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Synthesis of Some 4,6-*O*-Alkylidene and 4,6-*O*-Arylidene Derivatives of 2-Acetamido-2-deoxy-D-glucose

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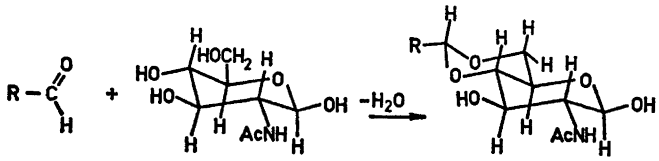
Some 4,6-*O*-alkylidene and 4,6-*O*-arylidene derivatives of 2-acetamido-2-deoxy-D-glucose have been prepared. Methylation analysis and NMR studies confirm the proposed structures.

A preliminary investigation has demonstrated that the 7,9-*O*-ethylidene derivative of 5-acetamido-3,5-dideoxy-D-*glycero*-D-*galacto*-nonulosonic acid (*N*-acetylneuraminic acid) had an inhibitory effect on neuraminidase isolated from *Vibrio cholerae*.[1] The present paper reports the synthesis of a number of 4,6-*O*-alkylidene and 4,6-*O*-arylidene derivatives of 2-acetamido-2-deoxy-D-glucose, which are intermediates in the synthesis of related neuraminic acid derivatives.[2]

The preparation of cyclic acetals by condensing aliphatic aldehydes with 2-acetamido-2-deoxy-D-glucose in the absence of solvent, yielded viscous syrups which were difficult to work up. When the reaction was performed in acetonitrile with concentrated hydrochloric acid as a catalyst, high yields of crystalline products were obtained.



Aromatic aldehydes did not react under these concitions but good yields of crystalline acetals were obtained when the reaction was performed without solvent or in dioxane using zinc chloride as a catalyst.

α,β-Unsaturated aldehydes, such as propenal, polymerized under the acidic reaction conditions. Attempts to prepare cyclic acetals of glyoxylic acid mono-

Table 1. Synthesis of 4,6-*O*-alkylidene derivatives. (10 g 2-acetamido-2-deoxy-D-glucose).

Aldehyde g		Acetonitrile ml	Reaction time h	Yield (crude prod.) g	%	Solvent for crystallization
Paraldehyde	30	100	20	11	92	Ethanol
Propanal	12	100	5	12	95	Ethanol
Butanal	15	100	5	13	97	Water
Pentanal	18	100+100[a]	6	13	93	Water
Hexanal	20	100+100[a]	6	13	90	Water

[a] The last portion which was added after 2 h of reaction contained 2 % concentrated hydrochloric acid.

Table 2. Synthesis of 4,6-*O*-arylidene derivatives. (5 g 2-acetamido-2-deoxy-D-glucose).

Aldehyde, g		Zinc chloride g	Dioxane ml	Reaction time h	Yield (crude prod.) g	%
o-Chlorobenzaldehyde	28	10	—	24	6.7	80
m-Chlorobenzaldehyde	28	10	—	10	7.8	94
p-Chlorobenzaldehyde	28	10	20	48	7.8	94
2-Formylthiophene	25	7	—	48	4.5	59
3-Formylthiophene	15	3.5	—	72	4.1	54

hydrate, 4-formylpyridine, *o*-, *m*-, and *p*-hydroxybenzaldehyde and *o*-, *m*-, and *p*-nitrobenzaldehyde were also unsuccessful.

All the acetals listed in Table 3 on methylation and hydrolysis with hydrochloric acid yielded 2-amino-2-deoxy-3-*O*-methyl-D-glucose hydrochloride indistinguishable from an authentic sample.[3-6]

This demonstrates that all the acetals are 4,6-*O*-derivatives [5] possibly contaminated with small amounts of 5,6-*O*-derivatives.[6] Acetal formation leads to the formation of a new asymmetric centre in the molecule. Previous studies have demonstrated [7] that when 6-membered cyclic acetals are formed under acidic conditions (thermodynamic control) the preponderating isomer is that with the equatorial alkyl or aryl group. This has been confirmed by an NMR study of the proton of the benzylidene acetal carbon atom of methyl 4,6-*O*-benzylidene-2,3-*O*-acetyl-α-glucopyranoside.[8] The corresponding proton of the β-glucoside showed the same chemical shift.

In the present work the τ-value (in methylsulfoxide—10 % deuteriumoxide) of the equivalent methine proton of the ethylidene and butylidene

Table 3. Physical properties of 4,6-*O*-alkylidene and 4,6-*O*-arylidene derivatives of 2-acetamido-2-deoxy-D-glucose.

