Synthesis of 3-acetamido-2,3,6-trideoxy-D-*lyxo*-hexose (*N*-acetyl-D-daunosamine) and its D-*arabino* isomer

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Received July 15, 1968

Two syntheses of 3-acetamido-2,3,6-trideoxy-D-*lyxo*-hexose (*N*-acetyl-D-daunosamine, **14**) are described. The first one starts from methyl 3-acetamido-2,3-dideoxy-β-D-*arabino*-hexopyranoside (**1**) which is converted via its 6-*O*-tosylate (**2**) and 4-*O*-acetyl 6-*O*-tosylate (**3**) into methyl 3-acetamido-4-*O*-acetyl-2,3,6-trideoxy-6-iodo-β-D-*arabino*-hexopyranoside (**5**). Under certain conditions the last step involves a partial anomerization giving the α-anomer (**6**) as an additional product. Both **5** and **6** may be reductively dehalogenated to the corresponding 4-*O*-acetates having a 6-deoxy function (**7** and **8**). Preferably, **5** is reduced and simultaneously de-*O*-acetylated to methyl 3-acetamido-2,3,6-trideoxy-β-D-*arabino*-hexopyranoside (**9**). This glycoside is converted into its β-D-*lyxo* isomer (**13**) by solvolysis of the 4-*O*-mesylate (**12**). Hydrolyses of **9** give 3-acetamido-2,3,6-trideoxy-D-*arabino*-hexose (**10**) and the corresponding amino sugar hydrochloride (**11**), while hydrolyses of **13** give *N*-acetyl-D-daunosamine (**14**) and a syrupy amino sugar hydrochloride. The second synthesis of **14** departs from the D-*lyxo* isomer (**15**) of **1** and proceeds in a similar sequence via the 4-*O*-acetylated derivatives with 6-*O*-tosyl (**16**), 6-deoxy-6-iodo (**17**), and 6-deoxy (**18**) functions, the two last-mentioned compounds being α-glycosides due to anomerization in the step **16** → **17**.

Canadian Journal of Chemistry, 47, 89 (1969)

Previous work in this laboratory on the utility of nitro sugars for amino sugar syntheses has furnished methyl 3-amino-2,3-dideoxy-β-D-*arabino*-hexopyranoside (**1**) (1) and its β-D-*lyxo* isomer (**15**) (2). The present article describes the conversion of these two glycosides into derivatives of D-daunosamine, the optical antipode of an antibiotics constituent. The natural product (L-daunosamine) has been obtained by Arcamone and co-workers as a fragment of daunomycin, a *Streptomyces* metabolite showing antitumor activity, and has been demonstrated to be 3-amino-2,3,6-trideoxy-L-*lyxo*-hexose (3). A chemical synthesis of L-daunosamine hydrochloride has recently been accomplished (4), as has a synthesis of the *N*-benzoyl derivative of the D-enantiomer (5). In both instances the introduction of nitrogen at C-3 of the sugars was based on the action of sodium azide upon suitable hexose derivatives which were prepared departing from L-rhamnal and methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside, respectively. As our starting compounds **1** and **15** originate from deoxynitro glycosides that are available via the nitromethane method commencing with methyl β-D-glucopyranoside, the present work offers an alternative entry into the D-daunosamine series. In addition it has afforded the isomer with D-*arabino* configuration.[2]

Compound **1** was treated with 1 mole of *p*-toluenesulfonyl chloride in pyridine and underwent monotosylation in position-6 in high yield. This result accords with findings of Richardson (5) who has reported and discussed a highly selective monotosylation of the α-anomer of **1**. The crystalline 6-*O*-tosylate (**2**) was then acetylated to give the 4-*O*-acetyl 6-*O*-tosyl derivative (**3**). Alternatively, **1** was tosylated and subsequently acetylated without isolation of **2**. For successful monotosylation it proved essential that rigorously dried pyridine be employed. In an experiment neglecting this precaution a sulfur-free mono-*O*-acetate arose; the *O*-acetyl group was presumed to be located in position-6 (**4**) and to have entered there as a consequence of abortive tosylation.

Next, displacement in **3** of the tosyl group by iodine was effected with sodium iodide in refluxing butanone. This reaction was investigated rather thoroughly because it was discovered in initial experiments that the displacement at C-6

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[2]In principle, the reaction sequences to be reported could also be carried out in the L-series. The requisite L-enantiomers of **1** and **15**, which have not yet been described, would have to be prepared according to the directions given for the D-compounds (1, 2), from the known nitro precursors with β-L-configuration that have been synthesized starting from methyl β-L-arabinofuranoside (2).

was unexpectedly accompanied by partial anomerization at C-1. The presence of two anomeric iodo compounds in the crude reaction mixture was revealed by a nuclear magnetic resonance (n.m.r.) spectrum to be discussed in a later paragraph. Careful fractional crystallization of such a mixture ($[\alpha]_D$ +33°) yielded the pure β-anomer **5** (m.p. 196–198°, $[\alpha]_D$ +5°) and the pure α-anomer **6** (m.p. 175–177°, $[\alpha]_D$ +111°). From the rotation data was calculated a β:α ratio of 2.8:1 for that particular run, which does not necessarily represent an anomeric equilibrium.

It was considered that partial anomerization was caused by traces of acid liberated in a side reaction during the displacement. This conclusion, which appeared reasonable in view of the high reactivity at the anomeric center generally observed in deoxy sugar derivatives (6–9), received support from two facts. First, crystalline **5** was not anomerized but recovered unchanged when it was refluxed with sodium iodide in butanone under the conditions of the displacement. Secondly, the optical rotation of a solution of **5** in butanone slowly increased, signifying progressive anomerization, when the solution was refluxed together with a trace of *p*-toluenesulfonic acid. Consequently, in order to prevent anomerization, the iodide exchange in **3** was performed in the presence of sodium bicarbonate. This became the preferred modification as it proceeded with complete retention of the β-configuration, pure **5** being isolable in yields up to 93% on a preparative scale.

The conversion of the 6-iodo function into a 6-deoxy function, which was required next, was possible with Raney nickel (or platinum) and hydrogen in the presence of diethylamine. The methyl 3-acetamido-4-*O*-acetyl-2,3,6-trideoxy-β- and -α-D-*arabino*-hexopyranosides (**7** and **8**) were in this manner obtained from the iodides **5** and **6**, respectively. However, the reductions were accompanied to a considerable extent by de-*O*-acetylation.

