH 8.2 AND 25°

Experiment	*Time (h)*	*Composition (%) by g.l.c.*			
		7 *or* **13**	**8** *or* **14**, & **9**	**11**	**12**
(a)	0	—	1	96	3
	1	trace	1	96	3
	26	2	1	95	3
	73	2	3	92	3
	194	2	4	91	3
(b)	0	—	—	—	100
	1	trace	trace	52	48
	26	trace	1	95	4
	73	1	2	94	3
	194	2	5	90	3
(c)	0	95	~5	—	—
	1	64	30	3	4
	26	29	59	11	1
	73	18	62	19	1
	193	14	50	35	1

When pure **7** was dissolved in ice-cold, 0.3M sodium hydroxide and the nitronate solution was acidified after 2 min, the isomers **7**, **8**, and **9**, and some hexose (presumably **5**) were formed in the ratios of ~4:3:2:1 according to g.l.c., n.m.r.

spectroscopy, and optical rotation*. Relevant to the present discussion is the observation that **7** is favored, but only slightly, over **8** in the kinetic protonation of their common nitronate. (In addition the experiment gave an indication, by producing **9** but no **11** or **12**, of the remarkable velocity and the preferred direction of nitronate β-epimerization in this system.) Epimerization of **7** in the presence of sodium hydrogen carbonate at pH 8.2 and 25° (Table IIIc) was a rather complex process which is to be described in a subsequent paragraph. However, one result should be noted at this point. Thermodynamically, **8** was more favored than **7**, in agreement with calculated[19] conformational energies. Now the data for the low-pH cyclization of **5** must be recalled (Table I). There, **7** was the main product, and it is now evident that the ratio of **7** to **8** did not reflect their thermodynamic stabilities (as could have been argued in the analogous case of **11** and **12**), but must be attributed to a kinetically controlled process. This process cannot have been protonation of the nitronate, which shows considerably less preference for **7** even under optimal conditions (*i.e.*, conditions that precluded reversibility). It is concluded, therefore, that inositol *nitronate* is not an intermediate in the cyclization at low pH, but that pairs of free nitromethine epimers arise independently under kinetic control, according to Scheme 3, paths *a*. Although we base this conclusion only on the experimental data pertaining to **7** and **8**,



Scheme 3

we believe it applies to the formation of the other isomers, including those epimeric at a carbinol carbon. At high pH, however, path *b* no doubt is utilized. This difference has not been realized previously. Customarily, preparative nitroalkane–aldehyde additions are performed with a stoichiometric or excess amount of base present, and the resulting nitronates have been isolated on several occasions. This led to the notion[3] that if the reaction was promoted by a catalytic amount of base, the primary

*It is possible that **7** and **8** were already racemized, but only to some extent, since the optical rotation of the mixture was too large to be accounted for by the small proportion of hexose engendered. That the latter was **5**, rather than **6**, follows from the absence of **11** and **12** which would certainly have been conspicuous among the products had **6** arisen in the alkaline treatment.

product would still be the nitronate although this would rapidly equilibrate with free nitro compound according to its acidity constant. In the light of the present results, our earlier[3] notations referring to nitronates in cyclizations at low pH may have to be changed correspondingly.

The epimerization of **7** at pH 8.2 (Table IIIc) already referred to was monitored polarimetrically as well as by g.l.c., and was revealed to consist of several processes. The shape of the mutarotation curve suggested that there was an initial first-order reaction having $T_{0.5}$ 50 min, and a slow reaction with a $T_{0.5}$ of ~10 h which caused the rotation to become zero within ~3 days. After that point, an even slower reaction continued, as seen from the change in the g.l.c. pattern during the next 5 days. The data invite the following interpretation. The initial, fast process is the equilibration **7** ⇄ **8**; although one cannot determine the exact position of this (pseudo) equilibrium from available data, it appears from rotational values that **8** is favored. These optically active compounds then equilibrate more slowly with inactive **9** (and possibly **10**, although the latter has not been detected and may play an insignificant role only). Reversibility of the reaction demands that **9** concurrently equilibrates with the system **13** ⇄ **14**, which in effect constitutes racemization of **7** and **8**. Hence, the percentages indicated by g.l.c. (first column of Table III, c) represent **7** initially, **7** with increasing proportions of its enantiomer **13** as the process continued, and completely racemized **7/13** after 3 days. (The same interpretation applies to the entries in the second column.) The third, and slowest, process is epimeric equilibration of the system with **11** and **12**. The final equilibrium[19] between all the isomers was not reached within 8 days, as is evident from a comparison of parts a, b, and c (Table III).

Configurations and conformations

The products were characterized by *HRT*-values in g.l.c. (see Experimental). The major product (*HRT* 54) obtained by cyclization of **5** was optically active. Its origin and optical activity demanded either one or the other of the chiral structures **7** or **8** to be assigned. N.m.r. spectra of the product and its tetra-acetate each exhibited one large and one small splitting in the signal of the nitromethine proton, indicating that this α-proton is axial and vicinally coupled with one axial and one equatorial β-proton*. These, in turn, showed only small couplings with the respective γ-protons. The pattern is compatible only with structure **7** in the NO_2,OMe-diequatorial conformation.

