Carbohydrate Research, 45 (1975) 302–306

Note

An improved synthesis of the 2-acetamido-D-glucal derivative 3,4,6-tri-*O*-acetyl-2-(*N*-acetylacetamido)-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol*

NEVENKA PRAVDIĆ, IVANKA FRANJIĆ-MIHALIĆ, AND BORIS DANILOV
Department of Organic Chemistry and Biochemistry, "Rudjer Bošković" Institute, 41001 Zagreb, Croatia (Yugoslavia)

(Received June 12th, 1975; accepted for publication, July 15th, 1975)

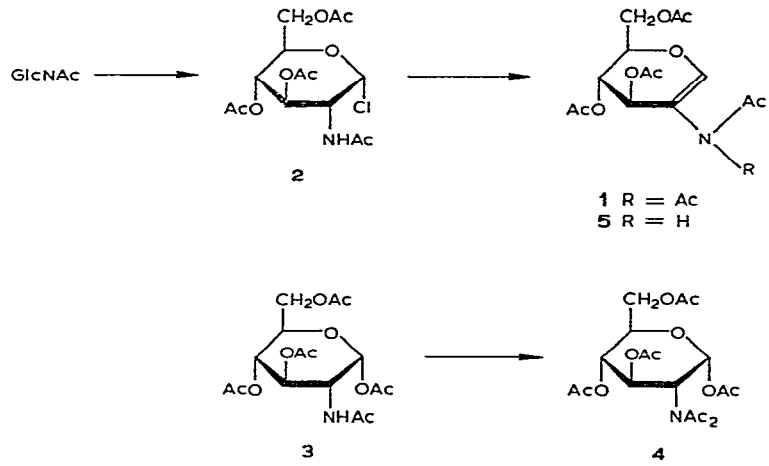
Earlier reports[1,2] on the utilization of unsaturated amino sugars (2-acetamido-D-glucal derivatives) showed that compounds of this class are useful intermediates for the formation of glycosidic bonds of various types. Unsaturated amino sugars, appropriately substituted, react under conditions of acid catalysis with nucleophiles producing C-1 ester[1], ether[1], and thioether[2] linkages.

The parent substance, from which a series of unsaturated amino sugars having the double bond in the C-1–C-2 or the C-2–C-3 position could be prepared, is the acetylated 2-acetamido-D-glucal, 3,4,6-tri-*O*-acetyl-2-(*N*-acetylacetamido)-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (**1**). Hitherto, this compound was synthetically accessible only from 2-acetamido-2-deoxy-D-mannose, either as one of the six products in the one-step reaction[3] or, in better yield, through the improved method *via* 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-mannopyranose[1,4].

We now report a synthesis of **1** starting from 2-acetamido-2-deoxy-D-glucose. The key step in the synthesis involved treatment of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride (**2**) with isopropenyl acetate, a reagent which effects the introduction of the second *N*-acetyl group[3,5].

A modified synthesis of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride[6–9] (**2**) was used because chloride of high purity was needed in the subsequent reaction-step. The chloride **2**, prepared by Horton's method[7], contains[8] an unidentified by-product which could not be completely removed by crystallization[9]. By chromatography on silica gel, we isolated the by-product (13%) and identified it as 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose (**3**). The presence of **3** in the crude preparations of **2** could be easily detected[8] by t.l.c., and the ratio of **3**:**2** can be determined by n.m.r. spectroscopy, since the signal ($\tau \sim 7.81$) for AcO-1 in **3** is well-separated[10] from the signals for the Ac protons of **2**. However, the physical constants are not sufficiently characteristic to allow assessment of the purity of crude samples of **2**. When the reaction of 2-acetamido-2-deoxy-D-glucose with acetyl

*Dedicated to the memory of Dr. Hewitt G. Fletcher, Jr.



chloride was monitored by t.l.c., **3** was found to be the first product, which then reacted to give **2**, this process being very slow in the later stages of reaction. When **3** was treated with acetyl chloride saturated with hydrogen chloride, the transformation of **3** into **2** was completed in 12 days.

