THE OXIDATION OF PARTIALLY SUBSTITUTED 2-ACETAMIDO-2-DEOXYALDOSES WITH METHYL SULFOXIDE–ACETIC ANHYDRIDE. SOME 2-ACETAMIDO-2-DEOXYALDONIC ACID DERIVATIVES

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ABSTRACT

The oxidation of 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose (**1**) by methyl sulfoxide–acetic anhydride gave crystalline 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucono-1,5-lactone (**2**) in high yield. Debenzylation of **2** yielded 2-acetamido-2-deoxy-D-glucono-1,5-lactone (**3**). The reaction of **2** with methanol gave methyl 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-gluconate (**4**), and this compound was debenzylated to give the free ester (**5**).

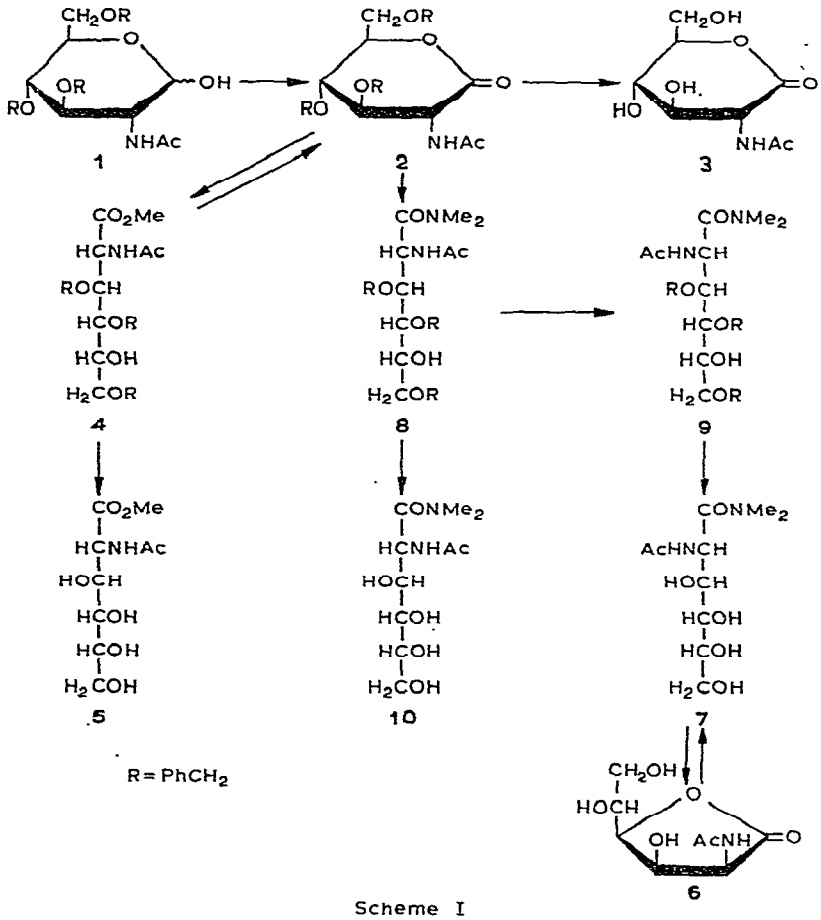
With dimethylamine, 2-acetamido-2-deoxy-D-mannono-1,4-lactone (**6**) gave a crystalline di-*N*-methylamide (**7**) that could also be obtained through the action of the same reagent on the mixture of compounds obtained by the oxidation of 2-acetamido-2-deoxy-D-glucose with unbuffered, aqueous bromine. Since **7** could be converted back into **6**, the two compounds are deemed to have the same configuration. With dimethylamine, the lactone **2** gave a mixture of two 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-di-*N*-methylhexonamides (**8** and **9**) that was debenzylated to afford a mixture of amides (**10** and **7**). The n.m.r. spectrum of **7** was clearly visible in the spectrum of the mixture of **10** and **7**. From this and from other evidence, it was concluded that **2** reacts with dimethylamine to give 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-di-*N*-methyl-D-gluconamide (**8**) and that this, in turn, is partially epimerized into its D-*manno* analog (**9**).

2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-D-glucopyranose (**11**) and its D-*manno* analog (**12**) are oxidized by methyl sulfoxide–acetic anhydride to the corresponding 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxyhexono-1,5-lactones (**13** and **14**, respectively); in each case, the saturated lactone is accompanied by an unsaturated compound. The i.r. and n.m.r. spectra of this substance showed that it is 2-acetamido-4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enono-1,5-lactone (**15**).