The two minor products arising from **5** both showed *HRT* 112, but were separated chemically. One was optically active, the other inactive. The former must be given formula **8** by exclusion. Although the ring-proton signals of **8** and its tetra-acetate **8a** were not well enough resolved for first-order analysis, the chemical shift values of the OMe signals suggested an axial OMe group as exists in the NO_2-

*We designate the nitromethylene carbon as the α-position, *etc.* Use of the numbers as positional indicators would be inconvenient and confusing in the discussion of n.m.r. data, since the proper numbering system does not always allocate the same numbers to constitutionally equivalent positions in isomers.

equatorial conformation; they fell in a range together with those of the OMe-axial compounds **11** and **12**, and **11a** and **12a**, respectively, downfield from the range for the OMe-equatorial compounds **7** and **9**, and **7a** and **9a**, respectively. The assumed conformation of **8** was supported by c.d. measurements. Thus, both **7** and **8** exhibit virtually the same (negative) Cotton effect in the region of the nitro group absorption, which requires that each molecule occupies the same geometrical disposition with respect to the moiety comprising the nitromethine and its two neighboring carbinol groups; the Cotton effect of α-nitro-β-hydroxy compounds is determined by the chirality of the β-carbon[14,15]. The steric identity of these moieties is readily recognized when one of the chair formulas is rotated by 180° about the C_{OMe}–C_{NO_2} axis.

The optically inactive product from **5**, which had *HRT* 112 like **8**, was *not* racemic **8/14**. This was evident from comparison of n.m.r. spectra of the free nitro compounds, their tetra-acetates, and their di-*O*-isopropylidene derivatives. Assignment of structure **9** followed from the splitting of 10.5 Hz of the nitromethine triplet, which indicated a β,α,β′ *trans,trans*-triaxial proton orientation. This ruled out the *cis*-configuration **10** and at the same time established for **9** the NO_2-equatorial conformation.

The major product of the cyclization of **6** was optically inactive. It showed *HRT* 128, clearly distinct from **7** and **8**, and therefore cannot have been racemic **7/13** or racemic **8/14**. Allocation of formula **11** was straightforward on the basis of a well-resolved n.m.r. spectrum of the tetra-acetate **11a**. The α-proton gave a triplet with two splittings of 10 Hz, indicative of a β,α,β′ *trans,trans*-triaxial proton arrangement, and thus, of the configuration as well as an NO_2-equatorial conformation of the compound. The spectrum of free **11** also exhibited this feature. By contrast, **12** (*HRT* 59) gave small splittings (5 Hz) in the α-proton triplet, whereas $J_{\beta,\gamma}$ and $J_{\gamma,\delta}$ were similar in **11** and **12** (10 and 2.5–3.0 Hz, respectively). These data prove the *neo*-2 configuration for **12** and show that the NO_2-axial conformer is preferred. (The relatively large $J_{\alpha,\beta}$ value of 5 Hz may suggest a flattened chair caused by an outward movement of the unfavorably disposed, axial nitro group.) Furthermore, the conversion into, and regeneration from, an identical nitronate confirms the relationship of **11** and **12** in terms of nitromethine epimerism. The n.m.r. spectrum of the nitronate revealed that the salt, in contrast to its parent compounds, prefers the OMe-equatorial conformation that has all four hydroxyl groups axially placed. This was deduced from the ring-proton coupling constants (all small) and from the OMe signal which was shifted upfield into the OMe resonance region of **7** and **9**. The preference of the nitronate for this conformation was not surprising in view of the strong $A^{(1,3)}$ interaction which would exist in the alternative chair form. As for the nitronate of **7** and **8**, the position of the OMe-signal tends to point to an OMe-equatorial conformation, but it was not possible to confirm this by analysis of all the ring-proton couplings, especially since a spectrum of the pure compound was unobtainable because of rapid, partial epimerization.

The di-*O*-isopropylidene derivative **9b** gave a rather simple n.m.r. spectrum which was interpretable in terms of the boat conformation depicted. For the di-*O*-

isopropylidene derivative **8b**, the distorted-chair conformation shown is proposed on the basis of the available n.m.r. data and a consideration of molecular models.

EXPERIMENTAL

General methods. — For general preparative and instrumental techniques, see previous papers[2,3]. Optical rotations (Table IV) were measured at room temperature in a Perkin–Elmer 141 automatic polarimeter, using a mercury lamp and 1-dm cells. Circular dichroism and u.v. absorptions were determined in a Jasco ORD/UV-5 instrument. Microanalytical data are recorded in Table IV. Unless otherwise indicated, the n.m.r. data refer to 100-MHz spectra; the internal standard was tetramethylsilane for $CDCl_3$ solutions, and acetone for CF_3CO_2D/D_2O and D_2O solutions.

TABLE IV

SPECIFIC ROTATIONS AND MICROANALYTICAL DATA

Compound	*Specific rotations (degrees)*					*Analyses*			
	$[\alpha]_{578}^{25}$	$[\alpha]_{546}^{25}$	$[\alpha]_{436}^{25}$	$[\alpha]_{365}^{25}$	*Solvent*[a]	*Found*			*Calc*[b]
						C	*H*	*N*	
2	+120	+133	+200	+189	A	45.53	6.56	5.23	a
3	+94	+106	+191	+421	A	45.62	6.37	5.19	a
4	+85	+96	+152	+216	B	43.18	5.79	8.99	b
5	+16	+15	+2	−127	A				
	+12	+12	+1	−108	C				
6	−14	−15	−9	+97	A				
	−5	−4	+9	+121	C				
7	+85	+93	+135	+53	D	37.69	5.94	6.37	c
8	+36	+39	+42	−125	D	37.74	5.94	6.41	c
9						37.85	6.03	6.34	c
11						37.88	5.80	6.42	c
12						37.83	6.01	6.31	c
7a	+2	+1	−13	−91	B	46.00	5.48	3.61	d
9a						46.18	5.42	3.65	d
11a						45.98	5.42	3.65	d
12a						45.87	5.40	3.44	d
7b	+77	+86	+138	+108	B	45.46	6.48	5.46	a
8b	−2	−3	−16	−82	B	51.31	6.99	4.56	e
9b						51.34	6.84	4.55	e

[a]A, methanol (*c* 0.4–0.6); B, chloroform (*c* 0.2); C, water (*c* 3); D, 0.1M acetic acid (*c* 0.2). [b]a, for $C_{10}H_{17}NO_7$ (263.2): C, 45.62; H, 6.51; N, 5.32; b, for $C_{11}H_{18}N_2O_8$ (306.3): C, 43.14; H, 5.92; N, 9.15; c, for $C_7H_{13}NO_7$ (223.2): C, 37.66; H, 5.87; N, 6.28; d, for $C_{15}H_{21}NO_{11}$ (391.3): C, 46.03; H, 5.41; N, 3.58; e, for $C_{13}H_{21}NO_7$ (303.3): C, 51.48; H, 6.98; N, 4.62.