Treatment of **2** with boiling isopropenyl acetate in the presence of catalytic amounts of toluene-*p*-sulphonic acid afforded **1** (80–86%). When **2** contaminated with **3** was used, the product **1** contained a contaminant of slightly lower mobility, which was isolated by column chromatography in ~ 10% yield and shown to be 1,3,4,6-tetra-*O*-acetyl-2-(*N*-acetylacetamido)-2-deoxy-α-D-glucopyranose[5] (**4**). Thus, **4** is formed by *N*-acetylation of **3**, and it appears that only **2** could be converted into the unsaturated amino sugar **1**. The reaction of 2-acetamido-2-deoxy-D-glucose with isopropenyl acetate[5] yields two 1,3,4,6-tetra-*O*-acetyl-2-(*N*-acetylacetamido)-2-deoxy-D-glucopyranoses which are not subject to any structural changes[4]. Although no di-*N*-acetyl derivative related to **2** has been detected, it is assumed that *N*-acetylation of **2** takes place prior to its conversion into **1**. The formation of the C-1–C-2 double bond in **2** involves *trans* elimination of hydrogen chloride, a process which could easily be faster than *N*-acetylation. That **1** is formed from **2** *via* its di-*N*-acetyl intermediate, but not from **4**, is explained by the fact that chlorine is a better leaving group than acetoxy. However, earlier studies[3,4,11] suggest that AcO-1 might take part in the elimination provided that it and the *N*-acetylacetamido group at C-2 are *trans* diaxial. In Table I, some examples of such eliminations are given, and the mechanism which was presumed[4,11] to be operative in the D-*manno* and the D-*galacto* series involves the participation of the *N*-acetylacetamido group at C-2.

The *trans* elimination occurring in the D-*gluco* series also appears to be dependent on neighbouring-group participation. Dehydrohalogenation of **2** with 1,5-diazabicyclo[5.4.0]undec-5-ene, a reagent which was been successfully used in carbohydrate chemistry[12,13], gave 2-acetamido-3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (**5**) in 24% yield. The ready conversion **2**→**1** mediated by

isopropenyl acetate indicates that the *N*-acetylacetamido group significantly facilitates the elimination.

TABLE I

SUMMARIZED DATA ON THE ELIMINATION REACTIONS

Configuration and conformation	*Substituents in the position*				*Elimination of*	*Ref.*
	C-1		*C-2*			
	ax	*eq*	*ax*	*eq*		
D-*gluco*, $^4C_1$	Cl			NHAc	—	[a]
	Cl			NAc_2	HCl	[a]
	OAc			NAc_2	—	[a], 3–5
		OAc		NAc_2	—	3–5
D-*manno*, $^4C_1$	OAc		NAc_2		CH_3COOH	3, 4
	$OCOC_6H_5$		NAc_2		C_6H_5COOH	4
		$OCOC_6H_5$	NAc_2		—	4
	SEt		NAc_2		EtSH	4
D-*galacto*, $^1C_4$	OAc		NAc_2		CH_3COOH	11
$^4C_1$	OAc			NAc_2	—	11

[a]This paper.

EXPERIMENTAL

General methods. — T.l.c. was conducted on silica gel (Merck), using *A* 1:1 ether–ethyl acetate, *B* 5:1 ether–acetone, with detection by charring with sulphuric acid. Column chromatography was performed on silica gel (Merck, 0.05–0.20 mm). Specific rotations were measured for solutions in chloroform at 20–24°. N.m.r. spectra were recorded at 60 MHz with a Varian A-60A spectrometer for solutions in $CDCl_3$ (internal Me_4Si).