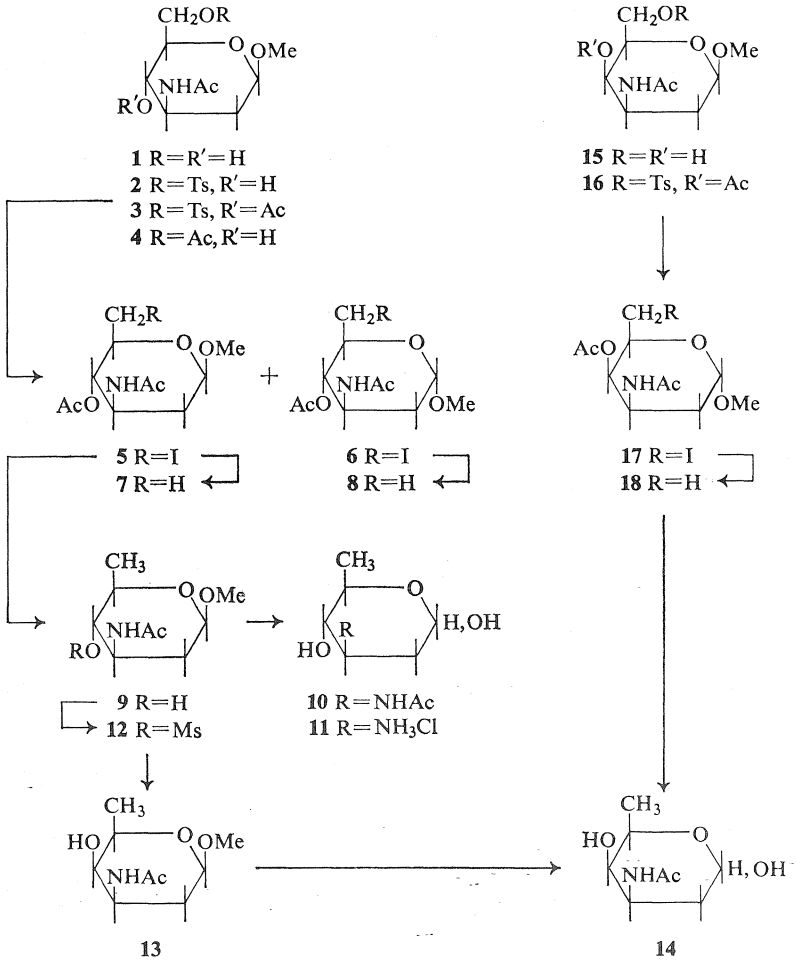
Experiments designed to carry on the plan of synthesis in the α-series were discontinued when it was learned that Richardson (5) had successfully pursued the same course. Efforts were therefore concentrated on the β-series, which happened to be more convenient too, when the β-derivative **5** had become readily accessible in pure form as outlined above.

As it appeared difficult to avoid partial loss of the 4-*O*-acetyl group during the reductive dehalogenation of **5**, and as this group was to be removed later on anyway, compound **5** was hydrogenated with platinum in the presence of sodium methoxide which effected complete de-*O*-acetylation. Methyl 3-acetamido-2,3,6-trideoxy-β-D-*arabino*-hexopyranoside (**9**) was thereby obtained in 80–90% yields. This glycoside was hydrolyzed, with 25% acetic acid to give 3-acetamido-2,3,6-trideoxy-D-*arabino*-hexose (**10**), and with hydrochloric acid to give 3-amino-2,3,6-trideoxy-D-*arabino*-hexose hydrochloride (**11**), a hitherto unknown stereoisomer of daunosamine.

Mesylation of the glycoside **9** afforded the 4-*O*-mesyl derivative **12**, which was isolated in crystalline form in 70% yield and then subjected to solvolysis with sodium acetate in water-containing 2-methoxyethanol, in order to effect inversion of configuration at C-4 by neighboring group participation (10). Methyl 3-acetamido-2,3,6-trideoxy-β-D-*lyxo*-hexopyranoside (**13**) was produced, again in a yield of 70%.[3] Hydrolysis of **13** by dilute acetic acid led to crystalline 3-acetamido-2,3,6-trideoxy-D-*lyxo*-hexose (**14**, *N*-acetyl-D-daunosamine), whereas D-daunosamine hydrochloride, expected to arise by hydrolysis with hydrochloric acid, was obtained as an impure syrup only.

The second synthesis commenced with methyl 3-acetamido-2,3-dideoxy-β-D-*lyxo*-hexopyranoside (**15**) which, with *p*-toluenesulfonyl chloride and acetic anhydride, was in part converted into the 4-*O*-acetyl-6-*O*-tosyl derivative (**16**). Displacement of the tosyl group by sodium iodide produced the calculated amount of sodium *p*-toluenesulfonate. However, only half the expected weight of a syrup containing iodo sugar could be extracted. The syrup apparently contained both anomers of methyl 3-acetamido-4-*O*-acetyl-2,3,6-trideoxy-6-iodo-α-D-*lyxo*-hexopyranoside, and preparative thin-layer chromatography furnished the preponderant product in crystalline form (yield, 20% based on **16**). This product (**17**) was assigned the α-configuration on the basis of its high dextrorotation, $[\alpha]_D$ +155°, which contrasted with the lower rotation, $[\alpha]_D$ +64°, of a second material that was obtained, though as a

[3]Richardson (5) similarly mesylated the α-anomer of **9** but encountered difficulties in attempting to isolate the ester (α-anomer of **12**). However, he found isolation unnecessary and proceeded directly with a solvolysis leading in 42% overall yield to the α-anomer of **13**.



syrup only, and that was probably an α,β-mixture. Further points in support of this assignment will be discussed in a later paragraph. Raney nickel reduction of **17** afforded methyl 3-acetamido-4-*O*-acetyl-2,3,6-trideoxy-α-D-*lyxo*-hexopyranoside (**18**), and this glycoside was converted by alkaline de-*O*-acetylation followed by hydrolysis with an acidic resin into *N*-acetyl-D-daunosamine, identical with **14** obtained in the previous synthesis.