RESULTS AND DISCUSSION

In a study of the oxidation of 2-acetamido-2-deoxyaldoses with unbuffered bromine-water[1], the need arose for certain 2-acetamido-2-deoxyaldonic acid deriv-

atives of unequivocal structure and configuration. Earlier work had shown that aldoses that are fully benzylated except at O-1 are readily oxidized by methyl sulfoxide–acetic anhydride to the corresponding aldonolactones[2,3], and the oxidation of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose to a D-gluconic acid derivative by methyl sulfoxide–phosphorus pentaoxide has also been reported[4]. As 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose (**1**, Scheme I) is readily preparable from 2-acetamido-2-deoxy-D-glucose[5,6], we initially turned our attention to the oxidation of this compound.



Scheme I

At room temperature, methyl sulfoxide–acetic anhydride converted **1** into 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucono-1,5-lactone (**2**). The product was isolated, in crystalline form, in 92% yield; it was dextrorotatory ($[\alpha]_D$ +123.3° in chloroform) as expected from the lactone rule[7], and its n.m.r. and i.r. spectral features were compatible with the assigned structure. Catalytic removal of the benzyl groups from **2** in a nonaqueous solvent afforded crystalline 2-acetamido-2-deoxy-D-glucono-1,5-lactone (**3**); it, too, is dextrorotatory ($[\alpha]_D$ +137.7° in water) and its i.r. spectrum

clearly shows the presence of a 1,5-lactone ring. The compound appeared to be identical with a sample prepared by the late Dr. N. M. Cross through the action of acetic anhydride–aqueous sodium hydroxide on 2-amino-2-deoxy-D-gluconic acid[8,*]. The lactone **3** was found to be stable in the crystalline form; dissolved in 2-methoxyethanol, it is chromatographically homogeneous, whereas, in aqueous solution, it changes rather quickly, yielding several products, one of which is 2-acetamido-2-deoxy-D-gluconic acid[1].

With methanol at room temperature, 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucono-1,5-lactone (**2**) gave a syrupy methyl ester (**4**) that appeared to be pure by all available criteria but, perhaps significantly, reverted to **2** on prolonged storage. In passing, it may be noted that, although **2** reacts readily with methanol at room temperature (to give **4**), it can be recrystallized without change from boiling 95% ethanol. Catalytic removal of the benzyl groups from the ester **4** gave methyl 2-acetamido-2-deoxy-D-gluconate (**5**); this compound proved to be identical with one obtained earlier[1] through the action of methanol on the mixture of compounds that had been obtained by the oxidation of 2-acetamido-2-deoxy-D-glucose with unbuffered bromine-water.

In the preceding paper[1], we described an epimerization caused by an amine. The mixture of products obtained on oxidation of 2-acetamido-2-deoxy-D-glucose with unbuffered bromine solution gave a crystalline salt of 2-acetamido-2-deoxy-D-gluconic acid when it was treated with an excess of dicyclohexylamine. Following this treatment, the remaining mixture afforded a lactone having i.r. and n.m.r. spectra identical with those of 2-acetamido-2-deoxy-D-mannono-1,4-lactone[1] (**6**). It appeared likely that the alkalinity of the dicyclohexylamine had caused this epimerization from the *gluco* to the *manno* series; in any case, the ease with which 2-acetamido-2-deoxyaldonic acid derivatives may be epimerized has a direct bearing on the utility of these substances for synthetic purposes, and so, in the course of the present research, we have devoted further attention to this matter.

The di-*N*-methylamides of aldonic acids are usually highly crystalline compounds; they have been shown to be of some synthetic utility[2,9,10]. Treatment of **6** with dimethylamine yielded a crystalline di-*N*-methylamide; that this was, indeed, 2-acetamido-2-deoxy-di-*N*-methyl-D-mannonamide (**7**) was shown by its elemental composition and by conversion of the compound back into **6**. Examination of the n.m.r. spectrum of **7** clearly showed two *N*-methyl signals at τ 6.91 and 7.15, and an *N*-acetyl signal at 8.17. The crude reaction mixture obtained on oxidation of 2-acetamido-2-deoxy-D-glucose with bromine water[1] was also treated with dimethylamine. A single crystalline product was isolated, and this was shown to be **7**. Thus, we have here a second example of a *gluco*-to-*manno* conversion taking place under the influence of an amine.

