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# THE STEREOCHEMISTRY OF PALLADIUM- AND PLATINUM-CATALYZED HYDROGENATIONS OF NITRO SUGAR EPOXIDES*

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ABSTRACT

The catalytic hydrogenation of carbohydrate α-nitroepoxides with palladium and platinum was investigated with regard to regiospecificity and stereochemistry of ring opening, and the fate of the nitro group. 5,6-Anhydro-1,2-*O*-isopropylidene-6-C-nitro-α-D-glucofuranose gave 6-amino-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose under platinum catalysis. The methyl 2,3-anhydro-4,6-*O*-benzylidene-3-C-nitrohexopyranosides having the β-D-*gulo* (**4**), β-D-*allo* (**9**), α-D-*manno* (**13**), and β-D-*manno* (**18**) configurations underwent facile, hydrogenolytic ring-opening in the presence of palladium, to give, regardless of the orientation of the oxirane ring, methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-nitro-D-hexopyranosides having an equatorial nitro group (**5**, **10**, **14**, and **19**, respectively). In addition, 3-deoxy-3-oximino derivatives arose in various proportions, and two of these (from **9**, and from **18**) were isolated crystalline. It was shown that the oximes did not result from over-hydrogenation of the 3-deoxy-3-*C*-nitro glycosides produced, and it is suggested that they originated from intermediary nitronic acids. By catalysis with platinum, the oxirane rings in **4**, **9**, **13**, and **18** were opened in the same regiospecific sense as with palladium, but notable differences were observed otherwise. Compound **4** gave the amino analog of **5**, whereas **9** retained the nitro group and gave the 4,6-*O*-(cyclohexylmethylene) analog of **10**. The α-D-*manno* epoxide **13** reacted with concomitant debenzylidenation, to yield methyl 3-amino-3-deoxy-α-D-altropyranoside hydrochloride, whereas the β-D-*manno* epoxide **18** gave the corresponding, debenzylidenated amino β-D-altroside together with the 4,6-*O*-(cyclohexylmethylene)-3-nitro- and -3-amino-β-D-mannosides. The results are compared with literature reports on the stereochemistry of hydrogenolysis of oxiranes, and mechanisms that may operate for the nitro derivatives are discussed.

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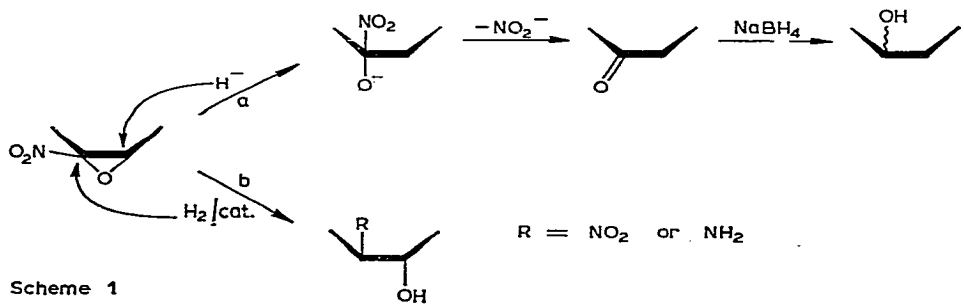
*Reactions of Nitro Sugars: Part XLII. For Part XLI, see ref. 1. A major part of the experimental results is taken from the Ph.D. thesis submitted in 1976 to this University by C. B. M., and described in a preliminary communication (see ref. 2). The interpretation was made possible on the basis of additional experimentation contributed by P. G. P. and, especially, by Z. S. H. Financial support of the work by the National Research Council of Canada is acknowledged.

## INTRODUCTION

In the course of our research on the synthesis[3,4] and chemical reactivity[2,5,6] of carbohydrate α-nitroepoxides, we became interested in the behavior of this class of compound towards reducing agents. A preceding article[5] described the action of sodium borohydride, a reagent that causes reductive denitration leading to deoxy sugars (see Scheme 1,*a*), although steric features in the epoxides have a marked influence on the ease of reaction. As a sequel to those studies, we now report on catalytic hydrogenations that, by contrast, could be expected to proceed by homolytic cleavage of the oxirane ring between the oxygen atom and the nitro-substituted carbon atom[7], resulting in the retention of a nitrogen function in the molecule (see Scheme 1,*b*). It appeared attractive to investigate what kinds of nitrogen derivatives might be formed under various reaction conditions, and whether steric factors influencing the course of hydrogenation might be discernible.



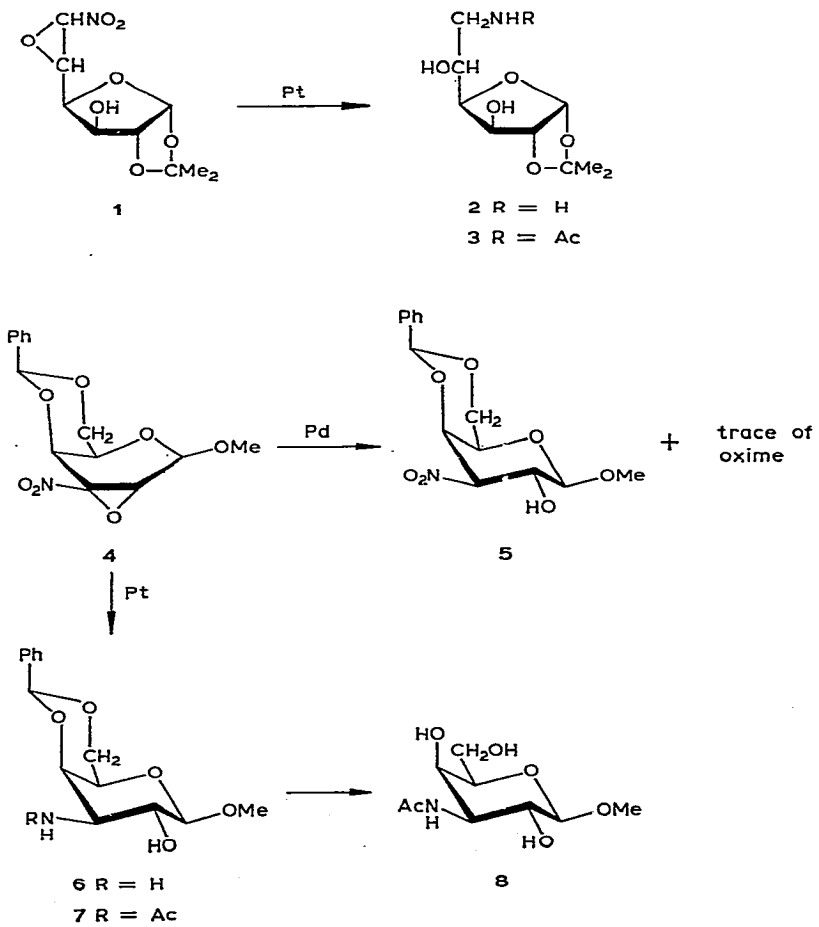

Scheme 1

Our main objective was to examine the hydrogenation of 2,3-anhydro sugars. The six methyl 2,3-anhydro-4,6-*O*-benzylidene-3-*C*-nitrohexopyranosides having the *β*-D-*gulo* (**4**), *β*-D-*allo* (**9**), α-D-*manno* (**13**), *β*-D-*manno* (**18**), α-D-*talo* (**26**), and *β*-D-*talo* (**27**) configurations are available, and it was interesting to compare their behavior with that of non-nitro analogs whose catalytic hydrogenation has been reported[8]. The unsubstituted epoxides previously studied[9−12] underwent ring opening with hydrogen under pressure at elevated temperatures in the presence of Raney nickel; a platinum catalyst was ineffective at 80° in one case examined[9]. For the nitro derivatives, a higher reactivity attributable to the presence of this group could be predicted. With regard to stereochemistry, it is to be recalled that the unsubstituted analogs of **13** and **26**, which bear the oxirane ring on the *β*-face of the pyranose ring, were hydrogenolyzed to give 3-deoxy glycosides possessing an axial OH-2 group, and the same mode of ring opening was observed with lithium aluminum hydride[10−12]. The unsubstituted (but α-anomeric) analogs of **4** and **9** also incurred catalytic hydrogenation at C-3, to give 3-deoxy glycosides having an equatorial OH-2 group, even though they carry the oxirane oxygen atom on the α-face of the pyranose ring[10,12], whereas hydride reduction gave[10,13] 2-deoxy glycosides in harmony with the Fürst–Plattner rule. The products formed (by catalytic hydrogenation) in contravention of the rule have been termed[8] "abnormal", and, although it was recognized that the

mechanism of hydrogenolysis differs from that of nucleophilic substitutions on which the rule is based[8], no satisfactory explanation appears to have been offered in the literature as to why none of the catalytic ring-openings should have occurred preferentially at C-2. For lack of a proper rationale, the preceding analogies could not, therefore, be meaningfully invoked to predict the behavior of our nitro derivatives. Nevertheless, it seemed reasonable to assume that an electronic effect of the nitro group would favor ring cleavage at C-3, but the eventual fate of the functionality and configuration at that center was more difficult to foretell.