The synthesis of *N*-acetyl-D-daunosamine was thus accomplished in two independent ways involving stereochemically unambiguous reactions and employing starting compounds whose configurations had been rigorously established (1, 2). This fact makes it unnecessary to adduce further configurational proof for the new compounds described, except that the assignment of anomeric configuration to the products arisen in the iodide exchange processes requires justification.

The n.m.r. spectrum of the crude product obtained from **3** by sodium iodide treatment in the absence of bicarbonate displayed two singlets attributable to methoxy groups (τ 6.44 and 6.58). After the material was separated into isomers by fractional crystallization, the τ 6.44 signal was seen to be associated with the anomer (**5**) of low dextrorotation, and the τ 6.58 signal, with the anomer (**6**) of high dextrorotation. Assignment of the β-configuration to the former, and of the α-configuration to the latter, primarily based on the rotations, is in accord with these chemical shifts as, in comparable compounds, protons in equatorial anomeric methoxyls usually resonate at lower field than those in axial

TABLE I

Chemical shifts (τ) of substituent resonances in $CDCl_3$ solution (60 MHz spectra)

	1-OCH_3 equatorial	1-OCH_3 axial	4-OAc axial	4-OAc equatorial	3-NHAc equatorial	Others
3	6.60			8.01	8.11	7.57*
5	6.44			7.90	8.06	
6		6.58		7.90	8.08	
7	6.54			7.94	8.10	8.75†
8		6.67		7.95	8.11	8.80†
$\mathbf{8}_{4-OH}$‡		6.66			7.99	8.72†
9§	6.51				ca. 8.0	8.66†
12	6.54				8.02	8.62†; 6.96‖
16	6.53		7.95		8.10	7.55*
17	(6.45)¶	6.58	7.85		8.08	
18		6.67	7.84		8.09	8.88†

*Aromatic methyl. In addition, 4 triplets belonging to the aromatic A_2B_2 system were in the τ 2 region.
†Doublet for C-6 methyl; splitting, 6 c.p.s.
‡Refers to a sample of **8** that had been de-*O*-acetylated.
§Signals from a spectrum of de-*O*-acetylated **8** that contained a small amount of **9**. Because of poor solubility no spectrum using crystalline **9** was taken.
‖Sulfonyl methyl.
¶Signal attributed to admixed β-isomer; intensity, ca. 5% of the axial methoxy signal.

ones. Pertinent examples in the literature (11–13) are supplemented by data given in Table I, special note being taken of the values for the anomeric pair **7** and **8** and of the value for **17** together with that listed in parentheses. Finally, the specific rotations of the α-compounds **6** and **8** were very close in magnitude to those reported (5) for the corresponding derivatives lacking the 4-*O*-acetyl group.

In the D-*lyxo* series the crystalline iodo derivative (**17**), which was assigned α-configuration, exhibited its methoxyl resonance at τ 6.58, and a weak signal suggesting contamination by about 5% of the β-anomer occurred at τ 6.45. The 6-deoxy derivative (**18**) had its methoxyl resonance at τ 6.67, and its melting point and specific rotation were in satisfactory agreement with data reported for the same compound (5) and its enantiomorph (4).

The chemical shifts of the acetoxy and acetamido methyl protons in the compounds of Table I were all in the expected regions (14–16). It is noteworthy that the acetoxy signals of **3** and **16** occurred at higher than usual field, which is attributable (15) to a shielding effect of the aromatic substituent.

Experimental

Melting points were taken in capillaries in an electric aluminium block apparatus equipped with a calibrated thermometer. All evaporations were performed *in vacuo* at a bath temperature of 35–40°. Petroleum ether refers to the fraction of boiling range 30–60°. Thin-layer chromatography (t.l.c.) was done on silica gel G (E. Merck A. G., Darmstadt) with the solvent systems benzene–acetone (2:3, v/v), (solvent *a*) and benzene–acetone (3:7, v/v) (solvent *b*), and spots were made visible with ceric sulfate – sulfuric acid spray. Column chromatography was carried out on silicic acid, 100 mesh (Mallinckrodt Analytical Reagent). Nuclear magnetic resonance (n.m.r.) spectra were obtained from deuteriochloroform solutions on a Varian HA-60 instrument and were calibrated with tetramethylsilane as internal standard. Optical rotations were measured at about 23° in 1-dm tubes, most readings being taken on a Perkin–Elmer 141 automatic polarimeter. Infrared spectra were taken by the Nujol mull technique on a Beckman IR-8 instrument unless otherwise indicated, and the most characteristic frequencies of new compounds are listed in Table II at the end of this section.

*Methyl 3-Acetamido-2,3-dideoxy-6-O-p-tolylsulfonyl-*β*-*D*-arabino-hexopyranoside (2)*

A sample (510 mg) of methyl 3-acetamido-2,3-dideoxy-β-D-*arabino*-hexopyranoside (**1**) (1) in pyridine (10 ml; distilled from sodium hydride) was chilled in a dry ice – acetone bath, and *p*-toluenesulfonyl chloride (530 mg; 1.2 *M* equivalents) was added. The reaction mixture was then stored at 0° for 48 h and at room temperature for 6 h. Water (0.5 ml) was introduced, and after 1 h the solution was concentrated *in vacuo* with several additions of 1% sodium bicarbonate solution, in order to remove most of the pyridine. Finally, the largely aqueous concentrate (ca. 10 ml) was extracted with several portions of chloroform, and the combined extracts were washed once with a small amount of water and dried over sodium sulfate. Inspection by t.l.c. (solvent *a*) of the chloroform phase revealed a strong spot (**2**) accompanied by a much weaker, faster moving spot which presumably represented the 4,6-ditosylate of **1**; the aqueous phase was seen to contain unreacted **1**. The chloroform solution was evaporated to give a crystalline residue (752 mg). Recrystallization from ethyl acetate – petroleum ether afforded **2** (586 mg; m.p. 143–148°). A second recrystallization gave **2** (542 mg) of m.p. 145–148° which could not be raised

further. Work-up of the mother liquors yielded another 62 mg of chromatographically pure **2**, the total thus being 604 mg (70%). The remaining syrup contained the fast-moving by-product. Compound **2** showed $[\alpha]_D$ +25.5 (*c*, 1, chloroform).