With this background, we turned our attention to 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucono-1,5-lactone (**2**). The optical rotation of the products from

*However, our attempts to prepare **3** by this method were not successful, the product being neither homogeneous nor crystalline.

the reaction mixture of **2** with dimethylamine (see Table I) was found to increase as the reaction period was extended to four days. The n.m.r. spectra of the reaction

TABLE I

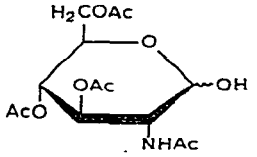
REACTION OF 2-ACETAMIDO-3,4,6-TRI-*O*-BENZYL-2-DEOXY-D-GLUCONO-1,5-LACTONE (**2**) WITH DIMETHYLAMINE

Duration of reaction	*Relative intensities of n.m.r. signals in products* **8** *and* **9**				$[\alpha]_D$ (*in* $CHCl_3$) *of the product (degrees)*
	N-*Methyl*		N-*Acetyl*		
	manno (**9**)	*gluco* (**8**)	*manno* (**9**)	*gluco* (**8**)	
τ:	*7.01, 7.15*	*7.08, 7.22*	*8.12*	*8.00*	
15 min	1	25	1	25	±0
1 h	1	9	1	9	+4.2
20 h	2	3	2	3	+17.6
4 days	3	1	3	1	+28.1

products obtained at various intervals (see Table I) were more revealing; the presence of two di-*N*-methylamides was plainly evident, as there were two pairs of *N*-methyl signals and two *N*-acetyl signals. The relative intensities of these signals (see Table I) were internally consistent, and clearly showed that one di-*N*-methylamide preponderated at the outset and that it was subsequently converted, to a considerable extent, into a second di-*N*-methylamide. After 20 h, the reaction mixture was processed, to afford a mixture that had the elemental composition of a 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-di-*N*-methylhexonamide (**8**, **9**) and an optical rotation of $[\alpha]_D$ +17.6° (chloroform); a different mixture, $[\alpha]_D$ ±0° (chloroform), was obtained by processing after a reaction time of 15 min. The two mixtures were separately debenzylated, and the n.m.r. spectra of the resulting products were studied. The conclusions reached were consistent with the results observed for the parent tri-*O*-benzyl derivatives. The de-*O*-benzylated material derived from the product having $[\alpha]_D$ +17.6° had an n.m.r. spectrum that clearly showed it to be a mixture of two isomers; two pairs of *N*-methyl signals and two *N*-acetyl signals were well delineated. The spectrum showed that one isomer in this mixture of di-*N*-methylamides, obtained after prolonged treatment of **2** with dimethylamine and subsequent debenzylation, was identical with 2-acetamido-2-deoxy-di-*N*-methyl-D-mannonamide (**7**). On the other hand, the de-*O*-benzylated material derived from the product having $[\alpha]_D$ ±0° appeared to have the n.m.r. spectrum of a single 2-acetamido-2-deoxy-di-*N*-methylhexonamide: signals at τ 6.85 and 7.18 indicating two *N*-methyl groups, as well as at τ 8.15 (one *N*-acetyl group), were evident. These signals were not identical with those in the n.m.r. spectrum of **7**. It appears, then, that 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucono-1,5-lactone (**2**) reacts promptly with dimethylamine to give a single product, presumably 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-di-*N*-methyl-D-gluconamide (**8**), and that partial epimerization to the corresponding mannonamide (**9**) then takes place. It is

concluded that amides of this type are susceptible to epimerization by amines, and that substitution on the hydroxyl groups at C-3, 4, and 6 by benzyl is without qualitative effect on the reaction. It should be emphasized that these epimerizations were all observed with 2-acetamido-2-deoxyaldonic acid derivatives. Non-nitrogenous aldonic acid derivatives, such as 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone[2], D-glucono-1,5-lactone[2], and D-idonolactone[9], have been shown to give the corresponding di-*N*-methylamides without detectable isomerization.