G.l.c. was performed in a Varian Aerograph, Series 1200, instrument with a hydrogen-flame detector and a recorder equipped with a 224 Disc. Mod. integrator. The stainless-steel coil (6 ft. × 0.125 in.) was packed with 3% of Silicone Rubber OV 17

on Chromosorb W 80/100. Operation was isothermal at 155°, with helium as carrier gas (pressure, 45 p.s.i.; flow rate, 45–50 ml.min^{-1}). Product components of 0.5% or less were identifiable. Retention times were measured in min (±0.05) and are expressed in *HRT* units ($T_R \times 100$) with reference to the main peak of 1-deoxy-4-*O*-methyl-1-nitro-DL-*myo*-inositol[3] (*HRT* = 100; absolute retention time 9–11 min). Calibration runs with individual compounds showed no significant variations in detector response. With one exception (see below), the trimethylsilylated samples were stable in solution for at least a week if stored in a refrigerator with exclusion of moisture, and repeated measurements using the same sample solution showed maximal deviations of 1% from the mean value. The exception was **12**; the pure compound underwent partial epimerization during trimethylsilylation, and this continued during subsequent storage. Under standard conditions, and when g.l.c. was performed on the same day, peaks of **12** (80%) and **11** (20%) were found. Therefore, the measured percentages of these two isomers in reaction mixtures were appropriately corrected. The possible error due to this circumstance is thought to be 1–2% in average mixtures, and perhaps as much as 5% if the content of **12** is very high.

The reagent for trimethylsilylation was made by mixing pyridine (2.0 ml; dried over CaH_2) with trifluoroacetic acid (0.2 ml) and adding hexamethyldisilazane (1.8 ml). When stored at 0° in a polythene-stoppered vial, the reagent was stable for months. The test sample (2 mg) was dissolved by brief shaking with the reagent (0.1 ml), and the solution was kept in a closed vial overnight at 25°; 1–2 µl were then used for g.l.c. The *HRT* values found were: **7**, 54; **8** and **9**, 112; **11**, 128; **12**, 59; for **5** and **6**, see below.

1,2-O-Isopropylidene-3-O-methyl-α-D-allofuranose[13] (**1**). — A solution of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose[20] (20.57 g) and methyl iodide (34.14 g) in *N*,*N*-dimethylformamide (210 ml) was shaken with powdered barium oxide (25.6 g) for 18 h at 25°. The mixture was filtered through Celite and processed[13]. The 3-methyl ether (17.1 g) was a yellow oil showing all the reported[13] n.m.r. signals; it contained up to 5% of residual *N*,*N*-dimethylformamide. A solution of the product in acetic acid (170 ml) and water (17 ml) was heated for 1 h at 40–45°, and the reaction was monitored[13] by t.l.c. Evaporation followed by co-evaporation with added toluene gave a syrup (17.7 g) which was crystallized from anhydrous ether to give **1** (13.3 g), m.p. 108–115°, $[\alpha]_D$ +97° (*c* 1, chloroform); lit.[13] m.p. 109–110°, $[\alpha]_D$ +105.1°.

Periodate oxidation[13] *of* **1**, *and reaction of the product with nitromethane.* — Sodium metaperiodate (10.7 g) was added in portions during 30 min to a cooled (8–10°) solution of **1** (10.0 g) in water (60 ml). The reaction mixture was then stirred at 25° for 90 min, cooled again, and treated with ethylene glycol (0.3 ml). Ethanol (50 ml) was added, inorganic material was filtered off, and the filtrate was evaporated. The residue was repeatedly dissolved in ethanol, freed from insoluble material, and recovered by evaporation. The colorless, syrupy oxidation product was dissolved in methanol (30 ml) and nitromethane (15 ml). The solution was flushed with nitrogen and basified by dropwise addition of 3M sodium methoxide in methanol (15 ml). It was then stirred in a closed vessel overnight at 25°, chilled in an ice bath, acidified

with glacial acetic acid (3 ml), diluted with water (150 ml), and extracted with chloroform (5 × 50 ml). The extract was washed once with water (20 ml), dried ($MgSO_4$), and evaporated to give a brownish syrup (9.8 g, 87% based on **1**). The product was chromatographed on a column of silica gel (400 g). Elution with 8:2 (v/v) carbon tetrachloride–ethyl acetate (3 l) furnished **4** (195 mg, 1.5%). Continued elution with the same solvents, but in 7:3 ratio, gave, first, **2** (1.92 g, 17% after crystallization from chloroform–petroleum ether). This was followed by mixed fractions (3.4 g, 30%; with **2** and **3** in an over-all ratio 2:3), and finally by **3** (2.44 g, 22%).