Anal. Calcd. for $C_{16}H_{23}NO_7S$ (mol. wt., 373.4): C, 51.47; H, 6.21; S, 8.59. Found: C, 51.50; H, 6.13; S, 8.57.

It was possible and worthwhile to recover unreacted **1** by pooling the extracted, aqueous bicarbonate solutions from several runs, evaporating them to dryness, and eluting **1** with ethyl acetate.

Methyl 3-Acetamido-4-O-acetyl-2,3-dideoxy-6-O-p-tolylsulfonyl-β-D-arabino-hexopyranoside (3)

(a) From 2

A solution of **2** (542 mg) and acetic anhydride (0.5 ml) in pyridine (10 ml) was allowed to stand at 23° for 12 h, after which time t.l.c. (solvent *a*) indicated complete acetylation. Excess water was added, and the reaction mixture was evaporated with several further additions of water. When most of the pyridine and acetic acid was removed, **3** began to crystallize as a hydrate from the remaining aqueous solution and was collected (559 mg) after a few hours of storage at 4°. Upon concentration to about 3 ml and chloroform extraction the mother liquor gave another 25 mg of **3**; total yield, 93%. The hydrate melted at 77–80° (crude) and at 80–82° (recrystallized from ethanol–water). It exhibited infrared absorption at 3600 cm^{-1} (OH) and, in $CDCl_3$ solution, displayed an n.m.r. signal near τ 7.8, with concentration-dependent chemical shift (water). *Anhydrous* **3**, in which these spectral features were absent, crystallized readily from ethyl acetate – petroleum ether, especially when seeded with crystals obtained by repeated evaporation of the hydrate with benzene; m.p. 121–123°, $[\alpha]_D$ +10.5° (*c*, 1, chloroform). Yields of chromatographically pure anhydrous **3** averaging 86% could be obtained when mother liquors of crystallization were worked up.

Anal. Calcd. for $C_{18}H_{25}NO_8S$ (mol. wt., 415.5): C, 52.03; H, 6.07. Found: C, 51.80; H, 6.03.

Anal. Calcd. (for monohydrate): S, 7.38. Found: S, 7.43.

(b) From 1

Compound **1** (600 mg) was tosylated as described for the preparation of **2**, except that 1.1 mole of *p*-toluenesulfonyl chloride and a reaction time of 6 h at 0° followed by 15 h at 4° and 7 h at 23° were employed. Acetic anhydride (1 ml) was then added and the mixture was kept at 23° for 16 h. Addition of water (0.5 ml) was followed after 15 min by dilution with chloroform (50 ml) and consecutive washing with 5% sulfuric acid, water, 1% sodium bicarbonate solution, and water. The organic solution was dried over sodium sulfate and evaporated to leave a residue (824 mg) which was dissolved in ethyl acetate, treated with activated charcoal and recovered by evaporation of the solvent. The hydrate of **3**, m.p. 79–81°, then crystallized from ethanol–water and was converted into the anhydrous form by recrystallization from ethyl acetate – petroleum ether. The product (712 mg; 62%) melted at 121–123°, undepressed on admixture of **3** from (*a*).

Methyl 3-Acetamido-6(?)-O-acetyl-2,3-dideoxy-β-D-arabino-hexopyranoside (4)

In an early attempt at preparing compound **3** an experiment was performed similar to that described in the preceding section (*b*). The reactants were compound **1** (214 mg), *p*-toluenesulfonyl chloride (204 mg), and acetic anhydride (0.2 ml). However, the solvent, reagent grade pyridine, had not been specially dried with sodium hydride. No **3** was produced. Instead, the chloroform phase obtained after washing yielded crystals (60 mg) which melted at 152–154°, showed $[\alpha]_D$ +8.3° (*c*, 0.8, ethanol), and displayed an infrared band at 1733 cm^{-1} (ester carbonyl) but no bands attributable to hydroxyl or tosyl groups. This material was identical with the previously described (1) 4,6-di-*O*-acetate of **1**, m.p. 157.5–158°, $[\alpha]_D$ +9.9° (*c*, 0.6 in ethanol). The aqueous washing liquids were combined, neutralized with sodium bicarbonate, and evaporated to dryness. The solid residue was extracted with ethyl acetate and the extract, upon removal of the solvent, was chromatographed on a column of silica gel (17 g). Benzene–ethanol (20:1) eluted an additional crop (40 mg) of the 4,6-di-*O*-acetate. Subsequent elution with benzene–ethanol (10:1) gave monoacetate **4** (88 mg) which after recrystallization from ethyl acetate – petroleum ether had m.p. 185–187°, $[\alpha]_D$ −19.8° (*c*, 0.4, ethanol).

Anal. Calcd. for $C_{11}H_{19}NO_6$ (mol. wt., 261.3): C, 50.56; H, 7.33; N, 5.36. Found: C, 50.53; H, 7.12; N, 5.46.

Methyl 3-Acetamido-2,3,6-trideoxy-6-iodo-β-D-arabino-hexopyranoside (5) and Methyl 3-Acetamido-2,3,6-trideoxy-6-iodo-α-D-arabino-hexopyranoside (6)

(a) Displacement in the Absence of Sodium Bicarbonate

For purification, commercial butanone (60 ml) was refluxed 1 h with sodium iodide (3 g) and distilled in the presence of anhydrous magnesium sulfate. The distillate dissolved sodium iodide without producing a yellow color.

Compound **3** (200 mg) and sodium iodide (150 mg) were refluxed for 20 h in purified butanone (10 ml). The mixture was then chilled, and sodium *p*-toluenesulfonate (91 mg; 97.5%) was filtered off and washed with chloroform. The filtrate was evaporated to give a pale-yellow residue to which was added chloroform (25 ml), water (5 ml), and 2 drops of 0.1 *N* sodium thiosulfate solution. After thorough shaking the chloroform layer was allowed to separate and, upon drying with sodium sulfate and evaporation, it gave a colorless crystalline material (174 mg; $[\alpha]_D$ +33.4°, *c*, 1.7, chloroform) which was a mixture of **5** and **6**.