*2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-*D*-glucopyranosyl chloride* (**2**). — (*a*) *Modified procedure.* A mixture of dry 2-acetamido-2-deoxy-D-glucose (20 g) and acetyl chloride (80 ml) was stirred until a clear solution was obtained (2 h). T.l.c. (solvent *A*) then revealed the presence of starting material and 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose (**3**) and traces of **2**. The reaction mixture was saturated with dry hydrogen chloride at ~0° and then stored in a tightly stoppered flask in the dark at room temperature, and the reaction was monitored by t.l.c. After 5–6 days, little **3** remained. The reagent was removed *in vacuo*, and dry benzene was repeatedly evaporated from the residue, a solution of which in chloroform (150 ml) was then washed with cold, saturated, aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and concentrated to ~40 ml. Addition of dry ether (100 ml) gave **2**. After 2 h, the product (25.8 g, 78%) was collected, washed with anhydrous ether, and dried; it was chromatographically homogeneous and had m.p. 116–117° $[\alpha]_D$ +115.5° (*c* 1); lit.[8] m.p. 123°, $[\alpha]_D$ +115° (chloroform).

N.m.r. data: τ 3.78 (d, $J_{1,2}$ 4.0 Hz, H-1), 3.98 (bd, NH), 7.92, 7.97 (6H), and 8.02 (OAc and NAc). There was no signal at τ 7.81 characteristic of AcO-1 of **3**.

(*b*) *From 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-*D*-glucopyranose*[14] (**3**). — Dry hydrogen chloride was passed for 5 h into a solution of **3** (2 g) in acetyl chloride (20 ml) at 0° and the mixture was then kept at room temperature. Monitoring by t.l.c. (solvent *A*) revealed **3** and **2** to be present in almost equal amounts after 24 h; after 12 days, **3** could not be detected. The reaction mixture was then worked-up as described in (*a*) to give chromatographically homogeneous **2** (1.58 g, 84%), m.p. 116–117°, $[\alpha]_D$ +114° (*c* 1). The n.m.r. spectrum showed the absence of impurities.

(*c*) *By chromatographic purification.* — Crude **2**, prepared by the procedure of Vercellotti and Luetzow[8], contained two components, R_F 0.68 and 0.32 (t.l.c., solvent *A*). The n.m.r. spectrum ($CDCl_3$) contained a singlet at τ 7.81, indicative of ~15% of **3**.

Elution of a sample (5 g) from silica gel (90 g), using solvent *B* (10-ml fractions), gave **2** (0.7 g, 14%) in fractions 18–19. Recrystallization from benzene gave material having m.p. 122–123°, $[\alpha]_D$ +117° (*c* 1).

Fractions 20–34 contained a mixture of **2** and the slower-moving substance (2.4 g). Fractions 35–60 contained the second component (645 mg, 13%), which after crystallization from propan-2-ol had properties (m.p., chromatographic behavior, and n.m.r. spectrum) indistinguishable from those of an authentic[14] 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose (**3**).

(*d*) *From crude samples of* **2** *containing* **3**. — A solution of the crude product (25 g) from (*c*) in acetyl chloride (75 ml) was saturated with hydrogen chloride at 0°, and then treated as described in (*a*) to give **2** (87%).

*3,4,6-Tri-*O*-acetyl-2-(*N*-acetylacetamido)-1,5-anhydro-2-deoxy-*D*-arabino-hex-1-enitol* (**1**). — (*a*) A solution of **2** (20 g) in isopropenyl acetate (350 mg) containing toluene-*p*-sulphonic acid monohydrate (350 ml) was boiled under reflux for 24 h. The solvent was evaporated *in vacuo*, and a solution of the dark, thick residue in chloroform (5 ml) was applied to a column of silica gel (25 g) prepacked in ether, and eluted with the same solvent. The first 20 ml of eluate was discarded. The next 200 ml contained chromatographically homogeneous material and was concentrated *in vacuo*. A solution of the residue in chloroform (150 ml) was washed twice with saturated, aqueous sodium hydrogen carbonate and then water, dried, and concentrated. The dry residue was triturated with anhydrous ether (15 ml), and the product (16.3–17.5 g, 80–86%), when recrystallized from ethanol, had m.p. 95–96° and i.r. and n.m.r. spectra identical with those reported[1,3] for **1**.