It was of particular interest to ascertain whether the oxidation by methyl sulfoxide–acetic anhydride, which proved so effective with 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucose (**1**), is of general applicability. 2-Acetamido-2-deoxyaldoses that are fully acetylated except at O-1 (*e.g.*, **11** and **12**) are relatively accessible, and we therefore extended our oxidation studies to 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-D-glucopyranose[11] (**11**, Scheme II). With methyl sulfoxide–acetic anhydride



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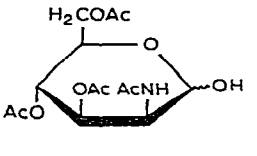

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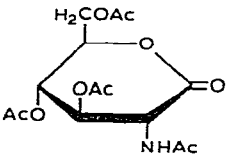

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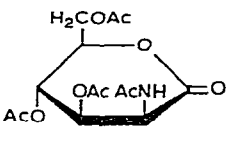

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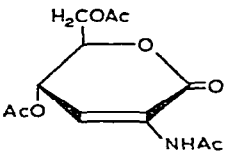

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Scheme II

at room temperature, **11** gave a mixture of two products that could be separated by column chromatography. One of the compounds, obtained in crystalline form in 15% yield, had the elemental composition and spectral properties of the product expected and is, therefore, assigned the structure and configuration represented by **13**, namely, 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-D-glucono-1,5-lactone. The major product of the oxidation of **11** was obtained as a syrup in 50% yield; its

elemental composition, chemical properties, and i.r. spectrum clearly showed it to be an unsaturated, acetamido lactone. The 100-MHz p.m.r. spectrum of the compound included a broad singlet at τ 1.98 and, hence, the acetamido group was attached to a double-bonded carbon atom. Also at low field was a doublet at τ 2.53 (spacing of 5.0 Hz) which was assigned to H-3. Irradiation at 2.53 collapsed a triplet, centered at τ 4.34, to a doublet. The triplet at τ 4.34 arose from H-4 and showed $J_{3,4} = J_{4,5} = 5.0$ Hz. A quartet at τ 5.25 having $J_{4,5} = J_{5,6} = 5.0$ Hz was assigned to H-5. Irradiation at τ 5.25 collapsed the triplet at τ 4.34, and irradiation at τ 4.34 collapsed the quartet at τ 5.25 to a triplet. At highest field, H-6 and H-6′ appeared as quartets, showing geminal splitting as well as coupling with H-5. These spectral observations are consistent with structure **15**, namely, 2-acetamido-4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enono-1,5-lactone. The mass spectrum of the compound clearly differed from that of the isomeric lactone, 2-acetamido-5,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enono-1,4-lactone, reported earlier[1]; although fragmentation of the 1,4-lactone had been initiated by the loss of acetic acid, that of the 1,5-lactone **15** occurred by two pathways, one resulting from the initial loss of ketene and another by the initial loss of acetic acid.

The oxidation of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-D-mannopyranose[12] (**12**) with methyl sulfoxide–acetic anhydride gave two products, as had the oxidation of **11**. One of these, obtained in 16% yield, proved to be the same unsaturated 1,5-lactone (**15**) encountered in the oxidation of **11**. The other product, obtained in crystalline form in 42% yield, was isomeric with **13**; it is presumed to be 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-D-mannono-1,5-lactone (**14**).

It is of interest to contrast the three oxidation reactions reported here. The very high yield of **2** from **1** and the failure to find an accompanying, unsaturated byproduct may be attributed to the relatively slight tendency of the benzyloxy group to act as a leaving group. On the other hand, the formation of **15** in the oxidation of **11** and of **12** may simply be a consequence of the effectiveness of the acetoxyl group as a leaving group[13]. In following the course of the oxidation of **11** and of **12** by t.l.c., the presence of the saturated lactones **13** and **14** was observed prior to the detection of **15**. Furthermore, both **13** and **14** were found to decompose, in part, to **15** when chromatographed on silica gel. There seems no doubt, therefore, that in the conversion of **11** and **12** into **15**, oxidation precedes elimination.

It may be relevant at this point to note that a methyl sulfoxide-based oxidation of closely related, but non-nitrogenous, acetylated sugar derivatives has also been found to give an unsaturated lactone[14]. Thus, oxidation of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose with methyl sulfoxide–sulfur trioxide–pyridine–triethylamine gives 2,4,6-tri-*O*-acetyl-3-deoxy-D-*erythro*-hex-2-enono-1,5-lactone in 81% yield. 2,3,4,6-Tetra-*O*-acetyl-D-mannopyranose gives the same product, but at only about one-third the rate. In the present state of our knowledge, the relative rates of these two oxidations, and the much higher yield of **15** from **11** than from **12**, do not appear adequate to justify speculations on the detailed mechanism of these eliminations.