## RESULTS

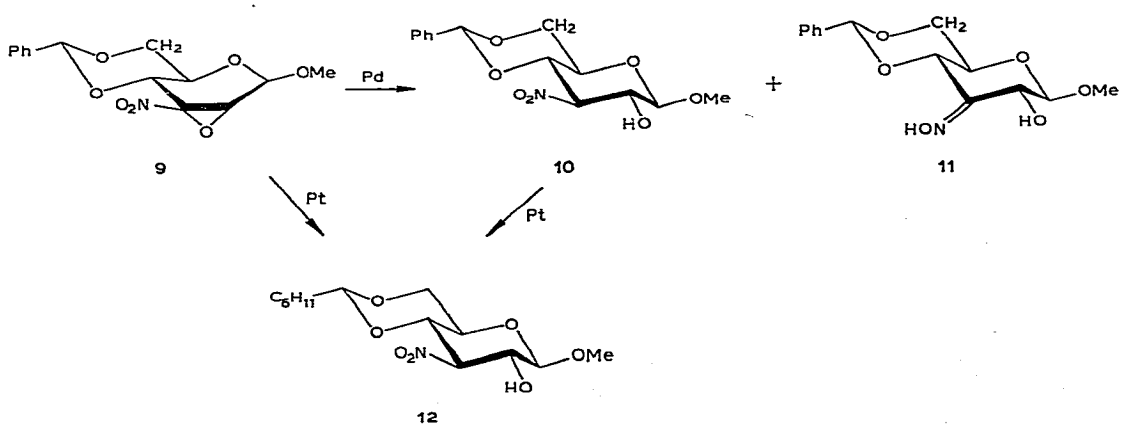
Before the results pertaining to the 2,3-anhydro glycosides just mentioned are described, we record a catalytic hydrogenation of 5,6-anhydro-1,2-*O*-isopropylidene-6-*C*-nitro-α-D-glucofuranose (**1**), a terminal nitroepoxide expected not to offer any stereochemical problems and to require little discussion. Hydrogenated in ethanolic

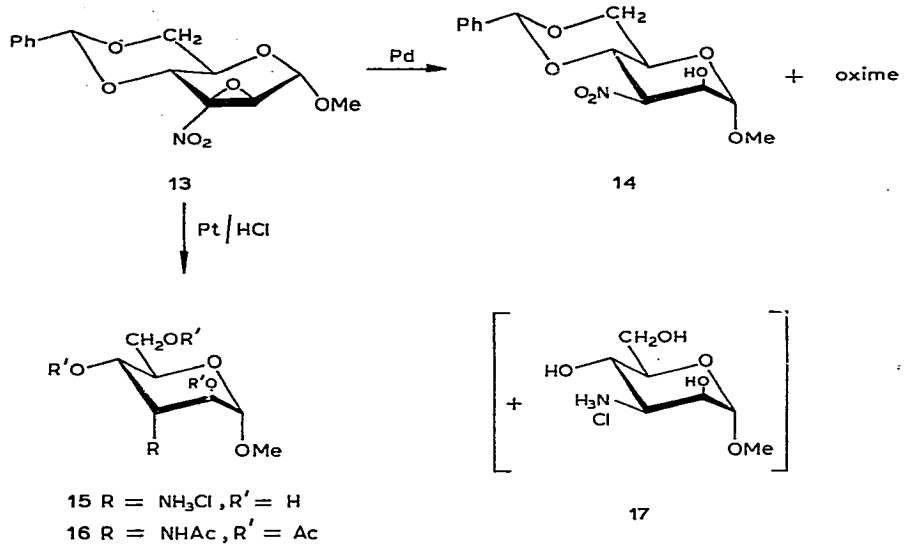


solution in the presence of platinum (referring, here and throughout this paper, to pre-hydrogenated platinum dioxide), **1** gave mainly 6-amino-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**2**), accompanied by traces only of unidentified by-products. The amine **2** was isolated crystalline in 65% yield, characterized by spectral and analytical data, and unambiguously identified by conversion into its known[14] *N*-acetyl derivative **3**. The purpose of this experiment had been to establish the C-5 stereochemistry in **1**, a compound newly prepared[5] at the time, and to be used[5,6] in other connections. Its conversion into **2** and **3** provided the desired proof, and, moreover, demonstrated that catalytic hydrogenation of a nitro sugar epoxide may effect ring opening coupled with reduction to the amino stage in a straightforward way.

Turning now to the 2,3-anhydro sugars **4**, **9**, **13**, and **18**, we shall first describe their hydrogenation catalyzed by *palladium* (referring, throughout, to 10% Pd-on-charcoal). The compounds were hydrogenated in ethanol solution, or in methanol–1,4-dioxane containing a small proportion of acetic acid, and, in each case, the oxirane ring was rapidly cleaved at ambient temperature and pressure. The times required for complete consumption of the epoxides ranged from 10 to 90 minutes; expectedly, the time depended on the proportion of catalyst employed. In general, it was somewhat shorter for methanol–1,4-dioxane than for ethanol solutions. However, no systematic studies of these matters were intended.

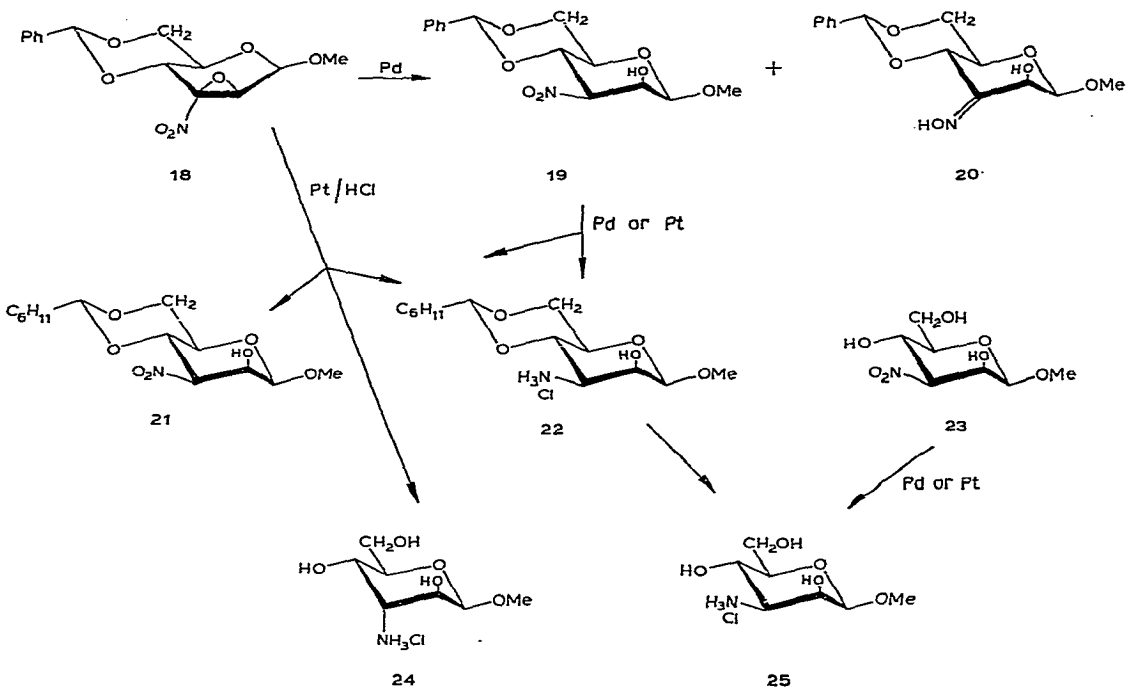
As anticipated, cleavage occurred exclusively between the oxirane oxygen atom and C-3, which led to 3-deoxy-3-nitro glycosides and not to 2-deoxy glycosides. Thus, the β-D-*gulo* (**4**) and β-D-*allo* (**9**) epoxides gave the known methyl 4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-galactopyranoside (**5**) and -β-D-glucopyranoside (**10**), respectively. The α- and β-D-*manno* epoxides **13** and **18** produced the corresponding α- and β-D-mannopyranosides, **14** and **19** (also known). In all of these palladium-catalyzed hydrogenations, oximino glycosides arose as secondary products in various proportions; this was unexpected, as oximes are not normally generated so easily by reduction of nitroalkanes (see the Discussion). Especially prone to oxime






formation was the β-D-*manno* epoxide **18**. After only a few minutes of hydrogenation in methanol–1,4-dioxane, when a considerable proportion of unchanged **18** was still present, a slow-moving spot corresponding to the by-product had already begun to appear in t.l.c., besides the spot for a compound that, at this point, seemed to be the main product **19**. After 45 min, at the time of complete consumption of the epoxide, the oxime had attained a spot intensity not much less than that of the nitro sugar **19**, and, after 36 h, the spot corresponding to **19** had disappeared, and the oxime could be isolated as the sole product, by direct crystallization. In a similar hydrogenation conducted in ethanolic medium, all of the starting material **18** reacted within 3 h, after which time, the t.l.c. spots of nitro glycoside and oxime had comparable intensities; after 24 h, the ratio of products had changed markedly in favor of the latter, and preparative t.l.c. then allowed the isolation of a small amount of crystalline **19** and a large amount of oxime which, in this instance, was obtained in two crystalline forms constituting geometric isomers. The constitution of methyl 4,6-*O*-benzylidene-3-deoxy-3-(oximino)-β-D-*arabino*-hexopyranoside (**20**) was allocated to it on the basis of microanalytical and spectral data.

The β-D-*allo* epoxide **9** similarly gave an oxime as a by-product, although in smaller proportion. It was isolated crystalline in 7% yield, and, although its n.m.r. spectrum was insufficiently resolved for full interpretation, there can be little doubt that it was the β-D-*ribo* isomer **11**. In the hydrogenation of the epoxides **4** and **13**, analogous oximes were not isolated, but their presence was indicated, as in the two preceding cases, by purple-color reactions exhibited in the Griess test (sulfanilic acid–1-naphthylamine) modified[15] for the detection of hydroxylamine derivatives. In the case of **13**, t.l.c. revealed the oxime as a slow-moving spot similar to those of **11** and **20**; no such spot was visible for the oxime from **4**, either because it coincided with




that of the rather slow-moving, main product **5**, or because very little oxime was formed.

In order to determine the origin of oximes in these palladium-catalyzed hydrogenations, crystalline nitro mannoside **19**, previously obtained in independent ways, was subjected to hydrogenation for 30 h under the same conditions as the epoxide **18**. Examination of the reaction mixture by t.l.c. in 1:4 methanol–chloroform showed that by far the major product ($R_F$ 0.5) was a ninhydrin-positive, amino sugar. There was also a ninhydrin-positive trace-spot of $R_F$ 0.75; it migrated like the oxime **20** in this solvent system, but more slowly than **20** in another system (1:2 ethyl acetate–petroleum ether), and, therefore, was not identical with it. Furthermore, there were two weak spots, $R_F$ 0.9 and 0.4, that turned yellow (not violet) on spraying with ninhydrin, and migrated like starting **19** and its debenzylidenated, parent glycoside **23**. The chief product ($R_F$ 0.5) was isolated as a crystalline hydrochloride, and proved to be methyl 3-amino-4,6-*O*-(cyclohexylmethylene)-3-deoxy-β-D-mannopyranoside (**22**); upon graded, acid hydrolysis, it yielded the known methyl 3-amino-3-deoxy-β-D-mannopyranoside hydrochloride (**25**). Apart from the interesting formation of a hexahydrobenzylidene acetal, the important result of this experiment was the absence of oxime **20** among the products. It thus became clear that the nitro glycoside **19** generated from the epoxide **18** is not the precursor of the oxime that is a prominent product in the same reaction. We also convinced ourselves that similar hydrogenation of the parent nitro mannoside **23** does not lead to an oxime; it gave only the expected amine, isolated as the hydrochloride **25**.