*6-Deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-6-nitro-α-*D*-allofuranose* (**2**). — The compound formed colorless needles, m.p. 127–128°, λ_{max} 272 nm (ε 43, methanol), $[\theta]_{281}$ −1420 (*c* 0.5, methanol); n.m.r. data in $CDCl_3$: δ 1.36 and 1.57 (s, 2 × 3 H, Me_2C), 2.95 (s, 1 H, hydroxyl), 3.47 (s, 3 H, MeO), 3.80 and 3.94 (octet, 2 H, split AB system, $J_{3,4}$ 9, $J_{2,3}$ 4, $J_{4,5}$ 3.5 Hz, H-3,4), 4.4–4.7 (m, 3 H, H-5,6,6′), 4.71 (t, 1 H, $J_{1,2}$ 3.5 Hz, H-2), 5.77 (d, 1 H, H-1).

*6-Deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-6-nitro-β-*L*-talofuranose* (**3**). — The compound, which formed large transparent prisms (from syrup), small needles (from carbon tetrachloride), or long silky needles (from anhydrous ether), had m.p. 85–85.5°, λ_{max} 272 nm (ε 50, methanol), $[\theta]_{284}$ +1650° (*c* 0.5, methanol). N.m.r. data ($CDCl_3$): δ 1.35 and 1.54 (s, 2 × 3 H, Me_2C), 2.77 (d, 1 H, *J* 7 Hz, OH), 3.48 (s, 3 H, OMe), 3.79 and 3.93 (octet, 2 H, split AB system, $J_{3,4}$ 9, $J_{2,3}$ 4, $J_{4,5}$ 2.3 Hz, H-3,4), 4.4–4.7 (m, 3 H, H-5,6,6′), 4.71 (t, 1 H, $J_{1,2}$ 3.5 Hz, H-2), 5.79 (d, 1 H, H-1).

*5,6-Dideoxy-1,2-*O*-isopropylidene-3-*O*-methyl-6-nitro-5-*C*-nitromethyl-α-*D*-ribo-hexofuranose* (**4**). — The compound gave long, colorless needles, m.p. 101–102°, from 1:1 chloroform–petroleum ether. N.m.r. data ($CDCl_3$): δ 1.34 and 1.44 (s, 2 × 3 H, Me_2C), 3.2–3.4 (m, 1 H, H-5?), 3.40 (s, 3 H, OMe), 3.51 (q, 1 H, $J_{2,3}$ 4, $J_{3,4}$ 9 Hz, probably H-3), 4.01 (q, $J_{4,5}$ 8, $J_{3,4}$ 9 Hz, probably H-4), 4.4–4.9 (m, 5 H, 2 CH_2NO_2 and probably H-2), 5.74 (d, 1 H, $J_{1,2}$ 4 Hz, H-1).

*6-Deoxy-3-*O*-methyl-6-nitro-*D*-allose* (**5**). — A solution of **2** (819 mg, 3.11 mmol) in trifluoroacetic acid (3.1 ml) and water (0.6 ml) was stirred for 40 min at 25° and then evaporated *in vacuo*. The residue was dissolved in 0.01M acetic acid (2 ml) and passed successively through layers (1 ml each) of Rexyn 101(H^+), Dowex-1x2 (acetate form), and Rexyn 101(H^+) resins contained in a burette. The column was then washed with water (20 ml) and the eluate evaporated to give a colorless syrup which was dried *in vacuo* and further dehydrated by repeated evaporations with ethyl acetate and benzene. Dried to constant weight at 40–45°, the product (0.75 g) invariably retained a small amount of acid from processing, but this was considered advantageous for its stability. It was used without further purification. In g.l.c., it exhibited 2 main peaks (ratio 1:1) at *HRT* 68 and 75, and trace peaks (1–2%) at *HRT* 40 and 45. Some samples showed small peaks (2–4%) corresponding to **7** and **8** (or **9**).

*6-Deoxy-3-*O*-methyl-6-nitro-*L*-talose* (**6**). — Compound **6** was obtained from **3** (514 mg) by the procedure described for **5**. It was a slightly yellow syrup (428 mg), showing 3 main peaks (ratio 4:1:1) at *HRT* 68, 75, and 90 in g.l.c., as well as 2 minor

peaks (2–3%) at *HRT* 39 and 45. Minor peaks (3–4%) having significantly different *HRT* values that corresponded to cyclization product were present in some samples. Contamination of **6** by **5** would not be detectable; however, the results of the cyclization experiments indicated that mutual contamination was not significant (not greater than 2–3%) as long as the free sugars were prepared from the pure isopropylidene derivatives.

Cyclization of **5** *at pH 7–8 and 0°.* — A solution of **5** (obtained from 3.11 mmol of pure **2**) in 0.01M acetic acid (3.1 ml) was cooled to 0°, and chilled barium hydroxide solution [4.2 ml containing 0.4 mequiv. of $Ba(OH)_2$] was added under nitrogen, to provide a pH of just over 7 (by indicator paper; the actual pH was probably near 8, *cf.* the cyclization of **6**). At specified time intervals (Table I), 0.10-ml aliquots were withdrawn and mixed with 0.1M acetic acid (0.90 ml). The optical rotations of these sample solutions (*c* 0.9, estimated) were recorded, the solutions were then freeze-dried, and the residues were dried *in vacuo* over $CaCl_2$ and KOH, trimethylsilylated, and analyzed by g.l.c. The total volume thus withdrawn from the reaction mixture amounted to 10%, leaving 2.80 mmol of products for further processing. After 23 h at 0°, the remaining solution was acidified with chilled 0.1M acetic acid (5 ml) and passed through a three-bed ion-exchange column (see the preparation of **5**) which was eluted with 0.01M acetic acid. The first 25 ml of effluent left a colorless, solid foam (619 mg, 99%) upon evaporation, and the second 25 ml gave another 14 mg.