EXPERIMENTAL

General methods. — Melting points are uncorrected. Optical rotations were measured at 20–23°. T.l.c. was conducted on Silica Gel (E. Merck), with the solvent system specified, and the components were detected by spraying with 10% sulfuric acid and heating. Column chromatography was conducted on silica gel of 0.05–0.20-mm particle size (E. Merck). Whatman No. 1 paper was used for chromatography with 80:5:15:1 acetonitrile–acetone–water–acetic acid[15], and components were detected with alkaline silver nitrate solution. I.r. spectra were recorded on a Perkin–Elmer Model 137 i.r. spectrometer. The p.m.r. spectra were recorded with tetramethylsilane as the internal standard; chloroform-*d* and a frequency of 60 MHz were used, unless otherwise specified.

*2-Acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-*D*-glucono-1,5-lactone* (**2**). — 2-Acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose[5,6] (**1**, 0.5 g) was dissolved in a mixture of methyl sulfoxide (3 ml) and acetic anhydride (3 ml), and the solution was kept overnight at room temperature. Dilution of the mixture with water (15 ml), and cooling, precipitated a thick oil that crystallized when rubbed: wt. 460 mg (92%), m.p. 136–138°. After two recrystallizations from ethanol, the product had m.p. 141–142° and $[\alpha]_D$ +123.3° (*c* 0.94, chloroform); ν_{max}^{KBr} 3340 (NH), 1780 (C=O), 1550 and 1650 (Amide I and II), 1500, 750, and 700 cm^{-1} (aromatic); the n.m.r. spectrum included signals at τ 2.70 (aromatic, 15 H), 3.40 (broad doublet, NH), 5.25, 5.29, and 5.48 (three singlets, 6 H in all, possibly CH_2 of benzyl group), 5.90–6.30 (signals totaling 6 H, ring and C-6 protons), and 8.18 (NAc).

Anal. Calc. for $C_{29}H_{31}NO_6$: C, 71.15; H, 6.38; N, 2.86. Found: C, 70.85; H, 6.16; N, 2.88.

Debenzylation of **2**. — To a solution of **2** (245 mg) in 2-methoxyethanol (15 ml) was added 10% palladium-on-carbon catalyst (200 mg), and the suspension was shaken with hydrogen overnight. The catalyst was removed by filtration, and the filtrate was passed through a layer of Celite, concentrated *in vacuo* to ~1 ml, and filtered through a cotton plug. The filtrate was diluted by careful addition of absolute ether (~2 ml), stoppered, and kept for 2 days at room temperature. During that period, an equal volume of ether was gradually added dropwise. Crystalline 2-acetamido-2-deoxy-D-glucono-1,5-lactone (**3**) was filtered off, and washed with ether; wt. 70 mg, m.p. 135–137°. From the mother liquor, a second crop was obtained; wt. 7 mg, total yield 70%.

For analysis, the sample was recrystallized from the same mixture of solvents; m.p. 148–150°; the mmp with a sample of **3** prepared by the late Dr. N. M. Cross was undepressed; $[\alpha]_D$ +137.7° (*c* 0.49, water, 2 min after dissolution). The optical rotation (1-dm tube) was observed over a period of 24 h and found to change from an initial value of +0.676° to a final (and constant) rotation of +0.220°; ν_{max}^{KBr} 3350 (OH), 3250 (NH), 1740 (C=O), and 1640 and 1530 cm^{-1} (Amide I and II).

Anal. Calc. for $C_8H_{13}NO_6$: C, 43.84; H, 5.98; N, 6.39. Found: C, 44.05; H, 6.04; N, 6.28.

Paper chromatography of a sample of **3** dissolved in 2-methoxyethanol revealed a single spot, whereas a solution of the sample in water, on being kept overnight, was found to contain several components; one that migrated slowly was chromatographically identical with 2-acetamido-2-deoxy-D-gluconic acid (detected in the mixture obtained by the oxidation of 2-acetamido-2-deoxy-D-glucose with unbuffered bromine water[1]).

*Methyl 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-*D*-gluconate* (**4**). — A solution of **2** (245 mg) in absolute methanol (35 ml) was kept overnight at room temperature and then examined by t.l.c. with 9:1 ether–methanol; the only component detected moved faster than **2**. The solvent was removed *in vacuo* to give a thick, colorless syrup: wt. 260 mg (quantitative), $[\alpha]_D$ +24.8° (*c* 1.01, chloroform); ν_{max}^{neat} 3500–3300 (OH and NH), 1750 (C=O), 1650 and 1540 (Amide I and II), and 740 and 700 cm^{-1} (aromatic); n.m.r. signals at τ 2.70 (aromatic, 15 H), 3.55 (broad doublet, disappearing after D_2O exchange, NH), 6.42 (OMe), 7.0 (1 H signal, disappearing after D_2O exchange, OH), and 8.03 (NAc). Prior to analysis, the syrup was dried under a high vacuum.