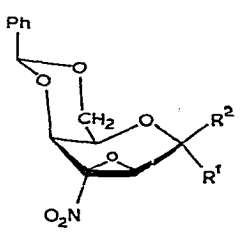
Hydrogenation of the 2,3-anhydro-3-nitro sugars in the presence of *platinum* also caused facile ring-opening at C-3. However, reduction of the nitro group, which, with this catalyst, generally leads smoothly to the amino group (*cf.*, also, the reaction **1**→**2**), was not equally straightforward in all of the examples examined. The β-D-*gulo* isomer **4**, hydrogenated in neutral, ethanolic solution for 50 h, did give the expected reduction product, methyl 3-amino-4,6-*O*-benzylidene-3-deoxy-β-D-galactopyranoside (**6**); it was isolated crystalline in high yield, and only traces of unidentified by-products were detected by t.l.c. The amine **6** was additionally characterized by means of its *N*-acetyl derivative **7**, and by partial hydrolysis of the latter, which furnished the known methyl 3-acetamido-3-deoxy-β-D-galactopyranoside (**8**). However, the β-D-*allo* epoxide **9** behaved quite differently under the same conditions. Although the oxirane ring was opened readily, as evidenced by a rapid and complete disappearance of **9**, the nitro group proved extraordinarily resistant in this system, in sharp contrast to the general experience with (non-benzylidenated) nitro sugars[16]. Instead of the nitro group, only the benzylidene group incurred reduction, and methyl 4,6-*O*-(cyclohexylmethylene)-3-deoxy-3-nitro-β-D-glucopyranoside (**12**) was isolated after 44 h as the only significant product that was formed, traces of by-products being visible in t.l.c. The same hexahydro derivative was produced from the benzylidene acetal **10** under identical conditions.

Hydrogenation of the D-*manno* epoxides **13** and **18** in the presence of the platinum catalyst in ethanolic medium were performed similarly, except that, for reasons to be discussed, stoichiometric amounts of hydrochloric acid were added. The chromatographic picture was more complicated than in the preceding examples. The α anomer **13** was entirely consumed within 1 h, and at least six products, differing widely in polarity ($R_F$ 0.9–0.1), were formed. The presence of amino derivatives among them was indicated by the ninhydrin reaction. As the hydrogenation progressed, the two fastest-moving (and ninhydrin-negative) intermediates disappeared, and, after 20 h, the most-slowly moving compound(s) preponderated. Crystallization then gave, in 54% yield, a debenzylidenated amino glycoside hydrochloride. It was probably not homogeneous, but, upon acetylation, it gave a high yield of crystalline methyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-altropyranoside (**16**), indicating that it must have consisted largely of the amino altroside **15**. It appears likely that a small proportion of the isomeric mannoside **17** was present in the crude hydrochloride.

Hydrogenation of the β-D-*manno* epoxide **18** resulted in its complete consumption within 4.5 h, at which point the reaction mixture, like that of the anomer just described, showed a t.l.c. pattern of at least six spots differing greatly in intensity and $R_F$ value. Processing at this stage permitted the isolation of three of the products by fractional recrystallization. The chief component ($R_F$ 0.5) thus separated, in 34% yield, proved identical with the (cyclohexylmethylene) amino glycoside hydrochloride **22** previously encountered in the palladium-catalyzed hydrogenation of the benzylidenenitromannoside **19**. The fastest-moving component ($R_F$ 0.95) was isolated in 5% yield, and shown to be the (cyclohexylmethylene)nitro analog **21**. The same com-

pound was also formed, and isolated by column chromatography, when a mixture of the nitro mannoside **19** and the oxime **20** (generated from **18** by palladium-catalyzed hydrogenation, as already mentioned) was hydrogenated for a further 24 h in the presence of platinum and hydrochloric acid. This second hydrogenation caused **19** and **20** to disappear, and produced, besides some **21**, mainly **22**, as well as deacetalated amino glycosides. The latter corresponded to the most slowly moving material (giving a double spot, $R_F$ ~0.1) in the preceding experiment, from which they were obtained as the third, crystalline fraction. The material had i.r. and n.m.r. characteristics according with those for a methyl aminodeoxy glycoside hydrochloride, but it was probably not isomerically homogeneous, as its specific rotation ($[\alpha]_D$ −127.6°) lay between the values for the β-D-altroside **24** ($[\alpha]_D$ −138°) and the β-D-mannoside **25** ($[\alpha]_D$ −68°). The optical rotation suggested, however, that **24** preponderated, and this was supported by the results of acid hydrolysis. The hydrolyzate showed, in t.l.c., an elongated spot that was consistent with the presence of 3-amino-3-deoxy-D-altrose and its 1,6-anhydride, and that differed from the somewhat slower spot of 3-amino-3-deoxy-D-mannose, as given by an authentic sample and by the product of total hydrolysis of **22**. The remaining products in the hydrogenation of **18** were all minor in proportion, and could not be isolated. They showed ninhydrin-negative spots at $R_F$ 0.85 and 0.4 (trace), and ninhydrin-positive spots at $R_F$ 0.75 and 0.35 (trace). The two former ones corresponded to those given by authentic samples of the nitro glycosides **19** and **23**.

For comparison, methyl 3-deoxy-3-nitro-β-D-mannopyranoside (**23**) was hydrogenated in ethanol with hydrogen in the presence of platinum and 1 equiv. of hydrochloric acid, and the corresponding, crystalline, amine hydrochloride **25** was obtained as the sole product, in accord with the results of previous work[17] in which an aqueous medium was used. The reaction was relatively slow, with (a roughly estimated) 50% of **23** still surviving after 4.5 h, and 25% after 21 h. Furthermore, authentic 4,6-*O*-benzylidene derivative **19** was hydrogenated under the same conditions. By t.l.c. all of the starting material was revealed to have reacted after 4 h, although reduction of the nitro group was not necessarily complete at that stage. Although ninhydrin-positive spots attributable to **22** and **25** were evident, there was also a spot due to **21**, and it took 30 h for the latter eventually to disappear. The final result was in agreement with the aforementioned, platinum-catalyzed hydrogenation




26 $R^1$ = OMe, $R^2$ = H

27 $R^1$ = H, $R^2$ = OMe

of the *mixture* of **19** and **20** that had originated from **18** by palladium-catalyzed hydrogenation, although, in that instance, some amino altroside stemming from reduction of **20** was possibly among the products.

Studies on the hydrogenation of the D-*talo* epoxides **26** and **27** are in progress.

*Characterization of new products.* The amine **2** gave readily interpretable infrared and n.m.r. spectra (see Experimental section) that were consistent with the postulated structure, and the physical constants of its *N*-acetyl derivative **3** agreed with literature data. The n.m.r. spectrum of the amine **6** clearly revealed the existence of the benzylidene acetal group (5-H multiplet centered at $\delta$ 7.6 and 1-H singlet at $\delta$ 5.52), and the signal for H-3, a quartet at $\delta$ 2.80 showing 3.5- and 10-Hz splittings, indicated a 2,3-diaxial proton arrangement, *i.e.*, the *galacto* configuration. This structure was supported by the substituent resonances, and the i.r. spectrum of the *N*-acetyl derivative **7**, and by identification of the debenzylidenated glycoside **8** with an authentic sample through comparison of physical and spectral data. The oximino glycoside **20** was characterized by an off-field signal ($\delta$ 11.2) observable in a $CDCl_3$–$(CD_3)_2SO$ solution spectrum and removable by deuterium exchange. The main part of the spectrum proved that the benzylidene group was intact and, moreover, that no hydrogen was attached to C-3, as H-2 and H-4 each gave a doublet (1.5 and 9.3 Hz, respectively) owing to coupling with one vicinal proton only. The signals for H-5, -6, and -6′ were also well resolved. The spectrum of the isomeric oximino glycoside **11** was similar in its general features, but, unfortunately, showed second-order effects in the signals attributable to H-1, -2, and -4, which were crowded together. Nevertheless, the formula assignment is corroborated by the microanalytical data, the positive Griess reaction, and the analogy of formation of **11**.

Compounds **12**, **21**, and **22** showed no resonances downfield from $\delta$ 5.0, but gave massive, unresolved multiplets in the $\delta$-1–2 region, indicating that their original benzylidene acetal groups had suffered perhydrogenation in the phenyl ring. The signal at lowest field for **12** was a symmetrical triplet attributable to H-3, indicative of the *gluco* configuration by reason of its 10-Hz spacing. The analogous signal for **21** was a quartet having 3.5- and 10.5-Hz splittings that revealed the *manno* configuration, and this was confirmed by the coupling constants of the remaining, well resolved, ring-proton signals. The (cyclohexylmethylene) acetal proton resonated at $\delta$ 4.45 as a doublet showing vicinal coupling of 5 Hz. The spectrum of the amine hydrochloride **22** afforded little additional information. However, the *N*-acetyl-*O*-acetyl derivative obtained from **22** exhibited, at lowest field, a quartet for H-2 ($J_{1,2}$ 1.3 Hz and $J_{2,3}$ 3 Hz) which was followed upfield by the anomeric-proton doublet ($J_{1,2}$ 1.3 Hz) and a quartet for H-3 ($J_{2,3}$ 3 Hz and $J_{3,4}$ 9.5 Hz), as well as an apparent triplet for H-4 ($J_{3,4} \approx J_{4,5}$ = 9–10 Hz). These features established the *manno* configuration. The chemical shifts of the acetoxyl and acetamido protons ($\delta$ 2.16 and 1.97 for $CDCl_3$ solutions) agreed with an axial and an equatorial orientation of the respective substituents.

## DISCUSSION

The smooth, hydrogenolytic opening of the oxirane ring in nitro sugars under catalysis with palladium or platinum contrasts with the much more severe reaction-conditions required[9-13] to achieve such cleavage in non-nitro analogs. The hydrogenolyses were uniformly regiospecific, with cleavage taking place between the oxygen atom and the carbon atom bearing the nitro group. Although this specificity cannot be solely due to the nitro group, as it was also manifest for the unsubstituted analogs (as mentioned in the Introduction), the enhanced reactivity clearly reflects the strong activating effect associated with this functionality.