1D-5-Deoxy-2-O-methyl-5-nitro-allo-*inositol* (**7**). — The foam just described was triturated with ethyl acetate, which yielded a first crop of crystals (273 mg) that consisted to >90% of **7**. By recrystallization from boiling ethyl acetate, a sparingly soluble part was removed, and pure **7** (166 mg) was obtained. Both mother liquors were processed by systematic fractional crystallization with ethanol or ethyl acetate, which increased the total yield of pure **7** to 217 mg (35% based on **2**); m.p. 168–170°, λ_{max} 271 nm (ε 76), and $[\theta]_{278}$ −1525° (*c* 0.2, 0.1M acetic acid). The compound showed mutarotation in (non-acidified) water. N.m.r. data (2M CF_3CO_2D/D_2O): δ 1.27 (s, 3 H, OMe), 1.40 (t, 1 H, $J_{1,2} = J_{2,3} = 3$ Hz, H-2), 2.04 (sextet, 1 H, $J_{1,2}$ 3, $J_{1,6}$ 4, $J_{1,3}$ 1.5 Hz, H-1), 2.20 and 2.27 (m, 2 H, split AB system with $J_{3,4}$ 3, $J_{2,3}$ 3, $J_{1,3}$ 1.5, and $J_{4,5}$ 10 Hz, H-3,4), 2.35 (t, 1 H, $J_{5,6}$ 3.5, $J_{1,6}$ 4 Hz, H-6), 2.84 (q, 1 H, $J_{4,5}$ 10, $J_{5,6}$ 3.5 Hz, H-5).

After isolation of crystalline **8** (see the next section) by the fractional crystallization mentioned, there remained crystalline (63 mg) and syrupy 229 mg) mixtures of isomers that resisted separation. Thus, the recovery of product was 87%. According to g.l.c., the non-separable mixtures contained **7** (~50%), **8** and **9** (~40%), and unreacted **5** (~10%).

1L-1-Deoxy-4-O-methyl-1-nitro-epi-*inositol* (**8**). — The sparingly soluble part removed from crude **7** and similar fractions from processing of mother liquors (see above) gave, on further recrystallization from ethanol, the isomer **8** (36 mg, ~5%) as lustrous plates, m.p. 173–175°, λ_{max} 273 nm (ε 78), and $[\theta]_{279}$ −2090° (*c* 0.2, 0.1M acetic acid). N.m.r. data (2M CF_3CO_2D/D_2O): δ 1.43 (s, 3 H, OMe), 1.45–1.75 (m, 3 H, H-3,4,5), 2.15–2.50 (m, 3 H, H-1,2,6).

*6-Deoxy-1,2:4,5-di-*O*-isopropylidene-3-*O*-methyl-6-nitro-*epi*-inositol* (**9b**). — A part (203 mg) of the syrupy mixture of isomers that had remained unseparated in the preparation of **7** was stirred at 25° with acetone (2 ml) containing conc. sulfuric acid (0.16 ml) and anhydrous cupric sulfate (0.5 g). After 4.5 h, the mixture was chilled with dry-ice, neutralized with conc. ammonia (0.4 ml), and filtered through a layer of Celite which was then washed with acetone. Evaporation gave a syrup which was partitioned between water and chloroform (3-funnel system). The aqueous phase gave unreacted material (120 mg), and the chloroform phase gave a syrup (160 mg) which was subsequently chromatographed on silica gel (5 g, with 10% of water added; E. Merck AG.). Elution with chloroform (5-ml fractions) furnished **9b** (28 mg) from fractions 2 and 3, **2** (38 mg, m.p. 126–127°, identified also by n.m.r. spectrum and optical rotation) from fractions 7 and 8, and finally **7b** (10 mg, impure) when ethyl acetate (16.6%) was added to the eluant. Recrystallized from carbon tetrachloride, **9b** formed optically inactive, long needles (25 mg), m.p. 203.5–204°. N.m.r. data ($CDCl_3$): δ 1.34 and 1.54 (s, 2 × 6 H, 2 Me_2C), 3.54 (s, 3 H, OMe), 3.80 (t, 1 H, $J_{2,3} = J_{3,4} =$ 3 Hz, H-3), 4.21 (q, 2 H, $J_{1,2} = J_{4,5} = 8$ Hz, H-2,4), 4.58 (q, 2 H, $J_{1,6} = J_{5,6} =$ 9 Hz, H-1,5), 5.25 (t, 1 H, H-6).

*1*L*-1-Deoxy-2,3:5,6-di-*O*-isopropylidene-4-*O*-methyl-1-nitro-*epi*-inositol* (**8b**). — The unreacted, water-soluble portion (177 mg) from an acetonation similar to that described in the preceding section was stirred at room temperature for 21 h in a mixture of acetone (4 ml) and triethyl orthoformate (1 ml) containing *p*-toluenesulfonic acid hydrate (15 mg). The reaction solution was then stirred for 30 min with dry sodium hydrogen carbonate (100 mg) which was filtered off and washed with acetone. Evaporation of the filtrate yielded a viscous syrup (214 mg) which was chromatographed with chloroform (6-ml fractions) on silica gel (6 g, +10% of water). Fraction 2 gave a small amount of **9b**; and fraction 3 gave **8b** (10 mg) that crystallized from carbon tetrachloride in short, lustrous needles, m.p. 189–190°. N.m.r. data ($CDCl_3$): δ 1.32, 1.41, and 1.52 (s, 3 H, 3 H, 6 H, 2 Me_2C), 3.53 (s, 3 H, OMe), 3.36 (q, 1 H, $J_{4,5}$ 2 and $J_{5,6}$ 9 Hz, H-5), 3.81 (q, 1 H, $J_{3,4}$ 5 Hz, H-4), 4.34 (t, 1 H, $J_{2,3}$ 5 Hz, H-3), 4.5–5.0 (m, 3 H, H-1,2,6).

Deacetonation of a sample of **8b**, as described below for **9b**, gave **8** (g.l.c.).

