Some Derivatives of 1,6-Anhydroglucosamine and Their Use as Aglycons in Disaccharide Synthesis[1]

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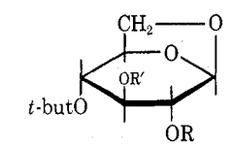
2-Acetamido-2-deoxy-4-*O*-(β-D-galactopyranosyl)-D-glucopyranose (*N*-acetyllactosamine) and 2-acetamido-2-deoxy-4-*O*-(β-D-glucopyranosyl)-D-glucopyranose (*N*-acetylcellobiosamine) have been synthesized. 2-Acetamido-3-*O*-acetyl-1,6-anhydro-2-deoxy-β-D-glucopyranose (VII) proved to be an excellent aglycon for the Koenigs–Knorr reaction.

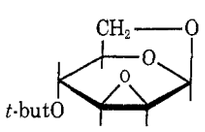
A number of naturally occurring substances contain glucosamine to which various hexose units are linked in position 4. Such sequences are found, *inter alia*, in blood group active oligosaccharides,[2,3] in bacterial cell-wall components,[4,5] and in chitin.[6] In view of the low reactivity of the C-4 hydroxyl in the C-1 conformation of glucopyranose, attempts to synthesize glycosides involving this position have met with limited success. Thus, condensation of acetobromogalactose with 2-acetamido-1,3,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranose gave only 4% of octaacetyl lactosamine.[7] Heyns, *et al.*,[8] employed an open-chain derivative of glucosamine as aglycon for the synthesis of *N*-acetylglucosamine-(1→4)-*N*-acetylglucosamine. This approach required a sequence of deblocking reactions which eventually resulted in a mixture of α and β isomers.

In recent publications we described a new aglycon, *viz.*, 2,3-di-*O*-acetyl-1,6-anhydro-β-D-glucopyranose,[9] and its utilization in the synthesis of oligosaccharides of the lactose type.[9-11] The selective substitution involves protection of the C-4 hydroxyl by the *tert*-butyl group and subsequent deblocking of I. We now wish to report the preparation of an analogous derivative of glucosamine which was found to be a most suitable aglycon for the synthesis of amino disaccharides. This was achieved by introduction of the amino function into levoglucosan already blocked at C-4.

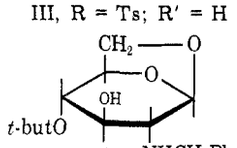
Catalytic deacylation of 2,3-di-*O*-acetyl-1,6-anhydro-4-*O*-*tert*-butyl-β-D-glucopyranose (I)[9] was followed by tosylation of II under controlled conditions, which gave, after column chromatography, a 72% yield of the 2-tosyl derivative III. The selective substitution is in accordance with the observation of Černý, *et al.*,[12] that tosylation of 1,6-anhydroglucose gives almost exclusively the 2,4-ditosyl derivative. The structure of III was, indeed, proved by removal of the *tert*-butyl group and isolation of 1,6-anhydro-2-*O*-*p*-tolylsulfonyl-β-D-glucopyranose.[13] Displacement of the tosyloxy group in III afforded 1,6:2,3-dianhydro-4-*O*-*tert*-butyl-β-D-mannopyranose (IV) in 90% yield.



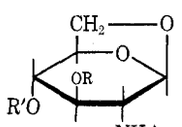
I, R = R′ = Ac
II, R = R′ = H
III, R = Ts; R′ = H



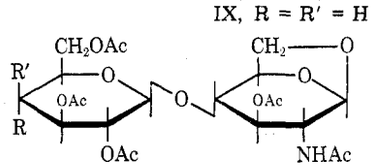
IV



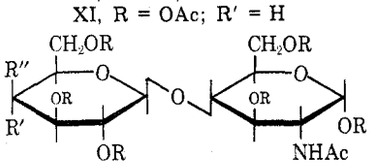
V



VI, R = Ac; R′ = *t*-but
VII, R = Ac; R′ = H
VIII, R = H; R′ = *t*-but
IX, R = R′ = H