Next, the question as to which configuration should be expected to arise at C-3 presents itself. Extensive investigations by Mitsui and co-workers[18,19] on the mechanism and stereochemistry of catalytic hydrogenolysis of epoxides and aziridines have revealed significant differences as to types of catalyst and reaction media. The authors suggested[18,19] that the compounds are adsorbed by Raney nickel on the side of, and through coordination with, the hetero atom, and are hydrogenolyzed in a manner stereochemically analogous to an SNi process, whereas palladium, showing no affinity for the hetero atom, was considered to initiate attack with SN2-like geometry from the opposite, stereoelectronically favored direction; platinum, apparently, can act by either mode. It should be noted, however, that the conclusions of Mitsui and co-workers pertain largely to α-phenyl-substituted (styrene oxide type) compounds, where anchoring on the catalyst surface through π-benzyl bonding is considered to be a prime factor. There seem to be few reports along these lines concerning purely aliphatic epoxides[19,20], and the antecedent findings in the area of benzylidenated[9-13] and other[8] carbohydrate oxiranes have not been commented upon in this context, so that it was uncertain how these precepts would relate to epoxynitro sugars in which other factors, both polar and steric, might come into play. Actually, no simple correlations were evident.

Whereas the platinum-catalyzed hydrogenations of the β-D-*gulo* (**4**) and β-D-*allo* (**9**) epoxides, giving equatorial orientation of the nitrogenous substituents in **6** and **12**, respectively, were consistent with hydrogen transfer from catalyst coordinated with the oxirane oxygen atom, the palladium-catalyzed reactions of these same substrates produced the same C-3 configuration (in **5** and **10**), and thus gave no evidence for the latter catalyst's attacking from the opposite direction*. In the hydrogenolysis of the α-D-*manno* epoxide **13**, platinum again acted from the side of the oxirane ring, at least mainly so, to the extent that the nitrogen atom was placed axially in the amino altroside **15**, the chief product. (The probable formation of a minor proportion of the D-*manno* isomer **17** could not be definitively ascertained.) The favored direction of attack by platinum was less clear-cut for the β-D-*manno*

*In a short communication that appeared while this work was in progress, Sudoh and his co-workers[21] reported, without giving experimental details, that the phenyl glycoside analog of **9** also reacts to give the D-*gluco* configuration, both with palladium-on-carbon and with Raney nickel.

epoxide **18**, from which substantial proportions of products having an equatorial nitrogen function were formed, with the derivatives **21** and **22** being isolated crystalline, and **25** considered a possible, if minor, companion of the amino altroside **24**. On the other hand, palladium catalysis for both of the D-*manno* epoxides (**13** and **18**) did not give any detectable products having an axial nitrogen function.

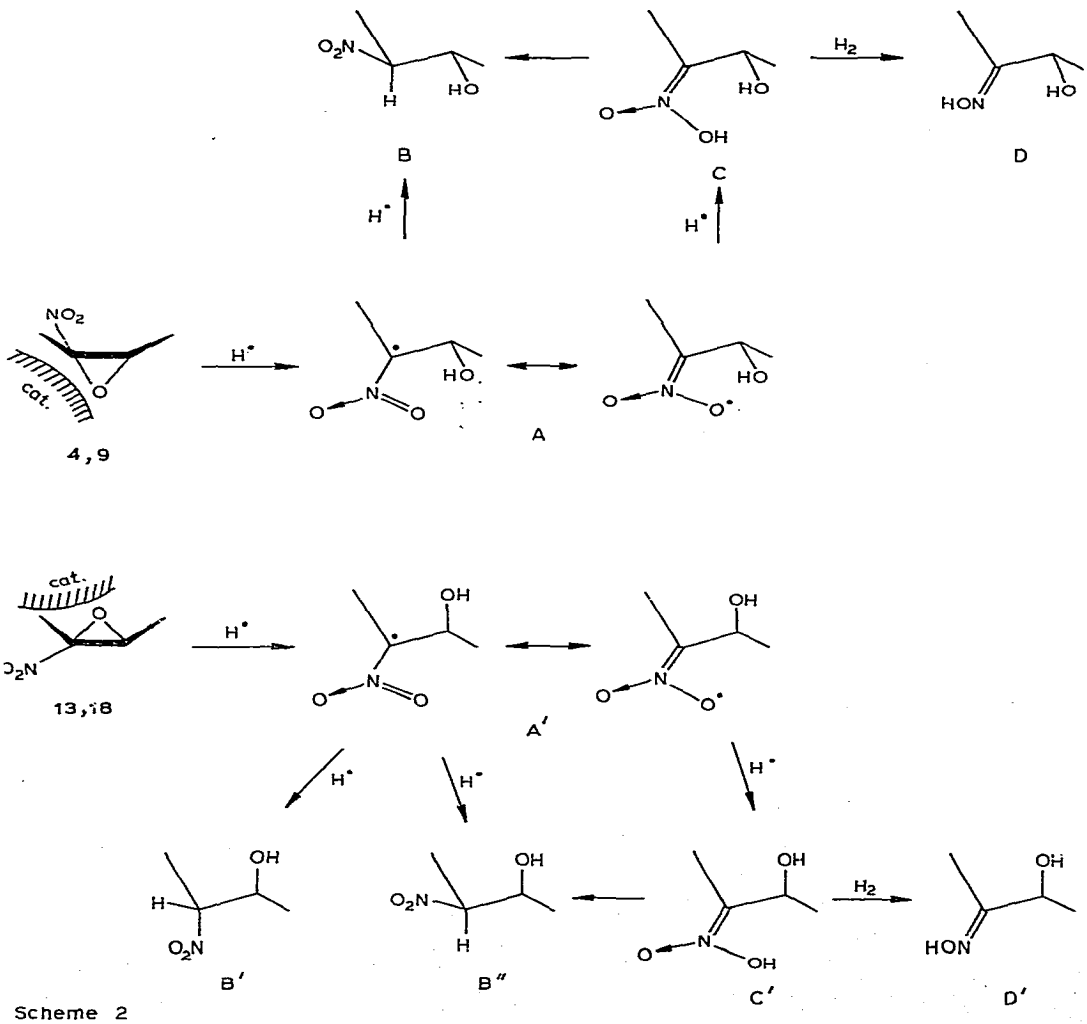
The foregoing results would appear to constitute *prima facie* indications that palladium acts from the rear side of the oxirane ring (in accord with the concept of Mitsui and co-workers) only for **13** and **18**, but from the oxygen side for **4** and **9**, and that platinum acts from the oxygen side exclusively (for **4** and **9**), predominantly (for **13**), or to a considerable degree (for **18**). However, the validity of such conclusions would have to rest on the premise that all of the reaction products *isolated* were in fact the same as those primarily engendered, and that they did not originate, in part, from a secondary epimerization of intermediates having an axial nitro group on C-3. It has been established that an axial nitro group on this atom in pyranosides, or on any ring-carbon atom in deoxynitroinositols, is thermodynamically highly disfavored; with one explicable exception, all of the numerous, known compounds of these classes display an equatorial nitro group[16,22]. Hence, it may be expected that axial-nitro glycosides, arising from epoxides by hydrogen donation to C-3 on the $\beta$-face of the pyranose ring, will be extremely prone to epimerization that might occur in the reaction medium, or during processing. This would afford the molecule a greater gain in stability than adoption of an alternative, non-chair conformation*. Assuming that possible axial-nitro intermediates would be instantly epimerized by catalytic amounts of base, we performed the platinum hydrogenations of **13** and **18** in the presence of hydrochloric acid. Formation of the amino altrosides **15** and **24** gave proof for oxirane ring-cleavage from "above", and allowed the inference to be drawn that the corresponding, axial-nitro glycosides were, indeed, intermediates in these instances. The large proportion of $\beta$-D-*manno* products formed simultaneously from **18** may have been due to competing hydrogenolysis from "below", facilitated in this substrate by absence of steric hindrance from an axial glycosidic substituent.

As concerns the palladium-catalyzed hydrogenations, we have so far been unable to find any evidence for axial-nitro intermediates, regardless of whether the reaction medium was neutral ethanol or methanol–1,4-dioxane acidified with acetic acid. Admittedly, this does not constitute proof for the absence of such intermediates, because epimerization may have been fast, even in a mildly acidic medium. Moreover, epimerizations may well have been induced by the silica gel used in t.l.c. and in the columns used in some of the processings. However, several runs were processed without the aid of chromatography, and yet, no nitro glycosides other than those mentioned were detected. It may, therefore, be stated, at least, that the palladium-

*Recently, a first derivative of methyl 4,6-*O*-benzylidene-3-deoxy-3-nitro-$\alpha$-D-altropyranoside has been described[23]. It carries a bulky 2-*C*-bis(methoxycarbonyl)methyl substituent replacing OH-2, and was reported to exist in a skew conformation. It epimerized to the more stable, D-*manno* isomer sufficiently slowly to permit its isolation.

catalyzed hydrogenations of **4**, **9**, **13**, and **18** were consistent with non-occurrence of axial-nitro intermediates, although such intermediates would necessarily have to be postulated in the cases of **4** and **9** should the hypothesis of an SN2 type of geometry for hydrogenolysis at C-3 be applied. Without intending to question its validity[18] for benzylic epoxides and related compounds, we contend in the following discussion that this hypothesis is inapplicable for carbohydrate α-nitroepoxides.

A clue to the mechanism operative in the palladium hydrogenations was found in the formation of oximino glycosides which were isolated crystalline (**11** and **20**), or detected by the Griess color reaction. Hydrogenation of nitroalkanes by noble-metal catalysts does not normally lead to oximes, but passes through the nitroso and hydroxylamino stages directly to the amine stage[24,25]. Arrest of the sequence in the nitroso oxidation-state by way of tautomerization to oximes (which are relatively




Scheme 2

resistant to further hydrogenation) is not a normal event, as nitroso compounds are more rapidly reduced than tautomerized*. In fact, hydrogenation of the nitro alcohol **19** under conditions that produced the oxime **20** from the epoxide **18** did not yield any **20**, nor did any oxime arise from **23**. However, it is well known that oximes can be readily obtained by hydrogenation of nitronic acids and nitronates, *i.e.*, from nitroalkanes, if these are first converted into their salts[24b]. Cyclohexanone oxime has also been obtained from 1-chloro-1-nitrocyclohexane by palladium hydrogenation that was considered to involve intermediary cyclohexanenitronic acid[30]. In view of these facts, a mechanism is proposed for the reactions of the nitroepoxides studied (see Scheme 2).