Anal. Calc. for $C_{30}H_{35}NO_7$: C, 69.08; H, 6.76; N, 2.69. Found: C, 68.84; H, 6.68; N, 2.51.

On storage for ~3 weeks at room temperature, the sample became crystalline; its chromatographic behavior, i.r. spectrum, and m.p. then identified it as **2**, and a mixed m.p. was undepressed.

*Methyl 2-acetamido-2-deoxy-*D*-gluconate* (**5**). — To a solution of **4** (260 mg) in 9:1 *p*-dioxane–water (12 ml) was added 10% palladium-on-carbon (200 mg), and the suspension was shaken with hydrogen overnight. The catalyst was removed by filtration, and the filtrate was evaporated *in vacuo*, giving a syrup that crystallized on standing; quantitative yield. Recrystallized from methanol, the product had m.p. 145–147° and $[\alpha]_D$ +11.2° (*c* 0.85, water); ν_{max}^{KBr} 3500 (OH), 3350 (NH), 1740 (C=O), and 1640 and 1560 cm^{-1} (Amide I and II); n.m.r. signals, in methyl sulfoxide-d_6, at τ 2.07 (doublet, NH), 6.38 (OMe), and 8.12 (NAc).

Anal. Calc. for $C_9H_{17}NO_7$: C, 43.03; H, 6.82; N, 5.57. Found: C, 42.88; H, 6.59; N, 5.79.

*2-Acetamido-2-deoxy-di-*N*-methyl-*D*-mannonamide* (**7**). — (*A*) *From 2-acetamido-2-deoxy-*D*-mannono-1,4-lactone* (**6**). Anhydrous dimethylamine (2 ml) was added to a solution of **6** (Ref. 1; 500 mg) in methanol (30 ml), and the mixture was kept overnight at room temperature. It was then evaporated *in vacuo* to a crystalline residue that was recrystallized from methanol: wt. 375 mg (62%). This material was recrystallized from ethanol: m.p. 177–178° (dec.), $[\alpha]_D$ −23.9° (*c* 1.03, water); n.m.r. signals (methyl sulfoxide-d_6) at τ 2.02 (doublet, *J* 9.0 Hz, removed on D_2O exchange, NH), 6.91 and 7.15 (NMe), and 8.17 (NAc).

Anal. Calc. for $C_{10}H_{20}N_2O_6$: C, 45.45; H, 7.63; N, 10.60. Found: C, 45.28; H, 7.82; N, 10.80.

(*B*) *From the crude oxidation mixture derived from 2-acetamido-2-deoxy-*D*-glucose.* A sample (500 mg) of the crude product obtained through the action of

unbuffered, aqueous bromine on 2-acetamido-2-deoxy-D-glucose (as described in an earlier paper[1]) was dissolved in methanol (15 ml), and anhydrous dimethylamine (2 ml) was added. The mixture was kept overnight at room temperature, and then evaporated *in vacuo*. Trituration of the residue with absolute ether and methanol caused crystallization; recrystallization of the product from methanol gave pure **7**; wt. 130 mg, m.p. 178–179°, $[\alpha]_D$ −21.9° (*c* 1.01, water). The i.r. and n.m.r. spectra of the product were identical with those of the specimen of **7** prepared from **6**.

2-Acetamido-3,4,5,6-tetra-O-acetyl-2-deoxy-di-N-methyl-D-mannonamide. — A suspension of 2-acetamido-2-deoxy-di-*N*-methyl-D-mannonamide (**7**, 100 mg) in a mixture of acetic anhydride (2 ml) and pyridine (3 ml) was stirred overnight at room temperature; the compound dissolved during the first hour. The solution was poured into ice–water, the product was extracted with chloroform, and the extract was washed successively with 2 M hydrochloric acid, saturated sodium hydrogen carbonate solution, and water, dried, and evaporated, to afford crystalline material; 122 mg (75% of theoretical); m.p. 150–152°, $[\alpha]_D$ +58.8° (*c* 1.0, chloroform). N.m.r. signals were noted at τ 3.41 (broad doublet, disappearing after D_2O exchange, NH), 4.4–4.9 (multiplet, 4 H), 5.7–6.0 (multiplet, 2 H), 6.83–7.06 (NMe, 6 H), 7.85, 7.96, and 8.06 (NAc and OAc, 15 H).