This mixture was fractionated in a process involving 20 recrystallizations, with the progress of separation being monitored polarimetrically and fractions of similar rotations being combined. Ether was used to recrystallize fractions of relatively low dextrorotation (rich in **5**), and ethyl acetate – petroleum ether was employed for fractions of relatively high dextrorotation (rich in **6**). The operation afforded 82 mg of pure **5**, m.p. 196–198° decomp., $[\alpha]_D$ +5.0°, (*c*, 1.5, chloroform), and 17 mg of pure **6**, m.p. 175–177° decomp., $[\alpha]_D$ +111°, (*c*, 1, chloroform), $[\alpha]_D$ +96° (*c*, 0.6, dimethyl sulfoxide[4]). In addition there remained mixed fractions totalling 65 mg. Nuclear magnetic resonance spectra of **5** and **6** (Table I)

[4]The rotation in this solvent was measured for comparison with the value, $[\alpha]_D$ +93° in DMSO, recorded (5) for the non-acetylated derivative of **6**.

indicated anomeric purity, whereas a spectrum of the combined mixed fractions showed a β:α ratio of roughly 2:1. Infrared spectra of **5** and **6** were extremely similar although there were minor differences in band positions and relative intensities (Table II).

(b) Displacement in the Presence of Sodium Bicarbonate

Compound **3** (484 mg), sodium iodide (370 mg) and sodium bicarbonate (100 mg) were refluxed with magnetic stirring in purified butanone (22 ml) for 17 h. After cooling, the insoluble matter (330 mg, sodium tosylate and bicarbonate) was filtered off and washed with chloroform, and work-up was proceeded with as described under (*a*). The crude crystalline product (456 mg) showed $[\alpha]_D$ +5.2° (*c*, 4.5, chloroform), i.e. virtually the value of pure **5**. Recrystallization from water (which proved superior to ether) gave **5** (310 mg) as long needles having m.p. 195–197° decomp. and $[\alpha]_D$ +4.9° (*c*, 1.5, chloroform). The yields in five experiments were 70–74%. Column chromatography on silicic acid, with benzene–ethanol (50:1) as eluent, of the material that had remained in the mother liquor of recrystallization furnished additional **5** (90 mg; $[\alpha]_D$ +5.9° in chloroform), thus increasing the yield to 93%.

Anal. Calcd. for $C_{11}H_{18}INO_5$ (mol. wt., 371.2): C, 35.59; H, 4.89; I, 34.19. Found: C, 35.81; H, 5.06; I, 34.00.

Methyl 3-Acetamido-4-O-acetyl-2,3,6-trideoxy-β-D-arabino-hexopyranoside (7)

A solution of **5** (500 mg) and diethylamine (0.14 ml) in methanol (30 ml) was shaken with Raney nickel-T4 (0.1 g) (17) in an atmosphere of hydrogen at room temperature for 5 h. The filtered solution was concentrated to a syrup which was dissolved in chloroform. The chloroform solution was washed successively with cold solutions of sodium thiosulfate, 0.5 *N* hydrochloric acid, sodium bicarbonate, and finally with water. It was then dried with magnesium sulfate and concentrated to a syrup that crystallized from ethyl acetate – petroleum ether. There was obtained 175 mg (53%) of **7**, m.p. 180°, $[\alpha]_D$ +23.4° (*c*, 1, chloroform). This preparation, made from a sample of **5** which was not entirely pure anomerically, contained as a consequence a small admixture of the α-anomer (**8**) accounting for too high a rotation. The n.m.r. spectrum showed a weak signal at τ 6.67 (α-OCH_3) beside the main OCH_3 signal at τ 6.54.

Anal. Calcd. for $C_{11}H_{19}NO_5$ (mol. wt., 245.3): C, 53.86; H, 7.81; N, 5.71. Found: C, 53.75; H, 7.67; N, 5.78.

A similar reduction was performed using *pure* **5** (116 mg), diethylamine (0.1 ml), and *platinum oxide* (50 mg) as catalyst; the solvent was methanol (10 ml). Hydrogen consumption (18 ml at room temperature) was rapid. After 2 h the filtered solution was shown by t.l.c. (solvent *a*) to contain 2 carbohydrate substances, namely fast-moving **7** and its slow-moving product of de-*O*-acetylation (**9**). In addition, diethylammonium iodide was present. The reaction solution was evaporated to give a residue which was treated with chloroform and water, the former dissolving most of **7** and the latter dissolving **9** and the ammonium salt. The chloroform solution was evaporated to yield crystalline **7** (48 mg; 62%), m.p. 177–180° after one and 185–186° after a second recrystallization from ethyl acetate – petroleum ether; $[\alpha]_D$ +7.4° (*c*, 0.4, chloroform). An n.m.r. spectrum showed no evidence for contamination by α-anomer.

The aqueous solution containing **9** was made alkaline by adding 0.35 ml of 1 *N* potassium hydroxide solution and was then evaporated to remove diethylamine. The dry residue (**9** plus potassium iodide) was extracted with ethyl acetate, which yielded 26 mg (40%) of **9**, m.p. 237–239°, identical in its infrared spectrum with **9** described in a subsequent section.

Methyl 3-Acetamido-4-O-acetyl-2,3,6-trideoxy-α-D-arabino-hexopyranoside (8)

A solution of **6** (190 mg) and diethylamine (0.075 ml) in methanol (15 ml) was shaken with Raney nickel-T4 (17) (40 mg) and hydrogen for 4.5 h at room temperature. The solution was evaporated, the residue taken up in chloroform and applied to 2 large t.l.c. plates which were irrigated with solvent *a*. The faster-moving band was scraped off and, upon elution with ethyl acetate, afforded the product **8** (61 mg), m.p. 162–163°, $[\alpha]_D$ +142° (*c*, 1, chloroform). In the n.m.r. spectrum a strong signal at τ 6.67 (α-OCH_3) was accompanied by a much weaker signal at τ 6.53 indicating a slight contamination by the β-anomer. The derivative of **8** lacking the 4-*O*-acetyl group has been reported (5) to show $[\alpha]_D$ +137° (methanol). Extraction of the slower-moving band from the t.l.c. plates afforded some of this derivative as a solid which was used without further purification for obtaining the n.m.r. spectrum ($\mathbf{8}_{4\text{-OH}}$ in Table I).