X, R = H; R′ = OAc
XI, R = OAc; R′ = H



XII, R = Ac; R′ = H; R″ = OAc
XIII, R = Ac; R′ = OAc; R″ = H
XIV, R = R″ = H; R′ = OH

Epoxides attached to the rigid 1,6-anhydro system are known to undergo scission by a nitrogen nucleophile to lead predominantly to trans-diaxial substitution.[14] This was advantageously effected by benzylamine to give accordingly 1,6-anhydro-2-benzylamino-2-deoxy-4-*O*-*tert*-butyl-β-D-glucopyranose (V) in 79% yield. Hydrogenolysis of V followed by acetylation afforded 2-acetamido-3-*O*-acetyl-1,6-anhydro-2-deoxy-4-*O*-*tert*-butyl-β-D-glucopyranose (VI, 73%). A synthesis of 4-methylated glucosamine derivatives proceeding *via* an epoxide has been reported previously.[15]

Since the *O*-acyl and *tert*-butyl groups can be selectively removed by mild alkaline or acid treatment to obtain at will VIII or VII, respectively, compound VI

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appears to be an excellent starting material for the synthesis of both 1→3 and 1→4 glycosides.

Removal of the *tert*-butyl group by 80% trifluoroacetic acid gave the desired 2-acetamido-3-*O*-acetyl-1,6-anhydro-2-deoxy-β-D-glucopyranose (VII) in 83% yield. Catalytic deacylation led to the known 2-acetamido-1,6-anhydro-2-deoxy-β-D-glucopyranose (IX).[16,17]

The new aglycon VII was successfully applied to the synthesis of *N*-acetyllactosamine and *N*-acetylcellobiosamine. The Koenigs–Knorr reaction of VII with acetobromogalactose afforded the disaccharide X in high yield. Acetolysis of the 1,6-anhydro ring led to the known octaacetate XII.[7] Kuhn and Kirschenlohr[18] synthesized the disaccharide by the cyanohydrin method from 3-*O*-β-D-galactopyranosyl-D-arabinose prepared by degradation of lactose.

Analogously, condensation of VII with acetobromoglucose yielded *N*-acetylcellobiosamine XIV *via* the anhydro derivative XI and the octaacetate XIII. A disaccharide to which this structure was tentatively assigned was obtained by partial acid hydrolysis of Type XIV pneumococcal polysaccharide.[19]

We have shown previously that introduction of the electrophilic *N*-dichloroacetyl group into hexosamines leads to stable and highly reactive bromides which permit the smooth synthesis of hexosaminylsaccharides.[20,21] The scheme outlined in the present report appears to offer an approach to similar bromides of hexosyl hexosamines, namely, by introducing the electrophile into the intermediate primary amine resulting from the hydrogenation of V.

Experimental Section[22]

1,6-Anhydro-4-*O*-*tert*-butyl-β-D-glucopyranose (II).—To a solution of I[9] (3.0 g) in absolute methanol (60 ml) was added 3 drops of methanolic 1 *N* sodium methoxide, and the mixture was kept at room temperature for 4 hr. The solution was neutralized with Dowex 50W-X8, H^+ form and the filtrate was evaporated *in vacuo*. The residue was crystallized from ether and a little hexane: yield 1.80 g (84%); mp 104–105°; $[\alpha]^{25}D$ −57.0°.

Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 55.20; H, 8.34.

1,6-Anhydro-4-*O*-*tert*-butyl-2-*O*-*p*-tolylsulfonyl-β-D-glucopyranose (III).—To an ice-cold solution of II (1.82 g) in pyridine (10 ml) was added dropwise with stirring a solution of toluene-*p*-sulfonyl chloride (2.37 g, 1.5 equiv) in pyridine (14 ml). The reaction mixture was stored in the refrigerator at 5° for 3 days. Tlc (ethyl acetate–methylene chloride, 15:85) showed one major spot and an upper faint spot, presumably of the ditosylate. The reaction mixture was concentrated *in vacuo* at room temperature to half its volume. Methylene chloride was added, and the solution was washed successively with cold water, saturated sodium hydrogen carbonate, and water, dried, and evaporated. The residue was passed through a silica gel column and the product was obtained by elution with ethyl acetate–methylene chloride (1:9), yield 2.23 g (72%). After crystallization from ethyl acetate–hexane, it melted at 125–126°, $[\alpha]^{25}D$ −38.5°.

Anal. Calcd for $C_{17}H_{24}O_7S$: C, 54.83; H, 6.50; S, 8.59. Found: C, 54.93; H, 6.43; S, 8.57.