Fractions 8 and 9 yielded **2** (26 mg, m.p. 128–129°, identified by n.m.r. spectrum). Continued elution with 5:1 chloroform–ethyl acetate produced **7b** (50 mg); see the following section.

*1*D*-5-Deoxy-3,4-*O*-isopropylidene-2-*O*-methyl-5-nitro-*allo*-inositol* (**7b**). — The product, as obtained chromatographically (see above), was recrystallized from chloroform–petroleum ether to give short, hard needles melting at 150–150.5°. N.m.r. data (60 MHz, $CDCl_3$): δ 1.42 and 1.57 (s, 2 × 3 H, Me_2C), 2.77 (s, 2 H, 2 OH), 3.58 (s, 3 H, OMe), 3.90 (t, 1 H, $J_{1,2} = J_{2,3} = 4$ Hz, H-2), 4.30 (t, 1 H, J 4 Hz, H-1 or H-3), 4.5–5.0 (m, 4 H).

Deacetonation of **7b** (7 mg), as described for **9b**, gave **7** (6 mg, crude, m.p. 163–168°), identified by g.l.c. and optical rotation.

*6-Deoxy-3-*O*-methyl-6-nitro-*epi*-inositol* (**9**). — Compound **9b** (30.6 mg) was

dissolved at 25° in trifluoroacetic acid (0.1 ml), and 2 drops of water were added. After 20 min, the reaction mixture (which had deposited crystals) was evaporated in a stream of nitrogen, and the residue was washed with a small volume of ethyl acetate and recrystallized from 90% ethanol. There was obtained **9** (19 mg, 85%) as optically inactive, large, colorless prisms, m.p. 219–221°. N.m.r. data (2M CF_3CO_2D/D_2O): δ 1.24 (t, 1 H, $J_{2,3} = J_{3,4} = 3$ Hz, H-3), 1.26 (s, 3 H, OMe), 1.92 (q, 2 H, $J_{1,6} = J_{5,6} = 10.5$ Hz, $J_{1,2} = J_{4,5} = 3$ Hz, H-1,5), 2.12 (t, 2 H, H-2,4), 2.77 (t, 1 H, H-6).

*1*D-*1,3,4,6-Tetra*-O-*acetyl-5-deoxy-2*-O-*methyl-5-nitro*-allo-*inositol* (**7a**) *and impure* DL-epi-*1 isomer.* — A mixture of compound **7** (25 mg) and boron trifluoride etherate (1 drop) in acetic anhydride (0.2 ml) was kept at 0° for 2 h, with occasional swirling. After addition of excess ethanol, the mixture was brought to dryness to give a quantitative yield of **7a** (pure according to n.m.r. spectrum). Crystallization from benzene–petroleum ether afforded **7a** as white crystals (19 mg, 43%), m.p. 152–153°. N.m.r. data ($CDCl_3$): δ 1.98, 2.10, 2.12, 2.14 (s, 4×3 H, 4 AcO), 3.35 (s, 3 H, OMe), 3.64 (t, 1 H, $J_{1,2} = J_{2,3} = 3.5$ Hz, H-2), 5.13 (q, 1 H, $J_{4,5}$ 11, $J_{5,6}$ 3.5 Hz, H-5), 5.35 (t, 1 H, $J_{3,4}$ 3.5 Hz, H-3), 5.72 (q, 1 H, H-4), 5.73 (t, 1 H, $J_{1,6}$ 3.5 Hz, H-1 or H-6), 5.84 (t, 1 H, H-6 or H-1),

Since there was insufficient pure **8** for preparation of its tetraacetate **8a**, a sample of racemic *epi*-1 isomer that contained more than 20% of **11** was acetylated as just described. Recrystallizations from chloroform–ethanol and benzene–petroleum ether gave a material, m.p. 172–173°, that was rich in DL-*epi*-1 tetra-acetate but still contained **11a**. N.m.r. signals ($CDCl_3$) attributable to the former compound were at δ 2.00, 2.06, and 2.07 (s, 3 H, 6 H, 3 H, 4 AcO), 3.51 (s, 3 H, OMe), 3.85 (t, 1 H, $J_{3,4} = J_{4,5} = 3$ Hz, H-4).

1,2,4,5-Tetra-O-*acetyl-6-deoxy-3*-O-*methyl-6-nitro*-epi-*inositol* (**9a**). — Acetylation of pure **9** (19 mg), as described for **7**, gave crystalline **9a** (33 mg). Recrystallized from ethanol, the colorless needles (23 mg, 70%) melted at 206–207°. N.m.r. data ($CDCl_3$): δ 2.00 (s, 6 H, 2 AcO), 2.15 (s, 6 H, 2 AcO), 3.34 (s, 3 H, OMe), 3.59 (t, 1 H, $J_{2,3} = J_{3,4} = 3$ Hz, H-3), 5.79 (t, 2 H, $J_{1,2} = J_{4,5} = 3$ Hz, H-2,4). There was a 3 H multiplet in the δ 5.1–5.5 region, in which could be discerned a 1 H triplet (J 10 Hz) for H-6 centered at 5.25, and a 2 H quartet for H-1 and H-5 at 5.38.

Cyclization of **6** *at pH 7.9–8.8 and 0°.* — A solution of **6** (obtained from 1.95 mmol of **3**) in water (9 ml) was placed in a 20-ml two-neck flask loosely fitted with the glass electrode of a pH-meter and a nitrogen gas-inlet. The flask was cooled (0°) and flushed with N_2 while 0.24M barium hydroxide solution was slowly introduced from a burette until the pH-meter reading was 7.9. (At that point, a spot test with indicator paper showed pH 6–7.) Aliquots (0.10 ml) were withdrawn at given times (Table II) and dealt with as described for the cyclization of **5**. Since the reaction progressed rather too slowly, the pH was adjusted to 8.7 (by meter; 7.5 by indicator paper) after 1 h. A total of 0.42 ml (0.20 mequiv.) of barium hydroxide was used. The total proportion of reaction mixture withdrawn for g.l.c. tests was 12%, which left 1.71 mmol of material (based on **3**) for further processing that was performed as in the cyclization of **5**. There was obtained a crystalline, crude product (351 mg, 92%),

m.p. 211–218° (dec.), which consisted to ~90% of **11** (n.m.r.). Attempts to isolate other isomers by crystallization or chromatography, or after acetylation, were unsuccessful.