Methyl 3-Acetamido-2,3,6-trideoxy-β-D-arabino-hexopyranoside (9)

A solution of **5** (276 mg; 0.75 mmole) in methanol (11 ml) containing 1.1 mmole of sodium methoxide was shaken with hydrogen in the presence of platinum catalyst (70 mg of PtO_2). Hydrogen uptake (22 ml) was rapid, about 20 ml being consumed within the first 5 min. After 3.5 h the solution was filtered and its pH was adjusted to about 9 by careful titration with 0.1 *N* sulfuric acid (2.8 ml) against phenolphthalein. The solution, which must stay weakly alkaline at all times, was then evaporated to give a solid. Two ways of further work-up were employed from hereon. In some experiments the solid was dissolved in water and **9** was isolated by exhaustive extraction with chloroform although the distribution coefficient is not very favorable. The method might be convenient for larger scale runs when a liquid–liquid extractor can be used. The dried extract was evaporated and the residue crystallized from ethanol – petroleum ether to give **9** (e.g., 114 mg, 75%). Recrystallized from the same solvents, an analytical sample had m.p. 224–226° and $[\alpha]_D$ −57.6° (*c*, 0.95, water).

Anal. Calcd. for $C_9H_{17}NO_4$ (mol. wt., 203.2): C, 53.19; H, 8.43; N, 6.89. Found: C, 53.28; H, 8.61; N, 7.03.

In runs of the small scale described we preferred chromatographic isolation of **9**. To this end the crude solid was placed on a short column of silicic acid (8 g) and **9** was eluted with benzene–ethanol (20:1) after minor impurities had been eluted with benzene. The yields in **9** were good, e.g. 123 mg (81.5%) in a 0.75 mmole run. The crystals showed m.p. 200–210°, raised to 223–225° by one recrystallization from ethanol – petroleum ether; $[\alpha]_D$ −57.9° (*c*, 1.1, water).

Compound **9** appears to be capable of existing in two crystal modifications. While the melting points just recorded were found in several experiments and could not be raised by further recrystallization of the samples, in two cases a m.p. 237–239° was observed. Such a sample showed the same rotation ($[\alpha]_D$ −57.5°, *c*, 1.2, water) and gave an infrared spectrum identical to that of the lower-melting material. Moreover, both modifications yielded identical reaction products with methanesulfonyl chloride (see a later paragraph).

*3-Acetamido-2,3,6-trideoxy-*D*-arabino-hexose (**10**)*

A solution of **9** (63 mg) in water (3 ml) and acetic acid (1 ml) was boiled under reflux for 25 min. The hydrolysis was monitored by t.l.c. (solvent *b*), which revealed the disappearance of **9** and concomitant formation of more slowly-moving **10**. The hydrolyzate was evaporated and the residue crystallized from 2-propanol – ether. The product (42 mg; 71.5%) had m.p. 196–200°, raised to 199–201° (decomp., sealed capillary) by one recrystallization. The mother liquor gave crystals of m.p. 198–201° decomp. Compound **10** exhibited downward mutarotation: $[\alpha]_D$ +30.4° (4 min) → +18.3° (6 h, constant) (*c*, 0.8, water).

Anal. Calcd. for $C_8H_{15}NO_4$ (mol. wt., 189.2): C, 50.79; H, 7.99; N, 7.40. Found: C, 50.68; H, 7.80; N, 7.25.

*3-Amino-2,3,6-trideoxy-*D*-arabino-hexose Hydrochloride (**11**)*

A solution of **9** (50 mg) in 1 *N* hydrochloric acid (2 ml) was boiled under reflux for 65 min, during which period gradual disappearance of **9** and formation of **11** with intermediary occurrence of **10** was observed by t.l.c. (solvent *b*). The hydrolyzate was evaporated to a syrup which was dried *in vacuo* and then crystallized from 2-propanol – ether giving **11** (43 mg), m.p. 160–170° decomp. One recrystallization from the same solvents gave **11** (31 mg), m.p. 168–170° decomp., unchanged by a further recrystallization. No mutarotation was observed: $[\alpha]_D$ +81.7° (*c*, 0.7, water). A sample reduced hot Fehling solution strongly.

Elemental analysis of a sample dried *in vacuo* at 56° gave a high carbon value which suggested retention of solvent of crystallization. The data did not correspond perfectly to 1 mole of 2-propanol, but its presence was strongly supported by mass spectrometry. A sample heated up to 100° in the high vacuum of the spectrometer released volatile matter that gave a weak parent peak at 60 *m/e* and a strong fragment peak at 45 *m/e* attributable to 2-propanol. We thank Prof. J. L. Holmes for this determination.

Anal. Calcd. for $C_6H_{14}ClNO_3 \cdot C_3H_8O$ (mol. wt., 243.7): C, 44.35; H, 9.10. Found: C, 44.69; H, 8.44.

*Methyl 3-Acetamido-2,3,6-trideoxy-4-O-methylsulfonyl-β-*D*-arabino-hexopyranoside (**12**)*

A solution of **9** (109 mg) in pyridine (5 ml; dried over sodium hydride) was cooled to −70°, and methanesulfonyl chloride (0.3 ml) was added. The reaction mixture was allowed to stand for 2 days at −10–0°. Water (0.1 ml) was then added to the brown solution which, after 15 min, was evaporated with several additions of 1% sodium bicarbonate solution in order to remove most of the pyridine. The remaining aqueous solution was extracted with chloroform (40 ml in several portions), the extract was dried with sodium sulfate and evaporated to a dark, crystalline mass (154 mg). Passage through a column of silicic acid (8 g), which was eluted first with benzene and then with benzene–ethanol (50:1), gave unidentified impurities in the benzene fractions while the mixed solvent fractions furnished 26 mg of **12** containing a trace of a contaminant (faster moving on t.l.c.) and subsequently 100 mg of chromatographically pure **12** (total yield, 83%). Upon one or two recrystallizations from ethyl acetate – petroleum ether **12** had m.p. 153–155° decomp., $[\alpha]_D$ −16.5° (*c*, 1, chloroform), unchanged on further recrystallization. Omitting the column chromatography we obtained from crude **12**, by recrystallization with use of decolorizing carbon, pure **12** in somewhat lower yields.

Anal. Calcd. for $C_{10}H_{19}NO_6S$ (mol. wt., 281.3): C, 42.70; H, 6.81; S, 11.40. Found: C, 42.78; H, 7.34; S, 11.10.