A sample of III (100 mg) was dissolved in 80% aqueous trifluoroacetic acid (3 ml). After standing for 20 min at room temperature, no starting material was present [tlc, ethyl acetate–methylene chloride (1:3)]. The residue resulting from evaporation of the reagent solidified on cooling and crystallized when triturated wih cold ether: yield 71 mg (83%); mp 115–117°; $[\alpha]^{25}D$ −47.5°; reported[8] for 1,6-anhydro-2-*O*-*p*-tolylsulfonyl-β-D-glucopyranose, mp 117–119°, $[\alpha]^{25}D$ −48 ± 1°.

1,6:2,3-Dianhydro-4-*tert*-butyl-β-D-mannopyranose (IV).— A solution of the tosylate III (4.3 g) in chloroform (60 ml) was cooled to 5°, and 1 *N* methanolic sodium methoxide (23 ml) was added. The reaction mixture was stirred at 5° for 2 hr and at room temperature overnight. Water was added to dissolve the precipitated salts and the aqueous phase was extracted twice with chloroform. The combined extracts were washed with water, dried, and evaporated. Crystallization from hexane gave 2.09 g (90%) of IV, mp 81–82°, $[\alpha]^{25}D$ −35.0°.

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.98; H, 7.91.

1,6-Anhydro-2-benzylamino-2-deoxy-4-*O*-*tert*-butyl-β-D-glucopyranose (V).—The epoxide IV (2.0 g) was dissolved in a mixture of dimethylformamide (14 ml) and freshly distilled benzylamine (6 ml) and the solution was heated with stirring at 110–115° for 40 hr. Tlc [ethyl acetate–methylene chloride (15:85)] showed the disappearance of starting material. The solvent and excess of reagents were distilled off at reduced pressure. The crystalline residue was triturated with water, dissolved in hot ethanol, and decolorized with charcoal. Tlc (ethyl acetate) showed one spot and only traces of a second compound moving close to the product. The filtrate was taken to dryness, and the residue was crystallized from 50% aqueous ethanol: yield 2.42 g (79%); mp 176–177°; $[\alpha]^{25}D$ −41.7°. The nmr spectrum showed signals at τ 2.66 (five aromatic protons) and 8.78 (nine *tert*-butyl protons).

Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.55; H, 8.32; N, 4.52.

2-Acetamido-3-*O*-acetyl-1,6-anhydro-2-deoxy-4-*O*-*tert*-butyl-β-D-glucopyranose (VI).—The preceding compound (3.1 g) was hydrogenated in 95% ethanol (100 ml) with prewashed 10% palladium on charcoal (2 g) at 40° and 50 psi. After 48 hr, the suspension was filtered through a Celite bed and the filtrate was concentrated *in vacuo*. The solid residue, dried over phosphorus pentoxide, was dissolved in pyridine (8 ml), and acetic anhydride (3 ml) was added. After standing overnight at room temperature, the reaction mixture was concentrated to dryness *in vacuo* and the last traces of acylating agent were removed by distilling with several portions of toluene. Crystallization from ethyl acetate–hexane yielded 2.23 g (73%), mp 131–133°. Recrystallized from the same solvents, VI had mp 133–134°, $[\alpha]^{25}D$ −41.9°, ir spectrum (KBr) 5.77 (ester), 6.05, and 6.5 μ (amide). The nmr spectrum showed signals at τ 7.84 (three *O*-acetyl protons), 7.95 (three *N*-acetyl protons), and 8.72 (nine *tert*-butyl protons).

Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.65. Found: C, 55.82; H, 7.88; N, 4.51.

2-Acetamido-3-*O*-acetyl-1,6-anhydro-2-deoxy-β-D-glucopyranose (VII).—Preliminary experiments showed that 10–20% trifluoroacetic acid in methylene chloride as described previously[9] did not remove the *tert*-butyl group of VI satisfactorily. Even after 6 hr, starting material was still present. Heating in 70% aqueous acetic acid at 90° for 20 min caused substantial deacetylation.

A solution of VI (1.42 g) in 80% aqueous trifluoroacetic acid (15 ml) was kept at room temperature and the course of disappearance of VI was followed by tlc [ethyl acetate–methanol (9:1)]. The reaction was complete in 20 min. The solution was concentrated *in vacuo* at room temperature and the residue was codistilled with several portions of toluene. The remainder was crystallized from ethyl acetate and a few drops of hexane, and recrystallized from ethyl acetate. The yield of pure VII amounted to 950 mg (83%), mp 147–148°, $[\alpha]^{25}D$ −71.0°. Tlc [ethyl acetate–methanol (9:1)] showed R_{VI} 0.70. The nmr spectrum showed signals at τ 7.86 (three *O*-acetyl protons) and 7.95 (three *N*-acetyl protons).