Anal. Calc. for $C_{18}H_{28}N_2O_{10}$: C, 50.00; H, 6.53; N, 6.48. Found: C, 50.15; H, 6.74; N, 6.29.

2-Acetamido-2-deoxy-D-mannono-1,4-lactone (**6**) *from 2-acetamido-2-deoxy-di-N-methyl-D-mannonamide* (**7**). — The procedure used by Kuzuhara and Fletcher[2] for a similar transformation was employed. Dry Dowex 50W-X8 (H^+) ion-exchange resin (1 g) was added to a solution of **7** (100 mg) in *p*-dioxane (15 ml), and the suspension was boiled for 1.5 h under reflux. Removal of the resin and of the solvent gave a crystalline product; wt. 41 mg (49%); its chromatographic behavior, as well as its i.r. and n.m.r. spectra, identified it as **6**.

Reaction of 2-acetamido-3,4,6-tri-O-benzyl-2-deoxy-D-glucono-1,5-lactone (**2**) *with dimethylamine.* — In a typical experiment, a suspension of **2** (350 mg) in methanol (10 ml) was treated with anhydrous dimethylamine (~2 ml), and the resulting solution was kept for 20 h at room temperature. After removal of the methanol and the excess of dimethylamine by evaporation *in vacuo*, the product was chromatographed on a column of silica gel (20 g) with 19:1 ether–methanol. Material that was chromatographically homogeneous in this solvent mixture was obtained as a colorless syrup, wt. 357 mg (94%); $[\alpha]_D$ +17.6° (*c* 0.95, chloroform); n.m.r. signals at τ 2.65 (aromatic, 15 H), 7.01, 7.08, 7.15, and 7.22 (N-Me, 6 H), 8.00 and 8.12 (NAc). The relative intensities of the two pairs at τ 7.01 and 7.15 and at 7.08 and 7.22 were both ~2:3. The elemental composition of the mixture was that of an acetamido-tri-*O*-benzyl-deoxy-di-*N*-methyl-hexonamide.

Anal. Calc. for $C_{31}H_{38}N_2O_6$: C, 69.64; H, 7.16; N, 5.24. Found: C, 69.42; H, 7.44; N, 4.96.

The experiment just described was repeated, the reaction time being varied, and the data thus obtained are presented in Table I.

*Catalytic debenzylation of the mixed 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-di-*N*-methylhexonamides* (**8** and **9**). — A solution of the mixed amides (370 mg, $[\alpha]_D \pm 0°$) in 9:1 *p*-dioxane–water (15 ml) was shaken with hydrogen in the presence of a palladium-on-carbon catalyst (200 mg) until absorption of the gas had ceased (2 h). After removal of the catalyst and solvent, the product was obtained in quantitative yield as a colorless, hygroscopic syrup; ν_{max}^{neat} 3300–3500 (NH and OH), 1640 (C=O), and 1540 cm^{-1} (Amide II); n.m.r. signals (methyl sulfoxide-d_6) at τ 2.02 (broad doublet, NH), 6.85, 7.18 (N-Me, 6 H), and 8.15 (NAc).

Another mixture of **8** and **9** ($[\alpha]_D$ +17.6°) was similarly reduced, to afford a product that gave n.m.r. signals for N-Me at τ 6.85, 6.91, 7.15, and 7.18 (6 H in all) and NAc signals at 8.15 and 8.17 (3 H).

*Oxidation of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-*D*-glucopyranose* (**11**). — A solution of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-D-glucopyranose[11] (**11**, 0.74 g) in methyl sulfoxide (5 ml) was diluted with acetic anhydride (3 ml), and the mixture was kept overnight at room temperature. It was then diluted with water (25 ml), the product was extracted into chloroform, and the extracts were combined, washed with water, dried, and evaporated *in vacuo*, giving an oily residue that was further evaporated under high vacuum to a thick syrup. T.l.c. in 6:1 ethyl acetate–chloroform revealed the presence of two products; preparative chromatography on a column of silica gel (70 g) with the same mixture of solvents readily separated the faster-moving component, 2-acetamido-4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enono-1,5-lactone (**15**), in the form of a colorless syrup, wt. 304 mg (50%); $[\alpha]_D$ +137.7° (*c* 0.9, chloroform). The chromatographic behavior and i.r. and n.m.r. spectra of this compound were identical with those of a sample that will be described more fully in the next section.