Compound	m.p. (dec.)°	$[\alpha]_D^{25}$ (c 1.0) Methylsulfoxide 2 min and 12 h	Pyridine[e] 2 min	Pyridine[e] 48 h[d]	Calc: C	Calc: H	Calc: N	Found: C	Found: H	Found: N
R-ethylidene-α-R_1	211–212	+73	+126	+104	48.8;	6.90;	5.70	48.7;	7.27;	5.78
R-propylidene-α-R_1	215–216	+73	+122	+100	50.7;	7.30;	5.36	50.7;	7.68;	5.55
R-butylidene-α-R_1	225–226	+68	+115	+94	52.5;	7.60;	5.30	53.1;	7.90;	5.21
R-pentylidene-β-R_1	225–226	+14	+25	+85	54.0;	8.01;	4.84	54.4;	8.24;	4.87
R-hexylidene-β-R_1	226–227	+13	+22	+81	55.4;	8.31;	4.61	55.8;	8.48;	4.66
R-(*o*-chlorobenzylidene)-β-R_1[a]	219–220	+11	+32	+63	52.4;	5.28;	4.07	53.1;	5.35;	4.10
R-(*m*-chlorobenzylidene)-β-R_1	241–242	−22	−31	+33	52.4;	5.28;	4.07	52.5;	5.25;	4.04
R-(*p*-chlorobenzylidene)-β-R_1	261–262	−24	−31	+25	52.4;	5.28;	4.07	52.5;	5.38;	4.07
R-(2-thienylidene)-β-R_1	232–233	−23	−25	+41	49.5;	5.44;	4.44	49.3;	5.45;	4.44
R-(3-thienylidene)-β-R_1	230–231	−17	−11	+38	49.5;	5.44;	4.44	49.0;	5.47;	4.54
R-benzylidene-β-R_1[b]	247–248	−24	−17	+37	58.2;	6.20;	4.53	58.3;	6.32;	4.66

R=2-Acetamido-2-deoxy-4,6-*O*. R_1=D-Glucose.
[a]=Constant value after 2 cryst.
[b]=Reported:[6] $[\alpha]_D^{20}$ −29.4°, *c* 1.0, methylsulfoxide, −16.2° (inital, extrapolated) +38.2°, *c* 1.0, pyridine, final, 24 h.
[d]=Final.
[e]=With traces of ammonium ion at the measurements of the alkylidene derivatives.

Table 4. τ-Values in methylsulfoxide—10 % deuteriumoxide of the proton on the alkylidene and arylidene acetal carbon atom of cyclic acetals of 2-acetamido-2-deoxy-D-glucose and D-glucose. J = ca. 5 cps.

Compound	τ (ppm)	
R-ethylidene-α-R_2	5.27	quart.
R-butylidene-α-R_2	5.41	tripl.
R_1-ethylidene-α-R_2	5.22	quart.
R_1-propylidene-α-R_2	5.42	tripl.
R_1-butylidene-α-R_2	5.37	»
R_1-pentylidene-β-R_2	5.37	»
R_1-hexylidene-β-R_2	5.38	»
R-benzylidene-β-R_2	4.37	singl.
R_1-benzylidene-β-R_2	4.35	»
R_1-(*o*-chlorobenzylidene)-β-R_2	4.08	»
R_1-(*m*-chlorobenzylidene)-β-R_2	4.30	»
R_1-(*p*-chlorobenzylidene)-β-R_2	4.30	»
R_1-(2-thienylidene)-β-R_2	4.05	»
R_1-(3-thienylidene)-β-R_2	4.27	»

R = 4,6-*O*.
R_1 = 2-Acetamido-2-deoxy-4,6-*O*.
R_2 = D-Glucose.

derivatives of 2-acetamido-2-deoxy-D-glucose was found to be close to the τ-value of 4,6-*O*-ethylidene- and 4,6-*O*-butylidene-α-D-glucose, respectively.

The chemical shift for the proton on the arylidene acetal carbon atom of the arylidene derivatives of 2-acetamido-2-deoxy-D-glucose, with the exception of the *o*-chlorobenzylidene and the thienylidene derivatives, was found to be close to the shift for the corresponding proton of 4,6-*O*-benzylidene-β-D-glucose; Table 4.

The low τ-values of the *o*-chlorobenzylidene and thienylidene derivatives are consistent with the observed values for benzaldehyde, *o*-, *m*-, and *p*-chlorobenzaldehyde, and formylthiophene.