Anal. Calcd for $C_{10}H_{15}NO_6$: C, 48.97; H, 6.17; N, 5.71. Found: C, 49.10; H, 5.97; N, 5.68.

A sample of VII was de-O-acetylated as described above for compound II. The residue resulting from the evaporation of the methanolic solution to dryness was crystallized from methanol–ether (2:1) to yield 85% of 2-acetamido-2-deoxy-1,6-anhydro-β-D-glucopyranose (IX): tlc [benzene–methanol (7:3)] R_{VII}

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(22) Optical rotations were determined in 1% chloroform solutions unless stated otherwise.

0.76; mp 193–194°; $[\alpha]^{25}D$ −47° (c 1.2, water) (reported mp 190–191°, $[\alpha]^{25}D$ −45.2°,[16] and mp 190°, $[\alpha]D$ −45.2[17]).

2-Acetamido-1,6-anhydro-2-deoxy-4-*O*-*tert*-butyl-β-D-glucopyranose (VIII).—Deacetylation of VI (150 mg) as above, followed by crystallization from ethyl acetate–ether–hexane afforded 102 mg (78%) of VIII: mp 139–140°; $[\alpha]D$ −25.3°; tlc [ethyl acetate–methanol (9:1)] R_{VI} 0.88; nmr τ 7.98 (three *N*-acetyl protons) and 8.74 (nine *tert*-butyl protons).

Anal. Calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.70; H, 8.24; N, 5.25.

2-Acetamido-3-*O*-acetyl-1,6-anhydro-2-deoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranose (X).—Tetra-*O*-acetyl-α-D-galactosyl bromide (1.03 g, 2.5 mmol) was dissolved in dry ethylene chloride (40 ml), the aglycon VII (0.37 g, 1.51 mmol) and mercuric cyanide (0.63 g, 2.5 mmol) were added, and the mixture was stirred at 40°, with protection from light, until no more aglycon was detectable on tlc (3 days). The cooled solution was poured into a mixture of ice–water and chloroform, and the organic layer was shaken thoroughly with 5% sodium hydrogen carbonate and washed with water. The residue obtained after evaporation of the solvent was dissolved in methylene chloride (5 ml) and chromatographed on a column (40 mm i.d.) of silica gel (E. Merck, 60, 70–230 mesh, 70 g). The compound eluted by a mixture of methylene chloride–ethyl acetate (3:7) weighed 0.72 g (83%) and was crystallized twice from 2-propanol: mp 187–188°; $[\alpha]^{25}D$ −79.4° (*c* 2, chloroform) tlc (ethyl acetate) R_{VII} 1.9. The ir spectrum (KBr) showed bands at 11.2 (β-glycoside) and 11.45 μ (galactopyranose ring).

Anal. Calcd for $C_{24}H_{33}NO_{15}$: C, 50.08; H, 5.78. Found: C, 50.02; H, 5.88.

2-Acetamido-3-*O*-acetyl-1,6-anhydro-2-deoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-β-D-glucopyranose (XI).—Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (2.5 mmol) in ethylene chloride (40 ml) was treated with aglycon VII (1.51 mmol) and mercuric cyanide (2.5 mmol) as described for X. Elution from the silica gel column with methylene chloride–ethyl acetate (2:8) gave 0.76 g (87%) of the chromatographically pure compound. After crystallization from ethyl acetate–ether (1:4) and recrystallization from 2-propanol–isopropyl ether (1:2) it had mp 118–119°; $[\alpha]^{25}D$ −77.5° (*c* 2, chloroform); tlc (ethyl acetate) R_{VII} 1.84, R_X 0.97; ir (KBr) 11.2 μ (β-glycoside).

Anal. Calcd for $C_{24}H_{33}NO_{15}$: C, 50.08; H, 5.78. Found: C, 50.30; H, 5.69.