The catalyst, either platinum or palladium, first transfers a hydrogen atom to the oxirane oxygen atom, generating a radical (A from **4** or **9**; A′ from **13** or **18**). With platinum, a second hydrogen atom is rapidly delivered from an adjacent site, to give nitro alcohols having equatorial (B) and axial (B′) nitro groups, respectively. The nitro alcohols are subsequently hydrogenated, as is usual[15] for platinum catalysis, with retention of configuration, to give the corresponding amines. (An exception is **10**, which was converted into the hexahydrobenzylidene derivative **12** without attack on the nitro group, even though the parent methyl 3-deoxy-3-nitro-β-D-glucopyranoside is readily hydrogenated[31] to the amine.) With palladium, on the other hand, donation of a second hydrogen atom is comparatively slow, and the radicals, being sufficiently long-lived because of resonance stabilization, may await an independent transfer-process, if that is energetically gainful. To the extent that the second transfer occurs at C-3, it will be so directed as to produce the more-favored, equatorial-nitro alcohol; *i.e.*, the same B would arise from A, but B″ would arise from A′. It is suggested that this mode of epoxide hydrogenolysis would also compete in the case of platinum, especially with the β-glycoside **18**, whose lower side is unhindered, accounting for the formation of **21**. However, the radicals A and A′ can alternatively accept hydrogen on the nitro group, thus giving rise to nitronic acid (C and C′). The nitronic acid is then hydrogenated by palladium to the oxime (D or D′), or it tautomerizes to the equatorial-nitro alcohol (B or B″). Differing stabilities of individual nitronic acids, owing to different amounts of $A^{(1,3)}$ strain that is present[22], presumably influence the final product-composition. The scheme explains why **19**, which was portrayed by t.l.c. as the major product, and was, in fact, isolable upon *short*, palladium-catalyzed hydrogenation of **18**, vanished during extended hydrogenation in favor of **20** (that eventually became the sole product isolable), whereas "genuine" **19** gave different products (mainly **22**) instead, and no oxime at all. From **18**, little

*2-Nitrosocyclohexanol and several 3-deoxy-3-nitroso glycosides obtained[26] by oxidation of the corresponding amines with *m*-chloroperoxybenzoic acid showed no tendency to tautomerize, but formed stable dimers. The catalytic hydrogenation of nitrocyclohexane to cyclohexanone oxime, studied[27] in great detail because of its industrial appeal, did not succeed with noble metals or Raney nickel, but required the development of special, metal oxide, mixed catalysts. Oxime formation by palladium-catalyzed hydrogenation of nitroalkenes, believed to take place *via* hydroxylaminoalkenes, is a different matter[24c,28,29].

if any **19** is directly engendered as such, but it arises as its nitronic acid tautomer, which presents itself as **19** in t.l.c. or upon isolation, but persists in solution until it is reduced to **20**.

There are precedents in the literature[9,11,12] for the formation of hexahydro derivatives from carbohydrate benzylidene acetals on hydrogenation in the presence of platinum or Raney nickel, but this type of reaction seems to have been encountered infrequently, and hydrogenolytic removal of the acetal might, rather, have been expected to prevail[32].

## EXPERIMENTAL

*General procedures.* — All catalytic hydrogenations were performed at ambient temperature (21–26°, unless otherwise indicated), with hydrogen at a pressure slightly above atmospheric, and efficient shaking of the vessel. The palladium catalyst (10% Pd-on-carbon) was obtained from Matheson Coleman & Bell, and was used without pretreatment. Adams' catalyst ($PtO_2 \cdot H_2O$) was purchased from Engelhard Industries, Inc., or BDH Chemicals of Canada, Ltd., and was prehydrogenated in a small volume of the reaction solvent. In experiments performed without the addition of acid, the prehydrogenated platinum catalyst was washed by several decantations with fresh solvent prior to use. For product isolation, the catalysts were filtered off and washed exhaustively with methanol or ethanol, and the filtrates were evaporated at 35° (bath temperature).

Optical rotations were recorded at room temperature with a Perkin–Elmer 141 automatic polarimeter. Infrared data refer to spectra obtained for Nujol mulls, unless otherwise specified; some absorption bands are characterized as bd (broad), ms (medium strong), s (strong), sh (shoulder), or w (weak). The n.m.r. data were taken from 100-MHz spectra of solutions containing tetramethylsilane as the internal standard, unless otherwise indicated. Thin-layer chromatography was performed on microscope slides coated with silica gel G (E. Merck), or on precoated plates (SIL G-25 $UV_{254}$; Macherey–Nagel & Co.), and spots were made visible by heating the plates after spraying with 0.5% ceric sulfate in 5% sulfuric acid. For detection of amino sugars, a spray of 0.2% ninhydrin in ethanol was also used. The $R_F$ values given are illustrative; they may vary somewhat with minor changes in solvent composition or temperature; starting compounds and authentic samples of products, where available, were routinely spotted alongside unknown products. The developing solvents (v/v) were *A*, 1:2 methanol–chloroform; *B*, 3:2 ethyl acetate–petroleum ether (b.p. 30–60°); *C*, 2:3 ethyl acetate–petroleum ether; *D*, 1:1 ethyl acetate–pentane; and *E*, 1:4 methanol–chloroform.

*6-Amino-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose* (**2**). — The nitro epoxide[5] **1** (300 mg) was hydrogenated for 26 h in 99% ethanol (8 mL) in the presence of platinum catalyst (150 mg). Complete replacement of **1** by a less-polar, main product (**2**), accompanied by traces of two faster-moving by-products, was indicated by t.l.c. (solvent *A*). Filtration, followed by evaporation, gave an oil that was purified

by passage, with solvent *A*, through a small column of silica gel. The fractions containing the contaminants were discarded, and the main product was obtained as a colorless, chromatographically homogeneous syrup that crystallized from methanol–ether, to give 165 mg (62%) of **2**, m.p. 123–125°, $[\alpha]_D$ −11.3° (*c* 0.3, water); $\nu_{max}$ 3400 (s, OH and NH), ~3200 (sh, NH bending overtone), 1615 (ms, NH bending), and 1080 $cm^{-1}$ (s, C–N stretching). The n.m.r. data for $D_2O$ solution, expressed as p.p.m. from the DOH lock-signal: −1.28 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), +0.46 (d, 1 H, $J_{3,4}$ 2.5 Hz, H-3), +0.75 (dd, 1 H, $J_{3,4}$ 2.5, $J_{4,5}$ 8.5 Hz, H-4), +0.90 (o, 1 H, H-5), +1.85 (dd, 1 H, $J_{5,6}$ 3.5, $J_{6,6'}$ 13.5 Hz, H-6), +2.09 (dd, 1 H, $J_{5,6'}$ 7, $J_{6,6'}$ 13.5 Hz, H-6′), and 3.24 and 3.39 (2 s, 3 H each, $Me_2C$).

*Anal.* Calc. for $C_{19}H_{17}NO_5$ (219.2): C, 49.30; H, 7.82; N, 6.39. Found: C, 49.31; H, 7.79; N, 6.41.

A few drops of acetic anhydride were added to a sample of **2** (15 mg) in methanol (0.5 mL). The solution was evaporated, and several portions of methanol were added to, and evaporated from, the crystalline residue, which was then washed thoroughly with ether, and dried in a desiccator. The N-*acetyl derivative* **3** (17 mg, 95%) showed m.p. 166–167°, $[\alpha]_D$ +6° (*c* 0.5, methanol) {lit.[14] m.p. 165–167°, $[\alpha]_D$ +5° (methanol)}; $\nu_{max}$ 3420 and 3340 (s, NH and OH), and 1660 $cm^{-1}$ (s, amide CO).

*Hydrogenation of β-*D*-gulo nitroepoxide*[3] **4**. — *A. With palladium.* Compound **4** (60 mg) was hydrogenated at 19° with Pd/C (30 mg) in 7:3 methanol–1,4-dioxane (6 mL), with addition of M acetic acid (0.3 mL). After 8 and 15 min, t.l.c. with solvent *B* showed a strong spot ($R_F$ 0.33) corresponding to that of authentic *β*-D-galactoside **5**, together with a small proportion of remnant **4** ($R_F$ 0.76); after 30 min, the latter was diminished to a mere trace seen only upon heavy spotting of the solution, and after 60 min, **4** was no longer visible. The suspension was filtered, and the filtrate showed $\alpha_D$ +0.31° (1-dm tube), which implied a specific rotation close to that reported[33] for *methyl 4,6-*O*-benzylidene-3-deoxy-3-nitro-β-*D*-galactopyranoside* (**5**) in *N,N*-dimethylformamide, $[\alpha]_D$ +24.8°. Evaporation gave a crystalline residue (58 mg) that, after recrystallizing from absolute ethanol and washing with ether–petroleum ether, melted at ~230° (dec.) and had an i.r. spectrum identical with that of authentic **5**; lit.[33] m.p. 230–231° (dec.). The mother liquor of recrystallization showed a faintly positive Griess test[15].

*B. With platinum.* Compound **4** (300 mg) in ethanol (15 mL) was hydrogenated for 51 h in the presence of platinum catalyst (300 mg). Filtration and evaporation gave a crystalline material (260 mg, m.p. 200–206°) which, according to t.l.c. (solvent *A*) consisted of a slow-moving product with a trace of a faster-moving by-product. The material was washed by trituration with water, air-dried and recrystallized from chloroform, to give *methyl 3-amino-4,6-*O*-benzylidene-3-deoxy-β-*D*-galactopyranoside* (**6**) as needles (176 mg, 63%), m.p. 217–218°, $[\alpha]_D$ −40° (*c* 0.35, ethanol); $\nu_{max}$ 3300 region (several bands; OH, NH), 3100 (ms, NH bending overtone), and 1575 $cm^{-1}$ (s, NH bending); n.m.r. data ($CDCl_3$): $\delta$ 7.6–7.25 (m, 5 H, Ph), 5.52 (s, 1 H, PhCH), 6.4–6.05 (m, unresolved, 5 H), 3.54 (s, 3 H, OMe), 3.45 (narrow m, H-5), 2.80 (dd, 1 H, $J_{2,3}$ 10, $J_{3,4}$ 3.5 Hz, H-3), and 2.45 (broad s, OH and $NH_2$).

*Anal.* Calc. for $C_{14}H_{19}NO_5 \cdot 1/3\ H_2O$ (287.3): C, 58.52; H, 6.90; N, 4.87. Found: C, 58.51; H, 6.60; N, 5.09.