*Methyl 3-Acetamido-2,3,6-trideoxy-β-*D*-lyxo-hexopyranoside (**13**)*

A solution of mesylate **12** (91 mg), sodium acetate trihydrate (170 mg), and water (0.5 ml) in 2-methoxyethanol (5 ml) was refluxed for 40 min. The reaction mixture was evaporated to dryness and the residue was chromatographed on silicic acid (5 g) by elution with benzene–ethanol (20:1). Crystalline **13** (46 mg; 70%) was obtained and melted, in a sealed capillary, at 208–212° after one and at 210–212° after a second and a third recrystallization from ethyl acetate; $[\alpha]_D$ +27.7° (*c*, 1, water). The compound sublimed *in vacuo*.

Anal. Calcd. for $C_9H_{17}NO_4$ (mol. wt., 203.2): C, 53.19; H, 8.43; N, 6.89. Found: C, 53.16; H, 8.40; N, 6.83.

*3-Acetamido-2,3,6-trideoxy-*D*-lyxo-hexose (**14**)*

*(a) From **13***

The glycoside **13** (37 mg) was hydrolyzed with acetic acid as described for the hydrolysis of **9** to **10**. The reducing sugar **14** crystallized from ethyl acetate in a yield of 28 mg (81%), m.p. 143–145°. After one recrystallization **14** had m.p. 145–146°, $[\alpha]_D$ +101° (ca. 4 min.) → +94.2° (10 min, constant) (*c*, 0.5, water). When the rotational sample was recovered by evaporation of the water, it melted at 151–153°.

Anal. Calcd. for $C_8H_{15}NO_4$ (mol. wt., 189.2): C, 50.79; H, 7.99. Found: C, 51.00; H, 7.99.

*(b) From **18***

The glycoside **18** (12 mg) was dissolved in 0.1 *N* sodium hydroxide solution (0.5 ml). After 15 min it was determined by t.l.c. (solvent *a*) that fast-moving **18** had disappeared completely, giving rise to a slower spot that travelled like the de-*O*-acetylated glycosides **9** and **13**. After another 10 min the solution was diluted with a few milliliters of water and stirred with 2 ml of cation exchanger, Rexyn 101(H^+), for 20 min at 60°. Thin-layer chromatography then revealed complete disappearance of the product of alkaline hydrolysis and showed the presence of a single spot moving at the still lower speed of **14**. The resin was filtered off and washed well with water, and the filtrate was treated with activated charcoal and evaporated to give 5 mg of white crystals. Recrystallization from ethyl acetate gave **14** (3 mg), m.p. 144–146°,

TABLE II

The most important infrared frequencies

Compound*	ν_{max} in cm^{-1} (group assignments in parentheses)
2†	3450 (NH); 3400–3200 (OH); 1655, 1510 (amide); 1590, 1360, 1170 (tosyl); 1070, 975.
3†‡	3450 (NH); 1740 (ester CO); 1670, 1515 (amide); 1595, 1370, 1175 (tosyl); 1050, 975; 1225 (ester C—O—C).
3‡	3400 (NH); 1750 (ester CO); 1670, 1555 (amide); 1610, 1380, 1180 (tosyl); 1245 (ester C—O—C); 1070, 1050, 1010–960, 930, 910, 880, 845, 820, 800.
3§	3600 (OH); 3400 (NH); 1740 (ester CO); 1660 and 1640, 1570 (amide); 1610, 1360, 1180 (tosyl); 1245 (ester C—O—C); 1070, 1050, 1010–975; 930, 910, 875, 840, 825, 803.
4	3400, 3280, 3120 (NH, OH); 1715 (ester CO); 1645, 1565 (amide); 1265 (ester C—O—C); 1140, 1075, 980, 950.
5	3250 (NH); 1730 (ester CO); 1635, 1535 (amide); 1230 (ester C—O—C); 1120, 1035, 970–940.
5†	3450 (NH); 1735 (ester CO); 1675, 1515 (amide); 1395 weak, 1375 strong; 1220 (ester C—O—C); 1285 strong singlet, 1150 weak, 1123, 1050.
6†	3450 (NH); 1735 (ester CO); 1675, 1515 (amide); 1375 strong (no band at 1395); 1220 (ester C—O—C); 1290–1275 weak doublet, 1130, 1040.
7	3400 (NH); 1750 (ester CO); 1660, 1560 (amide); 1245 (ester C—O—C); 1170, 1130, 1050, 965, 930.
8	3300 (NH); 1730 (ester CO); 1635, 1535 (amide); 1230 (ester C—O—C); 1120, 1040, 955, 920.
9	3400–3200, 3100 (NH, OH); 1642, 1560 (amide); 1300, 1070.
10	3400–3200, 3100 (NH, OH); 1640, 1560 (amide); 1310, 1120, 1090–1050, 990.
11	3450–3300 (OH); 3050, 1600, 1520 (NH_3^+); 1170–1100, 1065, 1010, 985.
12	3300 (NH); 1665, 1560 (amide); 1345, 1180 (mesyl); 1080, 1010, 970, 865, 730.
13	3480, 3310 (NH, OH); 1645, 1550 (amide); 1330, 1290–1220, 1195, 1150, 1080–1030, 980, 725.
14‖	3450, 3350 (NH, OH); 1650 and 1625, 1535 (amide); 1250, 1200, 1165, 1110–1025, 980, 800–700.
14¶	3430, 3320 (NH, OH); 1625, 1550 (amide); 1240, 1190, 1165, 1115, 1080, 1035, 990, 800–700.
16	3400 (NH); 1745 (ester CO); 1650, 1535 (amide); 1600, 1370, 1170 (tosyl); 1240 (ester C—O—C); 1070 1030, 990, 840, 815, 735.
17	3300 (NH); 1745 (ester CO); 1650, 1560 (amide); 1240 (ester C—O—C); 1125, 1050, 995, 955, 910, 885.
18	3400 (NH); 1745 (ester CO); 1645, 1530 (amide); 1240 (ester C—O—C); 1130, 1120, 1060, 1020, 990, 940.

*In Nujol unless indicated otherwise.
†In chloroform.
‡Anhydrous compound.
§Hydrate.
‖Melting point 145–146°.
¶Melting point 152–153°.

undepressed upon admixture of **14** from (*a*); $[\alpha]_D$ +117° → +95.7° (20 min, constant) (*c*, 0.11, water). Crystals recovered from the aqueous solution melted at 152–153°.