(*b*) Crude **2** [6 g, see (*c*)] was treated with isopropenyl acetate as described above; after 24 h, t.l.c. (ether) revealed several products. The solvent was evaporated *in vacuo*, and the residue was eluted from silica gel (160 g) with ether (15-ml fractions).

From fractions 26–43, **1** was obtained (3.5 g, 57%), and fractions 44–54 contained the mixture (985 mg).

Fractions 55–74 yielded a semicrystalline residue (740 mg, 10%), and recrystallization from ether gave a product having m.p. 104–105°, $[\alpha]_D$ +102° (*c* 1.4), which

was identical (i.r. and n.m.r. spectra) with 1,3,4,6-tetra-*O*-acetyl-2-(*N*-acetylacetamido)-2-deoxy-α-D-glucopyranose[5] (**4**).

Treatment of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl chloride (**2**) *with DBU.* — A solution of **2** (1.0 g) in *N,N*-dimethylformamide (5 ml) containing 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU, 0.5 ml) was stirred for 3 h. T.l.c. (solvent *A*) then revealed at least three products and the absence of **2**. The solvent was evaporated *in vacuo* and the residue was eluted from silica gel (60 g) with solvent *A* (8-ml fractions).

Fractions 39–55 contained a mixture (340 mg) which was not further purified. Concentration of fractions 56–75 gave a chromatographically homogeneous foam (214 mg, 24%), which was identical (chromatographic behavior, n.m.r. spectrum) with 2-acetamido-3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol[3,15] (**5**).

ACKNOWLEDGMENTS

This work was supported by a P. L. 480 grant from the National Institutes of Health, Bethesda, Md., Agreement No. 02-010-1. Valuable technical assistance of Mrs. N. Janeš is specially appreciated. We thank Mrs. L. Tomić, M.S., for recording the n.m.r. spectra.

REFERENCES

1 N. Pravdić, B. Židovec, and H. G. Fletcher, Jr., *Croat. Chem. Acta*, 42 (1970) 523–533.
2 N. Pravdić, B. Židovec, I. Franjić, and H. G. Fletcher, Jr., *Croat. Chem. Acta*, 45 (1973) 343–356.
3 N. Pravdić and H. G. Fletcher, Jr., *J. Org. Chem.*, 32 (1967) 1806–1810.
4 N. Pravdić and H. G. Fletcher, Jr., *J. Org. Chem.*, 32 (1967) 1811–1814.
5 T. D. Inch and H. G. Fletcher, Jr., *J. Org. Chem.*, 31 (1966) 1815–1820.
6 D. Horton and M. L. Wolfrom, *J. Org. Chem.*, 27 (1962) 1794–1800.
7 D. Horton, *Org. Synth.*, 46 (1966) 1–4.
8 J. R. Vercellotti and A. E. Luetzow, *J. Org. Chem.*, 31 (1966) 825–830.
9 S. E. Zurabyan, T. P. Volosyuk, and A. Ya. Khorlin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 7 (1968) 1612–1614.
10 D. Horton, *J. Org. Chem.*, 29 (1964) 1776–1782.
11 N. Pravdić and H. G. Fletcher, Jr., *Croat. Chem. Acta*, 41 (1969) 125–133.
12 D. R. Rao and L. M. Lerner, *Carbohyd. Res.*, 19 (1971) 133–134.
13 N. A. Hughes, *Carbohyd. Res.*, 25 (1972) 242–245.
14 O. Westphal and H. Holzmann, *Ber.*, 75 (1942) 1274.
15 N. Pravdić, B. Židovec, and H. G. Fletcher, Jr., *Croat. Chem. Acta*, 45 (1973) 333–342.