2-Acetamido-2-deoxy-1,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-glucopyranose (XII).—Opening of the 1,6-anhydro ring in X (115 mg) was effected by treating with acetic anhydride (7 ml), glacial acetic acid (3 ml), and concentrated sulfuric acid (0.05 ml) at 15° for 24 hr. Anhydrous sodium acetate (0.3 g) was added, and the suspension was taken to dryness by coevaporation *in vacuo* with toluene. The residue was extracted with chloroform, and the extract was washed with water, dried over sodium sulfate, and evaporated at reduced pressure. The residue was chromatographed on a silica gel column (10 g, 15 mm i.d.). The fraction eluted by ethyl acetate–methylene chloride (8:2) was crystallized from alcohol–ether and recrystallized from 2-propanol–isopropyl ether: yield 66 mg (45%); mp 223–225°; $[\alpha]^{25}D$ +57.9°; tlc [benzene–methanol (9:1)] R_X 0.9 (reported mp 224–225°, $[\alpha]^{18}D$ +57.7°[7]).

2-Acetamido-2-deoxy-1,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranose (XIII).—Acetolysis of XI (230 mg) as described for X yielded after column chromatography 124 mg (46%) of XIII. Crystallization from alcohol–ether (1:1) and recrystallization from ethyl acetate–isopropyl ether (9:1) gave the pure octaacetyl derivative: mp 229–230°; $[\alpha]^{26}D$ + 46.4°; tlc [benzene–methanol (9:1)] R_{XII} 0.93, R_{XI} 0.99.

Anal. Calcd for $C_{28}H_{39}NO_{18}$: C, 49.63; H, 5.80. Found: C, 49.68; H, 6.00.

2-Acetamido-2-deoxy-4-*O*-(β-D-glucopyranosyl)-D-glucopyranose (XIV).—Catalytic deacetylation of the preceding compound (XIII, 100 mg) gave the free disaccharide XIV, which was crystallized from methanol–ether (8:2) and recrystallized from 2-propanol: yield 39 mg (69%); mp 168–170°; $[\alpha]^{24}D$ +12.9 ± 1° (*c* 1, water); tlc [benzene–methanol (1:2)] $R_{lactose}$ 0.8; ir (KBr) 6.0, 6.45 (amide group), and 11.2 μ (β linkage).

Anal. Calcd for $C_{14}H_{25}NO_{11}\cdot 2H_2O$: C, 40.09; H, 6.97. Found: C, 40.10; H, 7.03.

Registry No.—II, 36949-97-0; III, 36949-98-1; IV, 36949-99-2; V, 37042-48-1; VI, 37042-49-2; VII, 37042-50-5; VIII, 37042-51-6; IX, 37042-52-7; X, 36954-61-7; XI, 36954-62-8; XII, 36954-63-9; XIII, 36954-64-0; XIV, 36954-65-1.

Levoglucosenone (1,6-Anhydro-3,4-dideoxy-Δ³-β-D-Pyranosen-2-one). A Major Product of the Acid-Catalyzed Pyrolysis of Cellulose and Related Carbohydrates

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Levoglucosenone (1,6-anhydro-3,4-dideoxy-Δ³-β-D-pyranosen-2-one) was isolated as the major component of the tar fraction from the acid-catalyzed pyrolysis of cellulose, D-glucose, or levoglucosan (1,6-anhydro-β-D-glucopyranose). Its structure was determined and a mechanism describing its formation from levoglucosan is proposed.

Until the early 1950's studies of the pyrolysis of cellulose and cellulosic fuels, neat and treated with various fire retardants, were largely confined to determination of such gross fractions as gas, tar, and char and to simple observation of how the combustibility of the sample varied with the relative proportions of these fractions. Such studies clearly established that high "tar" yields favor high flammability.[1,2]

As early as 1918, Pictet and Sarasin[3] isolated as a major constituent of the tar fraction a substance they named "levoglucosan." This constituent was subsequently identified by Josephson[4] as 1,6-anhydro-β-D-glucopyranose (I).

Unfortunately, many of the more recent studies of the combustion behavior of cellulose have tended to equate levoglucosan and tar. Since high levoglucosan yield—and, consequently, high tar yield—favors high flammability, it was assumed that reducing the levoglucosan yield—and, therefore, presumably the tar yield—would lower flammability. In particular, since both acidic and basic retardants were found to lower drastically the levoglucosan yield on pyrolysis of treated cellulose, such materials have frequently been

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