Further elution of the silica-gel column yielded a semicrystalline material (114 mg, 15%); this was triturated with absolute ether, the suspension filtered, and the solid washed on the filter with ether, to give 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-D-glucono-1,5-lactone (**13**), m.p. 130–132°; $[\alpha]_D$ +80.5° (*c* 0.50, chloroform); ν_{max}^{KBr} 3450 (NH), 1750 (C=O and OAc), and 1660 and 1540 cm^{-1} (Amide I and II); n.m.r. signals at τ 3.79 (doublet, *J* 3.8 Hz, 1 H), 4.27 (broad doublet, NH), 7.83, 7.92, 7.98, and 8.08 (OAc and NAc, 12 H).

Anal. Calc. for $C_{14}H_{19}NO_9$: C, 48.69; H, 5.55; N, 4.06. Found: C, 48.98; H, 5.59; N, 3.91.

*Oxidation of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-*D*-mannopyranose* (**12**). — A solution of **12** (Ref. 12; 0.5 g) in methyl sulfoxide (3 ml) was diluted with acetic anhydride (3 ml), and the mixture was kept overnight at room temperature, cooled, diluted with water (15 ml), and the product extracted into chloroform; the extracts were combined, washed with water, dried, and evaporated *in vacuo*, to afford a semicrystalline residue. Methanol (5 ml) was added, and the crystals were removed by filtration, wt. 207 mg (42%); m.p. 144–145°. After recrystallization from methanol, the 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-D-mannono-1,5-lactone (**14**) had m.p. 146–147° and $[\alpha]_D$ +188.3° (*c* 0.92, chloroform); ν_{max}^{KBr} 3280 (NH), 1780 (C=O), 1750

(OAc), and 1660 and 1550 cm^{-1} (Amide I and II); n.m.r. signals at τ 3.70 (broad doublet, NH), 7.83, 7.89, and 7.97 (OAc and NAc, 12 H).

Anal. Calc. for $C_{14}H_{19}NO_9$: C, 48.69; H, 5.55; N, 4.06. Found: C, 48.46; H, 5.43; N, 3.94.

The material remaining in the methanolic mother liquor from the preparation of **14** was chromatographed on a column of silica gel with 19:1 ether–methanol, to give a second product in the form of a syrup, wt. 68 mg (16%). Prior to analysis, this material was rechromatographed on silica gel with 6:1 ethyl acetate–chloroform. Chromatographically homogeneous fractions that gave a positive test for unsaturation were pooled, and evaporated to give 2-acetamido-4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enono-1,5-lactone (**15**) as a syrup; $[\alpha]_D$ +144.5° (*c* 0.96, chloroform); ν_{max}^{neat} 3400 (NH), 1760 (C=O), 1750 (OAc), 1700 (C=C), and 1650 and 1540 cm^{-1} (Amide I and II); n.m.r. signals (chloroform-*d*, 100 MHz) at τ 1.98 (broad singlet, NH), 2.53 (doublet, $J_{3,4}$ 5.0 Hz, H-3), 4.34 (triplet, $J_{3,4} = J_{4,5} = 5.0$ Hz, H-4), 5.25 (quartet, $J_{4,5} = J_{5,6} = 5.0$ Hz, H-5), 5.52 (quartet, $J_{5,6'}$ 5.0, $J_{6,6'}$ 11.5 Hz, H-6'), and 5.82 (quartet, $J_{5,6}$ 4.2 Hz, $J_{6,6'}$ 11.5 Hz, H-6), 7.85, 7.91, and 7.95 (OAc and NAc, 9 H). The parent peak, *m/e* 285, could be detected in the mass spectrum of the compound, and two modes of fragmentation were evident from the signals observed. One pathway, involving an initial loss of ketene, proceeded as follows: *m/e* 243 (M-C_2H_2O), *m/e* 201 (243-C_2H_2O), *m/e* 141 (201-AcOH), and *m/e* 158 (201-CH_3CO). A second pathway was initiated by the loss of acetic acid: *m/e* 225 (M-AcOH), *m/e* 183 (225-C_2H_2O), *m/e* 141 (183-C_2H_2O), and *m/e* 124 (183-$AcNH_2$).

Anal. Calc. for $C_{12}H_{15}NO_7$: C, 50.53; H, 5.30; N, 4.91. Found: C, 50.31; H, 5.26; N, 5.18.

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