*5-Deoxy-2-*O*-methyl-5-nitro-*myo*-inositol* (**11**). — The foregoing crude product, when recrystallized from 95% ethanol, melted at 232–237° (dec.) and was pure according to g.l.c. and n.m.r. spectrum. (After acetylation followed by deacetylation, the compound showed m.p. 248–250° (dec. at 251°), but no change in g.l.c. and n.m.r. spectrum was noticed.) It was optically inactive. N.m.r. data (2M CF_3CO_2D/D_2O): δ 1.44 (s, 3 H, OMe), 1.51–1.64 (m, 3 H, interpreted as containing at δ 1.59 a 1 H-triplet for H-2 with $J_{1,2} = J_{2,3} = 3$ Hz, and 4 lines of an AB_2 part of a complex system for H-1 and H-3), 2.20 (t, 2 H, $J_{3,4} = J_{4,5} = J_{1,6} = J_{5,6} = 10$ Hz, H-4,6), 2.31 (t, 1 H, J 10 Hz, H-5).

*1,3,4,6-Tetra-*O*-acetyl-5-deoxy-2-*O*-methyl-5-nitro-*myo*-inositol* (**11a**). — A suspension of pure **11** (140 mg) in acetic anhydride (1.4 ml) containing boron trifluoride etherate (2 drops) was stirred for 2 h at 0° and then kept overnight at 0°. The crystalline deposit (m.p. 216–217°) was collected, and washed with ethanol (1.5 ml), and the filtrate was evaporated with added ethanol to give a second crop of crystals (m.p. 216–217°); combined yield, 230 mg (94%). Recrystallization from 1:1 chloroform–ethanol gave white prisms (220 mg), but the melting point tended to decrease and values of 211–212° or 202–204°, for example, were found in various instances. N.m.r. data ($CDCl_3$): δ 2.00 (s, 6 H, 2 AcO), 2.07 (s, 6 H, 2 AcO), 3.57 (s, 3 H, OMe), 3.88 (t, 1 H, $J_{1,2} = J_{2,3} = 2.5$ Hz, H-2), 4.70 (t, 1 H, $J_{4,5} = J_{5,6} = 10$ Hz, H-5), 4.99 (q, 2 H, $J_{1,6} = J_{3,4} = 10$ Hz, H-1,3), 5.97 (t, 2 H, J 10 Hz, H-4,6).

A sample of **11a** (150 mg) was deacetylated in refluxing dry methanol (15 ml) containing methyl *p*-toluenesulfonate (0.3 ml). After 17 h, the solution was evaporated and the residue triturated with ethanol followed by ethyl acetate. Crystals were obtained and recrystallized from 95% ethanol to give **11** (71 mg, 83%), m.p. 248–250° (dec.), identical in every respect with the product before acetylation.

Cyclization at high pH and 25°. — The solution of a syrupy 3:1 mixture of **5** and **6** (612 mg, 2.74 mmol) in water (2.74 ml) was stirred under nitrogen and basified with saturated (242.5mM) barium hydroxide (6.22 ml, 3.02 mequiv.). The pH was >12 (by indicator paper). The solution slowly turned yellow and then dark brown, and it gradually deposited a precipitate. Test samples (0.10 ml, withdrawn after swirling) were acidified with M acetic acid (0.5 ml) and treated with a small quantity of activated charcoal before further processing for polarimetry and g.l.c. as described earlier. The starting sugars were absent after 1 h, and the rotation was practically zero after 24 h. There was little change in the g.l.c. pattern after 48 h, when the remaining reaction mixture (97%, 2.65 mmol) was chilled to 0°, acidified with M acetic acid (6.22 ml), treated with charcoal, and passed through consecutive beds of Rexyn 101(H^+), Dowex-1x2 (acetate), and Rexyn 101(H^+) resins (4, 1, and 1 ml), which were rinsed with water. The first 32 ml of effluent yielded a light-brown solid (0.47 g) on evaporation. No additional material could be eluted. Crystallization from ethanol gave a mixture (106 mg, m.p. 215–216°) of **11** and **12** in the ratio 2:3 (by g.l.c.). The mother

liquor (dry weight 0.34 g) contained **11**, **12**, and racemic *allo* and *epi* isomers. An additional 49 mg of crystalline **11**,**12**-mixture was obtained from the residue of subsequent acetonation; total yield, 155 mg (26%). The acetonation was performed as described for the preparation of **8b**. Chromatography of the resultant mixture on silica gel gave **9b** (17 mg), racemic **8b** (44 mg), and racemic **7b** (22 mg) as crude products that were identified by their n.m.r. spectra and by g.l.c. after hydrolysis.