Attempted Preparation of D-*Daunosamine Hydrochloride*

The glycoside **13** (44 mg) was hydrolyzed, first with 0.2 *N* hydrochloric acid at 80° for 2 h and at 100° for 1.5 h, and thereafter with increased acid strength (0.43 *N*) at 100° for 1 h. Thin-layer chromatography (solvent *b*) then indicated complete conversion of **13** into material that remained at the starting point. Evaporation of the hydrolyzate gave a syrup which was dried to glassy consistency in a desiccator. The substance failed to crystallize from a variety of solvents. It reduced hot Fehling solution and showed $[\alpha]_D$ +63.7° (*c*, 1.7, water). Reported (4) for crystalline L-daunosamine hydrochloride, $[\alpha]_D$ −54.2° (water).

*Methyl 3-Acetamido-4-O-acetyl-2,3-dideoxy-6-O-p-tolylsulfonyl-*β-D-*lyxo-hexopyranoside (16)*

To a chilled solution of 1.12 g of methyl 3-acetamido-2,3-dideoxy-β-D-*lyxo*-hexopyranoside (**15**) (2) in dried pyridine (7.5 ml) was added a chilled solution of *p*-toluenesulfonyl chloride (1.02 g; 1.05 molar equivalents) in dry, ethanol-free chloroform (28 ml). The mixture was kept at −8° for 24 h. Acetic anhydride (0.53 ml) was then added, and the mixture was allowed to stand at −8° for another 24 h. It was then shaken briefly with a small quantity of water, diluted with excess chloroform, and washed successively with dilute sulfuric acid, sodium bicarbonate solution, and water. The organic phase was dried over magnesium sulfate and evaporated to give a syrup which was crystallized from ethyl acetate – petroleum ether. Crude **16** (1.06 g; 50%), m.p. 140–142°, was recrystallized from ethyl acetate to give fibrous needles

(0.84 g) of m.p. 148–149°, $[\alpha]_D$ +13.8° (*c*, 1, chloroform).

Anal. Calcd. for $C_{18}H_{25}NO_8S$ (mol. wt., 415.5): C, 52.03; H, 6.07; S, 7.72. Found: C, 51.94; H, 6.36; S, 7.24.

The mother liquor remaining in the crystallization of **16** gave 3 spots on t.l.c. (solvent *a*). Application to large plates allowed the separation into bands which were scraped off and extracted with acetone. The slowest band afforded crystals that were identified as the known (2) *4,6-di-O-acetate* of **15** by comparing infrared and n.m.r. spectra with those of an authentic sample. The middle band gave crystals of **16**, m.p. 148–150°. The third and fastest band furnished a syrupy *di-O-tosylate*. Its infrared spectrum showed peaks at 3350 (NH), 1650 and 1540 (amide I and II), and 1610, 1470, and 1180 cm^{-1} (tosyl). The last three bands were more intense with respect to the amide absorptions than the corresponding bands in the spectrum of **16** (Table II). There were no peaks attributable to *O*-acetyl in the 1730 and 1250 cm^{-1} regions. The n.m.r. spectrum exhibited methyl proton singlets at τ 6.60 (*O*—CH_3), 7.56 (arom. CH_3), and 8.09 (*N*—Ac). The signal at τ 7.56 was twice as intense as either one of the others. (Compare also the spectra of **3** and **16**, Table I.)

*Methyl 3-Acetamido-4-O-acetyl-2,3,6-trideoxy-6-iodo-α-*D*-lyxo-hexopyranoside (17)*

A solution of **16** (840 mg) and sodium iodide (610 mg) in dry acetone (6 ml) was heated in a bomb for 18 h at 100–110°. After the mixture had cooled, sodium *p*-toluenesulfonate (392 mg, 99%) was filtered off and the red filtrate concentrated. Water was added to the residue, and the mixture was extracted three times with chloroform. The combined extracts were washed with sodium thiosulfate solution and water, dried with magnesium sulfate, and evaporated to give a syrup (0.37 g) which did not crystallize. The syrup was dissolved in a small amount of chloroform and applied to 3 large t.l.c. plates which were developed with solvent *a*. Two bands separated. Extraction with acetone of the faster-moving, and major, band afforded a crystalline material which was recrystallized from ethyl acetate – petroleum ether to give **17** (152 mg) m.p. 167–169°, $[\alpha]_D$ +155° (*c*, 1.5, chloroform). A Beilstein test indicated the presence of halogen.

Anal. Calcd. for $C_{11}H_{18}NIO_5$ (mol. wt., 371.2): C, 35.59; H, 4.89. Found: C, 35.83; H, 5.02.

The slower band afforded a syrupy material (47 mg) that had $[\alpha]_D$ +64° (*c*, 1.5 in chloroform). It showed infrared bands at 3350 (NH), 1750 (ester CO), 1660 and 1530 cm^{-1} (amide I and II). Presumably this syrup contained the β-anomer of **17**; however, it was not investigated further.

*Methyl 3-Acetamido-4-O-acetyl-2,3,6-trideoxy-α-*D*-lyxo-hexopyranoside (18)*

A solution of **17** (130 mg) and diethylamine (0.04 ml) in methanol (8 ml) was shaken with Raney nickel-T4 (30 mg) and hydrogen for 3 h at room temperature. The solution was filtered and concentrated to a syrup which was dissolved in a small amount of chloroform and subjected to preparative t.l.c. (solvent *a*). As the main component a crystalline material (48 mg) was obtained. Recrystallization from ethyl acetate – petroleum ether gave **18** (25 mg), m.p. 189–190°, $[\alpha]_D$ +186° (*c*, 0.5, chloroform). Reported (5) for **18**: m.p. 183–185°, $[\alpha]_D$ +192° (chloroform); reported (4) for the L-enantiomer of **18**: m.p. 187–188°, $[\alpha]_D$ −204° (chloroform). A small amount of the β-anomer was present in our sample, causing low rotation and a (very weak) n.m.r. signal at τ 6.50.

Anal. Calcd. for $C_{11}H_{19}NO_5$ (mol. wt., 245.3): C, 53.86; H, 7.81. Found: C, 53.93; H, 7.85.

Acknowledgment

Support of this work by the Life Insurance Medical Research Fund, Rosemont, Pennsylvania, is gratefully acknowledged.

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