This confirms the 6-membered ring structure of the synthesized cyclic acetals and an equatorial configuration of the alkylidene and arylidene groups.

EXPERIMENTAL

NMR-Analyses were performed with a Varian A-60 A instrument, and elemental analyses with a Hewlett Packard Model 185 CHN Analyser. Optical rotations were determined with a Perkin-Elmer 141 polarimeter using a 10 cm cell.

When a substance melted under decomposition the m.p. (decomp.) was defined as the lowest temperature, at which the substance was completely decomposed within 60 sec. Melting points are corrected. Concentrations were performed under reduced pressure at a temperature not exceeding 50°.

The reactions were followed by TLC, using silica gel (Merck HF_{254}) activated at 120° for 30 min. Butanol—ethyl acetate 1:1 (v/v) was used as a solvent. Spots were detected by spraying with 2,4-dinitrophenylhydrazine-orthophosphoric acid reagent [9] and heating for 10—20 min at 125°.

Table 5. Elemental analyses of methylated cyclic mono-alkylidene and mono-arylidene derivatives of 2-acetamido-2-deoxy-D-glucose.

Type of dimethyl derivative	Calc: C	H	N	Found: C	H	N
Ethylidene	52.4;	7.69;	6.09	52.3;	7.81;	5.04
Propylidene	54.0;	8.01;	4.84	54.0;	8.18;	4.85
Butylidene	55.4;	8.30;	4.62	55.3;	8.33;	4.63
Pentylidene	56.8;	8.57;	4.41	56.2;	8.69;	4.28
Hexylidene	58.3;	8.82;	4.22	58.2;	8.99;	4.24
o-Chlorobenzylidene	54.9;	5.96;	3.77	54.9;	6.10;	3.79
m-Chlorobenzylidene	54.9;	5.96;	3.77	55.3;	6.08;	3.79
p-Chlorobenzylidene	54.9;	5.96;	3.77	55.7;	6.20;	3.79
2-Thienylidene	52.5;	6.16;	4.08	52.5;	6.35;	4.13
3-Thienylidene	52.5;	6.16;	4.08	53.2;	6.45;	4.13

General procedure for the synthesis of the alkylidene derivatives. A mixture of 2-acetamido-2-deoxy-D-glucose, aldehyde and conc. hydrochloric acid (to a final amount of 2 %) in acetonitrile was stirred vigorously at 25° for various lengths of time. The mixture was initially sticky but after about 2 h, crystals were formed. When the reaction was complete, the crystals were filtered off and dissolved in dry methanol. The methanolic solution was neutralized with solid sodium carbonate decahydrate, filtered and treated with a mixture of Dowex 1-X8 (OH^-) and Dowex 50W-X8 (H^+) (previously washed with methanol) until a negative reaction with silver nitrate was obtained. Concentration of the solution yielded a solid which was crystallized. Details of the preparation of the different cyclic acetals are given in Table 1, physical properties and analyses in Table 3.

General procedure for the synthesis of the arylidene derivatives. A mixture of 2-acetamido-2-deoxy-D-glucose, aldehyde, zinc cloride (fused and finely powdered) and in some preparations, dioxane, was stirred vigorously at 25° for various lengths of time. When the reaction was complete, the mixture was poured into water (200—300 ml), and the precipitate briefly agitated with a glass rod. The water was decanted and the solid washed with ethyl ether (3 × 100 ml), dried in a desiccator and crystallized from water. Details of the preparation are given in Table 2, physical constants and analyses in Table 3.

Methylation analysis. The pure cyclic acetals were methylated with methyl sulfate and sodium hydroxide in methylsulfoxide under conditions giving the dimethyl derivative of 2-acetamido-2-deoxy-4,6-*O*-benzylidene-*β*-D-glucose.[6] The methylated products were recrystallized once from abs. ethanol. Elemental analysis showed that the products obtained were dimethyl derivatives and are probably mixtures of α- and *β*-glucosides. No attempt was made to separate these mixtures; Table 5.

The methylated acetals were hydrolysed as follows: 500 mg acetal in 20 ml of 2.5 M hydrochloric acid was refluxed for 4 h. The mixture was evaporated to dryness, dissolved in water, treated with activated carbon and evaporated again. The residue was extracted with ethyl ether, dissolved in hot methanol and precipitated with acetone. The precipite was indistinguishable from an authentic sample of 2-amino-2-deoxy-3-*O*-methyl-D-glucose hydrochloride. A typical experiment gave: m.p. (decomp.) 210—215°; $[\alpha]_D^{20} =$ +112°, 7 min, +90°, 18 h final (*c* 1.0, water).

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