A sample (30 mg) of **6** was *N*-acetylated as described for **2**. The crystalline, crude product **7** (37 mg) was homogeneous in t.l.c. (solvent *A*), and had m.p. 283–285°, raised to 294–295° by recrystallization from chloroform–ether; $[\alpha]_D$ +23° (*c* 0.5, ethanol); $\nu_{max}$ 3450 (bd, OH), 3300 (sharp, NH), 1650 (s, amide CO), and 1555 $cm^{-1}$ (s, NH bending); n.m.r. data ($Me_2SO$-$d_6$): $\delta$ 7.4 region (m, 5 H, Ph), 5.54 (s, 1 H, PhCH), 4.23 (d, 1 H, $J_{1,2}$ 7.5 Hz, H-1), 4.05 (narrow m, superposed on broad m, 4 H total intensity), 3.60 (narrow m, 1 H), 3.43 (s for OMe superposed on unresolved m, 6 H total intensity), and 1.85 (s, 3 H, NAc).

The acetamido derivative **7** (30 mg) was debenzylidenated with 70% aqueous acetic acid at 98°. The reaction was complete after 20 min (t.l.c. with solvent *A*). The solution was evaporated to dryness, with co-evaporation of added methanol, and the solid product was recrystallized from methanol–ether, to give *methyl 3-acetamido-3-deoxy-β-*D*-galactopyranoside* (**8**) as needles (19 mg, 70%), m.p. 230–232°, unchanged on further recrystallization, and undepressed on admixture with authentic **8**; $[\alpha]_D$ +50° (*c* 0.5, water), lit.[17] $[\alpha]_D$ +52°.

*Hydrogenation of β-*D*-allo nitroepoxide*[3] **9**. — *A. With palladium in methanol–1,4-dioxane.* In a pilot experiment, **9** (21 mg) in 7:3 methanol–1,4-dioxane (3.8 mL) plus M acetic acid (0.2 mL) was hydrogenated with Pd/C (12 mg). After 1 h, it was seen in t.l.c. (solvent *B*) that **9** ($R_F$ 0.82) had been completely replaced by a major product ($R_F$ 0.72) and a minor one ($R_F$ 0.31), corresponding to the known[34] *β-*D-glucoside **10** and the hitherto unknown oxime **11**, respectively. There was also an unidentified trace spot ($R_F$ 0.62). The suspension was filtered, and the filtrate showed $\alpha_D$ −0.49° (1-dm tube), corresponding to a specific rotation of ~−93°. (Pure **10** has[34] $[\alpha]_D$ −72.5° in ethanol.) Solvent removal, followed by evaporation of added methanol and ethyl acetate from the partially crystalline residue, gave a material that, on crystallization from ethanol, yielded **10**, m.p. 182–183° (lit.[34] m.p. 181–182°), identified with an authentic sample through i.r. spectra. The mother liquor gave a pronounced, purple color in the Griess test[15].

*B. With palladium in ethanol.* Compound **9** (400 mg) in 99% ethanol (40 mL) was hydrogenated with Pd/C (100 mg) for 24 h. The t.l.c. pattern was similar to that in A. The crystalline product (415 mg) was chromatographed on a column (19 × 1 cm) of silica gel by means of solvent *C*. The faster-moving component (the main product) was obtained crystalline, and homogeneous in t.l.c. (345 mg, 90%), m.p. and mixture m.p. 181–183°, identical with *methyl 4,6-*O*-benzylidene-3-deoxy-3-nitro-β-*D*-glucopyranoside* (**10**) according to i.r. and n.m.r. spectra.

Subsequent fractions from the column furnished crystalline *methyl 4,6-*O*-benzylidene-3-deoxy-3-oximino-β-*D*-ribo-hexopyranoside* (**11**) in a yield of 27 mg (7%), m.p. 169° (dec.), unchanged on recrystallization from ethyl acetate–petroleum ether; $[\alpha]_D$ −55.7° (*c* 0.4, chloroform); $\nu_{max}$ 3390–3100 (bd, C-OH and N-OH) and 1600–1570 $cm^{-1}$ (w, C=N); n.m.r. data ($Me_2CO$-$d_6$): $\delta$ 7.4 (m, 5 H, Ph), 5.70

(s, 1 H, PhCH), 4.8 region (m, 3 H, H-1,2,4), 4.4–3.6 (m, 3 H, H-5,6,6'), 3.39 (s, 3 H, OMe), and 2.90 (broad peak, 1 H, OH-2).

*Anal.* Calc. for $C_{14}H_{17}NO_6$ (295.3): C, 56.93; H, 5.80; N, 4.74. Found: C, 57.11; H, 5.92; N, 4.60.

*C. With platinum.* Compound **9** (30 mg) was dissolved in hot, 99% ethanol (5 mL) with addition of a few drops of 1,4-dioxane. The warm solution was introduced into the hydrogenation vessel containing prehydrogenated, ethanol-washed, platinum catalyst (30 mg). The starting material partly crystallized on cooling the solution to room temperature, but redissolved within the first 20 min of hydrogenation. After 90 min, the epoxide **9** ($R_F$ 0.82, solvent *B*) was absent, and a single, strong spot at $R_F$ 0.75 in t.l.c. was indicated by the sulfuric acid spray. An additional, but weak, spot at $R_F$ ~0.38 was revealed by ninhydrin (on a separate plate). No significant change in the pattern seemed to occur within the next 16 h. However, at this point, it was ascertained by repeated, careful comparison with authentic **10** that the main spot had a marginally greater $R_F$ value. Presumably, it was a combination spot caused by **10** and a new product (**12**). Hydrogenation was continued, with addition of a further 20 mg of $PtO_2$ (not prehydrogenated), and, after a total reaction-time of 44 h, the preponderant spot, detected by sulfuric acid spray, appeared unchanged (in solvent *B*), whereas ninhydrin now indicated only a trace spot at $R_F$ 0.62, and none of the spot previously seen at $R_F$ 0.38. By use of the somewhat less-polar solvent *D*, it was found that, at this stage, the fast-moving spot ($R_F$ 0.77) was clearly distinct from that of authentic **10** ($R_F$ 0.70) which was applied for comparison.

Filtration of the suspension, and evaporation of the filtrate gave a colorless, partially crystalline syrup whose i.r. spectrum displayed a strong, sharp nitro band at 1560 and broad hydroxyl absorption at 3300 $cm^{-1}$; n.m.r. data (60 MHz; $CDCl_3$): $\delta$ 4.67 (t, 1 H, *J* 10 Hz, H-3), 3.57 (s, OMe), and 1.9–0.9 (broad m, ~11 H, cyclohexyl); the remaining protons gave unresolved multiplets in mid-field, and there was no trace of phenyl resonances. According to all of the spectral and chromatographic evidence available, the product was identical with **12** (described in the following section).

*Methyl 4,6-O-(cyclohexylmethylene)-3-deoxy-3-nitro-β-D-glucopyranoside* (**12**). — Methyl 4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside[34] (**10**, 150 mg) was hydrogenated in 99% ethanol (15 mL) in the presence of the platinum catalyst (75 mg, washed after prehydrogenation), the reaction being monitored by t.l.c. with solvent *D*. A trace of **12** ($R_F$ 0.75) appeared above **10** ($R_F$ 0.67) after 30 min, and considerably increased after 5 h; after 26 h, the product ratio, visually estimated, was 1:2. A further 35 mg of catalyst (not prehydrogenated) was added, and the hydrogenation was continued for a total of 46 h. After this period, all of the **10** had disappeared, and **12** was the only fast-moving (and major) product. (There were some trace spots of intermediate and low mobility, the latter being ninhydrin-positive.) Processing gave a colorless syrup which, upon dissolution in a small volume of ethyl acetate, addition of pentane to incipient opalescence, and storage for several days at −15°, yielded a deposit of hard crystals. Isolated by decantation, and washed with

pentane, they weighed only 20 mg, and proved to be a mixture of **12** and the slow-moving by-product(s). The mother liquor, containing the bulk of the reaction product, was allowed to evaporate in the air (with eventual addition of hexane to displace ethyl acetate) to give syrupy **12** that was only very slightly contaminated by slow-moving impurities. Dried in a desiccator, the glassy film (125 mg) showed an i.r. spectrum identical with that of **12** from **9**, and, upon trituration with water and methanol, it readily crystallized as microscopic needles, m.p. 115–116.5°, $[\alpha]_D$ −40.4° (*c* 1.4, chloroform); $\nu_{max}$ 3450 (bd, OH) and 1555 $cm^{-1}$ (s, $NO_2$), and, in the fingerprint region, obvious differences from the benzylidene analog **10**; n.m.r. data ($CDCl_3$): $\delta$ 4.63 (t, $J_{2,3} = J_{3,4}$ = 10 Hz, H-3), 4.32 (d, $J_{1,2}$ 7.5 Hz, H-1), 4.24 (d, *J* 5 Hz, with an additional, very small splitting, cyclohexyl-$CHO_2$), 4.23 (dd, $J_{5,6e}$ 4.3, $J_{6a,6e}$ 10 Hz, H-6e), 3.98 (dd, *J* 7.5 and 10 Hz, H-2), 3.82 (dd, $J_{3,4}$ 10, $J_{4,5}$ 9 Hz, H-4), 3.56 (s, 3 H, OMe), 3.57 (t, *J* 10 Hz, H-6a), 3.33 (o, *J* 4.3, 9, and 10 Hz, H-5), 2.9 (broad, 1 H, exchangeable with $D_2O$, OH-2), and 1.9–0.9 (m, 11 H, cyclohexyl).

*Anal.* Calc. for $C_{14}H_{23}NO_7$ (317.3): C, 52.99; H, 7.31; N, 4.41. Found: C, 52.96; H, 7.35; N, 4.24.

*Hydrogenation of* α-D-manno *nitroepoxide*[3] **13**. — *A. With palladium in methanol–1,4-dioxane.* A solution of **13** (30 mg) and M acetic acid (0.2 mL) in 7:3 methanol–1,4-dioxane (5.5 mL) was hydrogenated in the presence of Pd/C (30 mg). After 5 min, the reaction mixture showed a strong spot migrating like authentic nitro mannoside **14** ($R_F$ 0.8) and a spot of similar strength attributed to the corresponding oximino glycoside ($R_F$ 0.6); a trace spot had $R_F$ 0.35 (t.l.c. in solvent *B*). After 15 min, the epoxide **13** ($R_F$ 0.9) had completely disappeared, and the product pattern was essentially unchanged, remaining so for 19 h. Solvent evaporation then gave a syrup having $[\alpha]_D \sim +50°$ (*c* 2.3, chloroform) and showing a positive Griess reaction[15].