1,3,4,6-Tetra-O-*acetyl-2-deoxy-5*-O-*methyl-2-nitro*-neo-*inositol* (**12a**). — A suspension of the crystalline mixture (135 mg) of **11** and **12** in acetic anhydride (1.5 ml) containing 2 drops of boron trifluoride etherate was stirred at 0°. The heterogeneous reaction was monitored by t.l.c. on phosphate-buffered (pH 5) silica gel, using 1:1 chloroform–ethyl acetate. The solid as well as the soluble materials were completely acetylated after 75 min. The mixture was filtered through sintered glass, and the crystals were washed with cold ethanol (3 × 0.5 ml) and air-dried (yield, 134 mg, 56%); they were pure **12a** according to the n.m.r. spectrum; m.p. 252–256°. Recrystallization from 2:1 chloroform–ethanol gave hard, lustrous prisms that melted at lower temperatures (anywhere between 180–210°), but showed an unchanged n.m.r. spectrum ($CDCl_3$): δ 2.03 (s, 6 H, 2 AcO), 2.07 (s, 6 H, 2 AcO), 3.51 (s, 3 H, OMe), 4.06 (t, 1 H, $J_{4,5} = J_{5,6} = 2.5$ Hz, H-5), 5.3–5.8 (m, 5 H).

The filtered acetylation solution was kept overnight at 0° and then evaporated. The residue was triturated with water and recrystallized from chloroform–ethanol to give **11a** (70 mg, 30%), m.p. 205–209°, identical (n.m.r.) with **11a** from pure **11**.

2-Deoxy-5-O-*methyl-2-nitro*-neo-*inositol* (**12**). — A suspension of **12a** (132 mg) was refluxed for 24 h in dry methanol (13 ml) containing methyl *p*-toluenesulfonate (0.13 ml). The residue of subsequent evaporation was triturated with ethyl acetate (1 ml) to give crystals melting at 231–235° (dec.). Recrystallization from 4:1 ethanol–water gave colorless prisms of **12** (70 mg, 93%), m.p. 215–218° (dec., with foaming at 221°). N.m.r. data (2M CF_3CO_2D/D_2O): δ 1.39 (s, 3 H, OMe), 1.65 (t, 1 H, $J_{4,5} = J_{5,6} = 2.5$ Hz, H-5), 1.94 and 2.06 (two q, 2 × 2 H, analyzed as a split AB system, with $J_{1,2} = J_{2,3} = 5$ Hz, $J_{1,6} = J_{3,4} = 10$ Hz, H-1,3 and H-4,6,), 3.12 (t, 1 H, H-2).

Formation and protonation of nitronates. — (*a*) *From* **11** *and* **12**. To a solution of **11** (26 mg) in deuterium oxide (0.40 ml) was added a 1.2M sodium deuteroxide solution (0.10 ml). The n.m.r. spectrum (60 MHz) was scanned within 3–5 min: δ 1.26 (s, 3 H, OMe), 1.55 (t, 1 H, $J_{\gamma,\delta} = J_{\gamma',\delta} = 3$ Hz, H-δ), 1.92 (q, 2 H, $J_{\beta,\gamma}$ and $J_{\beta',\gamma'}$ 5 Hz, H-γ,γ'), 2.81 (d, 2 H, H-β,β'). The same spectrum was analogously obtained from **12**. After the scanning, the solution was pipetted without delay into M acetic acid (1 ml), and passed through layers of Rexyn 101(H^+), Dowex-1x2 (acetate), and Rexyn 101(H^+) resins. The crystalline residue (22 mg) obtained upon evaporation of the deionized solution was acetylated as for the preparation of **12a**. Spectroscopically homogeneous **12a** (19 mg) and 90% pure **11a** (13 mg) were isolated by crystallization.

(*b*) *From* **7**. The n.m.r. spectrum given by **7** (20 mg) in alkaline solution, as in (*a*), showed the following data: δ 1.26 (s, 3 H, OMe), 1.43 (t, 1 H, $J_{\gamma,\delta} = J_{\gamma',\delta} = 3$ Hz,

H-δ), 1.7–2.0 (m, 2 H, H-γ,γ'), 2.73 (d, 1 H, J 5 Hz, H-β or H-β'). The fifth ring-proton signal was probably obscured by the DOH peak.

For the isolation of products following protonation, an ice-cold solution of **7** (23 mg) in 0.33M sodium hydroxide (0.45 ml) was introduced within 2 min into 0.1M acetic acid (2 ml). The solution was passed through ion-exchange resins as described in (*a*), and the volume was made up to 10.0 ml; $[\alpha]_{546}$ +36°, $[\alpha]_{436}$ +48°, $[\alpha]_{365}$ −30°. The solution was evaporated to dryness, and g.l.c. of the residue indicated the presence of **7** (40%), **8** and **9** (50%), and **5** (10%). The 60-MHz n.m.r. spectrum (CF_3CO_2D/D_2O) showed that the ratio of low-field to high-field methoxyl proton signals was 7:3, with the former being assignable to **7**, **9**, and **5**, and the latter to **8**. Combination of these results leads to ratios of ~4:3:2:1 for **7**, **8**, **9**, and **5**.

Epimerizations at pH 8.2 and 23°. — Solutions (0.01M) of single nitroinositol isomers (**7**, **11**, and **12**) in 1% aqueous sodium hydrogen carbonate were kept at 23° in vials sealed with rubber septa. At time intervals given in Table III, 1.0-ml aliquots were withdrawn by syringe and injected into M acetic acid (1.0 ml). Processing for g.l.c. analysis was performed as described previously.

The mutarotation of a solution of **7** in 1% aqueous sodium hydrogen carbonate (*c* 0.345) was recorded (in parentheses, times in min): $[\alpha]_{436}^{23}$ +142° (initial, extrapolated), +140° (2), +136° (5), +132° (10), +127° (17), +122° (23), +115° (32), +108° (41), +97° (65), +90° (88), +83° (112), +71° (169), +67° (205), +63° (226), 0° (3 days). The values up to 88 min obey first-order kinetics; calculation gave a theoretical end-rotation for this phase of +72.5°, and a half-time of 44 min. The value +72.5° corresponds to a ratio close to 3:7 for **7** and **8**.

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