*B. With palladium in ethanol.* In a pilot experiment, hydrogenation of **13** (20 mg) with Pd/C (5 mg) in 99% ethanol (5 mL) gave a result similar to that in A, except that the oxime spot was produced more slowly, and was weaker (relative to the spot attributed to **14**). A small proportion of **13** was still present after 1 h, but, on addition of another 5 mg of catalyst, it disappeared within the next 30 min. The syrup obtained on evaporation had $[\alpha]_D$ +48° (*c* 1, chloroform) and responded weakly to the Griess test.

On a larger scale, **13** (200 mg) was hydrogenated, initially as a partial suspension, with Pd/C (20 mg) in 99% ethanol (20 mL). Processing after 26 h gave a syrup which was chromatographed on a column of silica gel (110 g) by means of solvent *C*. The fractions containing only the fast-moving product ($R_F$ 0.8 in t.l.c. with solvent *B*) yielded 140 mg (70%) of prisms when crystallized from chloroform–petroleum ether, m.p. 143–144° (unchanged on recrystallization), $[\alpha]_D$ +27.3° (*c* 1, chloroform); lit.[35] m.p. 138–139°, $[\alpha]_D$ +27.7°. Identity of the product as *methyl 4,6-O-benzylidene-3-deoxy-3-nitro-*α-D-*mannopyranoside* (**14**) was ascertained by i.r.- and n.m.r.-spectral comparison with an authentic sample.

*C. With platinum.* Compound **13** (100 mg, 0.3 mmol) was hydrogenated as a partial suspension in 99% ethanol (10 mL) containing 0.3 mL of M hydrochloric

acid and 100 mg of platinum catalyst. After 1 h, t.l.c. with solvent *E* indicated absence of **13**, and showed 6 discrete spots: $R_F$ ~0.9, 0.8, and 0.5 (all weak), and ~0.6, 0.2, and 0.07 (strong). As the reaction progressed, the two fast-moving spots disappeared, and those having intermediate $R_F$ values decreased in proportion. After 20 h, the slowest spot was strongly predominant ($R_F$ 0.07 in solvent *E*, and 0.2 in solvent *A*). Processing gave a partly crystalline material (71 mg) from which crystalline, but very hygroscopic, *methyl 3-amino-3-deoxy-α-*D*-altropyranoside hydrochloride* (**15**) (40 mg) could be isolated with difficulty by trituration with absolute ethanol and acetone; $[\alpha]_D$ +84° (*c* 0.3, water); lit.[36] $[\alpha]_D$ +88.2°; $\nu_{max}$ 3340 and 3170, with a shoulder at 3100–3050 $cm^{-1}$, several weak bands in the 2600-$cm^{-1}$ region, and bands at 1600, 1575, and 1500 $cm^{-1}$ that had counterparts in the spectrum of the D-*manno* isomer **17**, but the fingerprint patterns clearly differed.

Acetylation of **15** with acetic anhydride and sodium acetate during 30 min at 98° gave a chromatographically homogeneous product (t.l.c. with solvent *A*), isolated crystalline in almost quantitative yield by the customary procedure involving extraction with chloroform. It was *methyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-*D*-altropyranoside* (**16**), m.p. 176–177° (from chloroform–petroleum ether), $[\alpha]_D$ +34° (*c* 2.7, chloroform); lit.[37] m.p. 177°, $[\alpha]_D$ +34.1° (chloroform); $\nu_{max}$ 3330 (sharp, NH), 1726 (ester CO), and 1665 $cm^{-1}$ (amide CO); n.m.r. data ($CDCl_3$): $\delta$ 6.54 (d, 1 H, *J* 10 Hz, NH-3), 5.08 (dd, 1 H, $J_{3,4}$ 4, $J_{4,5}$ 10 Hz, H-4), 4.82 (dd, *J* 2 and 3.5 Hz, H-2), ~4.7 (m, 2 H), 4.25 (m, 2 H), 4.08 (m, 1 H, H-5), 3.46 (s, 3 H, OMe), 2.13 (s, 3 H, OAc-2), 2.09 (s, 3 H, NAc-3), 2.00 and 1.98 (2 s, 3 H each, OAc-4 and -6). For comparison, we record the n.m.r. data ($CDCl_3$) of the D-*manno* isomer of **16**, prepared by similar acetylation of authentic[38] hydrochloride **17**: $\delta$ 5.90 (d, 1 H, *J* 9 Hz, NH-3), 5.04 (dd, 1 H, $J_{3,4}$ 10.5, $J_{4,5}$ 10 Hz, H-4), 4.95 (dd, 1 H, $J_{1,2}$ 1.5, $J_{2,3}$ 3 Hz, H-2), 4.75 (d, *J* 1.5, H-1), 4.66 (o, *J* 3, 9, and 10.5 Hz, H-3), 4.34 (dd, $J_{5,6}$ 5.3, $J_{6,6'}$ 12 Hz, H-6), 4.17–3.95 (dd, on m, 2 H, H-5,6'), 3.42 (s, 3 H, OMe), 2.17, 2.10, 2.06, and 1.93 (4 s, 3 H each, OAc-2,4,6, and NAc-3).

*Hydrogenation of β-*D*-manno nitroepoxide*[4] **18**. — *A. With palladium in ethanol.* A pilot experiment with **18** (25 mg) and Pd/C (5 mg) in 99% ethanol (5 mL) showed that **18** was replaced after 3 h by two products in the ratio of 1 : 1 (t.l.c. with solvent *B*). One of these migrated like authentic nitro mannoside **19** (somewhat more slowly than **18**), and the other appeared as a slow-moving, double spot attributable to the oximino glycoside **20** (possibly a mixture of geometric isomers). After 24 h, the spot corresponding to **19** had largely, but not entirely, disappeared. A similar experiment, performed on a larger scale (100 mg of **18**), was interrupted after 3 h, and the products were separated by preparative t.l.c. (solvent *B*). Isolated crystalline, the fast-moving product melted at 199°, and had i.r. and n.m.r. spectra identical with those of authentic *methyl 4,6-*O*-benzylidene-3-deoxy-3-nitro-β-*D*-mannopyranoside* (**19**), lit.[33] m.p. 198–199° and[35] 202°; n.m.r. data ($Me_2CO$-$d_6$): $\delta$ 7.4 (m, 5 H, Ph), 5.75 (s, 1 H, PhCH), 4.99 (o, 1 H, $J_{2,3}$ 3.8, $J_{3,4}$ 10.8, $J_{3,OH}$ 1 Hz, H-3), 4.75 (d, 1 H, $J_{1,2}$ 1 Hz, H-1), 4.66 (dd, 1 H, $J_{2,OH}$ 4.5; signal removed by $D_2O$ exchange, OH-2), 4.57 (dd, 1 H, $J_{3,4}$ 10.8, $J_{4,5}$ 9.3 Hz, H-4), 4.50 (septet, 1 H, $J_{2,OH}$ 4.5, $J_{2,3}$ 3.8, $J_{1,2}$ 1 Hz; collapsing

to narrow q on $D_2O$ exchange, H-2), 4.32 (dd, 1 H, $J_{5,6e}$ 5, $J_{6a,6e}$ 10 Hz, H-6e), 3.93 (t, 1 H, $J$ 10 Hz, H-6a), 3.55 (o, H-5, partially overlapped by OMe signal), and 3.51 (s, 3 H, OMe).

The slow-moving material from the preparative t.l.c. was obtained as two fractions (A and B), both crystallizing from chloroform and giving a positive Griess reaction[15]. They were *methyl 4,6-O-benzylidene-3-deoxy-3-oximino-β-*D-arabino-*hexopyranoside* (**20**) melting with decomposition at 179–180° (A) and 165–166° (B), and showing virtually identical 60-MHz n.m.r. spectra, as well as very similar i.r. spectra: $\nu_{max}$ for A, 3360 (sharp, with broad shoulder at 3200), and, for B, 3540 (sharp) and 3350 $cm^{-1}$ (bd, with sh at 3200); there were very slight differences in the well resolved, fingerprint-patterns. The 100-MHz, n.m.r. data for A in $Me_2CO$-$d_6$: $\delta$ 7.4 (m, 5 H, Ph), 5.70 (s, 1 H, PhCH), 5.30 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 4.64 (d, 1 H, $J_{3,4}$ 9.5 Hz, H-4), 4.49 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-2), 4.30 (dd, 1 H, $J_{5,6e}$ 5, $J_{6a,6e}$ 10 Hz, H-6e), 3.88 (t, 1 H, $J$ 10 Hz, H-6a), and 3.51 (s, 3 H, OMe, superposed on m, H-5). The =N-OH proton was seen as a peak at $\delta$ 11.2 (removable by $D_2O$ exchange) in a separate spectrum of a $CDCl_3$ solution containing $Me_2SO$-$d_6$.

*Anal.* Calc. for $C_{14}H_{17}NO_6$ (295.3): C, 56.94; H, 5.80; N, 4.74. Found: C, 57.12; H, 6.00; N, 4.63.

*B. With palladium in methanol–1,4-dioxane.* When **18** (100 mg) was hydrogenated in the presence of Pd/C (50 mg) in 7:3 methanol–1,4-dioxane (10 mL) and 0.1M acetic acid (2 mL), t.l.c. with solvent *D* after 8 min indicated spots of **19** ($R_F$ 0.45) and **20** ($R_F$ 0.25); after 45 min, all of the **18** ($R_F$ 0.6) had disappeared, and the products were present in comparable proportions, as estimated visually. (Some runs were processed at this stage, attempts being made to separate the products, without recourse to chromatography, by trituration of the solid mixture with ether, and fractional recrystallization therefrom. However, it was not possible to obtain **19** and **20** in pure form in this way, and only crystalline fractions enriched in one or the other compound could be elaborated.) When hydrogenation was continued without interruption for 36 h, **20** remained as the sole product detectable, and it was subsequently isolated crystalline (from ethyl acetate–petroleum ether) in high yield; m.p. 167–168° (dec.); i.r. and n.m.r. spectra as in section A; the 60-MHz, n.m.r. spectrum ($CDCl_3$) showed a small satellite, slightly upfield of the main PhCH signal, which was possibly due to *syn-anti* isomerism.

*C. With platinum.* Compound **18** (1.00 g, 3.24 mmol) was hydrogenated for 4.5 h as a partial suspension in 95% ethanol (90 mL) in the presence of M hydrochloric acid (4 mL) and platinum catalyst (1.0 g). At least six spots, as described in the Results section, were seen in t.l.c. (solvent *A*). Filtration, and evaporation of the solvent, gave a solid from which, by recrystallization from hot ethanol and a small proportion of ethyl acetate, the product corresponding to the strongest spot ($R_F$ 0.5) was obtained in pure form. It was the monohydrate of *methyl 3-amino-4,6-O-(cyclohexylmethylene)-3-deoxy-β-*D-*mannopyranoside hydrochloride* (**22**); yield, 340 mg (31%), m.p. 210–212°, $[\alpha]_D$ −77.6° (*c* 0.7, 90% ethanol); $\nu_{max}$ 3400 (s, with sh at 3100), several weak bands in the 2600-$cm^{-1}$ region, 1590 and 1530 $cm^{-1}$ (ms);

n.m.r. ($Me_2SO$-$d_6$): no low-field, Ph signals, but intense multiplets at $\delta$ 1.9–0.9 attributable to cyclohexyl.

*Anal.* Calc. for $C_{14}H_{26}ClNO_5 \cdot H_2O$ (341.8): C, 49.19; H, 8.25; N, 4.10. Found: C, 48.87; H, 8.53; N, 4.05.

A sample of **22** was quantitatively acetylated with acetic anhydride in pyridine during 90 min at 25°, to give chromatographically homogeneous N-*acetyl*-O-*acetyl* derivative of **22**, crystallized from chloroform–petroleum ether; m.p. 210–211°, $[\alpha]_D$ −78.3° (*c* 1, chloroform); n.m.r. ($CDCl_3$): $\delta$ 5.52 (dd, $J_{1,2}$ 1.3, $J_{2,3}$ 3.3 Hz, H-2), 5.42 (broad signal, NH), 4.57 (d, *J* 1.3 Hz, H-1), 4.38 (dd, $J_{2,3}$ 3.3, $J_{3,4}$ 10.4 Hz, with lines broadened by coupling with NH, H-3), 4.3–4.1 (m, 2 H), 3.7–3.2 (two superposed t, *J* 10 Hz, for H-4 and H-6a, with upfield line obscured by OMe; and adjoining m for H-5), 3.48 (s, 3 H, OMe), 2.16 (s, 3 H, OAc), 1.97 (s, 3 H, NAc), and 1.9–0.8 (m, 11 H, cyclohexyl).

*Anal.* Calc. for $C_{18}H_{29}NO_7$ (371.4): C, 58.20; H, 7.87; N, 3.77. Found: C, 57.96; H, 7.99; N, 3.64.

The procedure of fractional recrystallization from ethanol–ethyl acetate was repeated with the evaporated mother liquors of crystallization of **22**, to give a mixed fraction consisting of **22** and more-polar material, not investigated further. Another repetition of the process afforded crystals (50 mg) of the fastest-moving hydrogenation product ($R_F$ 0.95), characterized by insolubility in water, and a negative ninhydrin reaction. It was *methyl 4,6-O-(cyclohexylmethylene)-3-deoxy-3-nitro-β-*D*-mannopyranoside* (**21**), m.p. 212–214° after recrystallization from methanol–water; $[\alpha]_D$ −77.4° (*c* 0.9, chloroform); $\nu_{max}$ 3400 (s, OH) and 1560 $cm^{-1}$ (s, $NO_2$), with a fingerprint pattern clearly distinct from that of the benzylidene analog **19**; n.m.r. data ($Me_2CO$-$d_6$): $\delta$ 4.85 (dd, 1 H, $J_{2,3}$ 3.5, $J_{3,4}$ 10.5 Hz, H-3), 4.71 (d, 1 H, $J_{1,2}$ 1.2 Hz, H-1), 4.46 (2 H, dd for H-2 superposed on d, *J* 5 Hz, for cyclohexyl-$CHO_2$), 4.28 (dd, 1 H, $J_{3,4}$ 10.5, $J_{4,5}$ 9.3 Hz, H-4), 4.17 (dd, 1 H, $J_{5,6}$ 4.7, $J_{6a,6e}$ 10 Hz, H-6e), 3.66 (t, 1 H, *J* 10 Hz, H-6a), 3.50 (s, 3 H, OMe), 3.36 (o, H-5), and 1.9–0.8 (m, cyclohexyl).

*Anal.* Calc. for $C_{14}H_{23}NO_7$ (317.3): C, 52.99; H, 7.31; N, 4.41. Found: C, 52.97; H, 7.47; N, 4.24.

Finally, a crystalline fraction that contained only slow-moving ($R_F$ ~0.1), ninhydrin-positive material could be elaborated from the hydrogenated product mixture; it showed $[\alpha]_D$ −127.6° (*c* 1.2, water); reported for *methyl 3-amino-3-deoxy-β-*D*-altropyranoside hydrochloride*[39] (**24**), −138°, and for its *β-*D*-manno* isomer[17] (**25**), −68.5°. The product, judged to be mainly **24** on the basis of these data, gave an i.r. spectrum quite different from that of authentic[17] **25**. Its $R_F$ value (0.4) was also different from that of **25** ($R_F$ 0.25), although both samples showed considerable trailing (in solvent *A*). After hydrolysis in refluxing, M hydrochloric acid for 2 h, the corresponding $R_F$ values were 0.3 (elongated spot) and 0.25.

*D. With palladium followed by platinum.* Compound **18** (50 mg) was hydrogenated for 45 min in the presence of palladium, as described under B. The suspension was filtered, and the filtrate was evaporated to dryness; the residue was dissolved in

95% ethanol (4 mL), and hydrogenated for 24 h in the presence of platinum catalyst (50 mg) and M hydrochloric acid (0.15 mL). T.l.c. then indicated the absence of **19** and **20**, which were replaced by a small proportion of a faster-moving, ninhydrin-negative product (subsequently identified as **21**) and three slow-moving, ninhydrin-positive compounds as the major products. The most mobile of the latter corresponded to **22**, and the others were, evidently, deacetalated amino glycosides. Processing of the reaction mixture gave a crystalline mixture of amino sugar hydrochlorides (from ethyl acetate–petroleum ether) that could not be separated. Because of the relatively low levorotation ($[\alpha]_D$ −51°, water) and the results of paper chromatography after total acid hydrolysis, it was concluded that the D-*manno* configuration predominated. The nitro glycoside **21** was isolated from the mother liquor by chromatography on a small column of silica gel, with 1:2 ethyl acetate–petroleum ether as the eluant; yield, 10 mg from two combined runs. It was identified by its i.r. and n.m.r. spectra.

No differences in the results were detected when, in an identical experiment, the palladium-catalyzed hydrogenation solution was stirred with silica gel for 24 h prior to the platinum-catalyzed hydrogenation.

Another palladium-catalyzed hydrogenation of **18** was performed on the same scale, but for 36 h, in order to effect complete conversion into oxime **20** (see method B). Subsequent hydrogenation (24 h) in the presence of platinum as just described, followed by acid hydrolysis of the products, gave a mixture of amino sugars showing the same pattern as the preceding in paper chromatography.

*Hydrogenation of benzylidenenitro-β-*D*-mannoside*[33] **19**. — Compound **19** (400 mg) in 7:3 methanol–1,4-dioxane (40 mL) was hydrogenated in the presence of Pd/C (200 mg) for 30 h. The ninhydrin-positive, strongly preponderant product ($R_F$ 0.5, in t.l.c. with solvent *E*) was the (cyclohexylmethylene) acetal **22** (as the free base); see the Results section concerning 3 minor, t.l.c. spots. Part of the reaction mixture was slightly acidified with acetic acid, evaporated to dryness, and the residue further hydrogenated, in the presence of platinum, in ethanol containing a small proportion of hydrochloric acid. No visible change occurred as far as **22** was concerned, although the ninhydrin-negative, minor by-products disappeared, and a slow-moving, small spot of deacetalated amino glycoside appeared (9 h; unchanged after 24 h). Processing then gave **22** as fine needles from ethanol–ethyl acetate, m.p. 210–212° (dec.), identical with **22** obtained from **18** (i.r. spectra). Another part of the original hydrogenation solution was briefly warmed after addition of aqueous hydrochloric acid (~0.7 molar excess) and then evaporated to dryness, whereby deacetalation occurred. The white, crystalline product had $[\alpha]_D$ −66° (*c* 0.5, water) and $R_F$ 0.1 (solvent *E*); its i.r. spectrum confirmed the identity with known[17] **25**.

Hydrogenation of **19** (25 mg) with platinum (25 mg) in ethanol (5 mL) containing M hydrochloric acid (0.1 mL) was examined by t.l.c. with solvent *A*.

*Hydrogenation of nitro-β-*D*-mannoside*[17] **23**. — Compound **23** (100 mg) was hydrogenated in the presence of Pd/C (50 mg) in 7:3 methanol–1,4-dioxane (10 mL) and 0.1M acetic acid (2 mL). Inspection by t.l.c. (solvent *A*) revealed remaining **23**

($R_F$ 0.7) after 1 and 3 h; virtually all of it was consumed after 10.5 h, and a strong, ninhydrin-positive spot ($R_F$ 0.1) was produced, accompanied by trace spots having intermediate mobilities. The Griess test[15] was negative. Evaporation of the solution, to which an equivalent amount of hydrochloric acid had been added, followed by evaporation of added ethanol from the residue, gave a colorless syrup that yielded crystalline **25** on treatment with ethanol and ethyl acetate; m.p. 202–203° (dec.), $[\alpha]_D$ −62.5° (*c* 0.7, water). The i.r. spectrum was superposable on that of an authentic sample, although the crystal shape and m.p. were different. Recrystallized from absolute methanol, the product was obtained as fine, rectangular prisms that melted at 230–231° (dec.) as reported[17].

A hydrogenation of **23** in the presence of *platinum and ethanol* (as described for **18**) was slow, with a visually estimated 50 and 25% of starting compound remaining after 4.5 and 21 h, respectively. The only reaction-product detected chromatographically, and isolated crystalline, was **25**. The same reaction had previously been performed[17] in *aqueous* solution, wherein it was noticeably faster (2–3 h for completion, according to unpublished records).

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