Carbohydrate Research, 103 (1982) 286–292
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

Note

A facile synthesis of 2-methyl-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)-[2,1-*d*]-2-oxazoline

VINAI K. SRIVASTAVA

Department of Chemistry, State University of New York, College of Environmental Science and Forestry, Syracuse, New York 13210 (U.S.A.)

(Received April 27th, 1981; accepted for publication in revised form, August 15th, 1981)

Per-*O*-acetyl[1,2]oxazolines prepared from 2-acetamido-2-deoxy-β-hexose derivatives have been widely used as precursors for the stereospecific synthesis of 1,2-*trans*-glycosides[1,2], 1,2-*trans*-glycosyl phosphates[3], 1,2-*cis*-glycosyl phosphates, and *N*-diacetylchitobiose[4,5]. However, carbohydrate oxazolines have not been prepared from 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-hexoses. The oxazoline **3** has been prepared by treating 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose (**2**) with anhydrous ferric chloride in dichloromethane[6] or by treatment of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride with silver nitrate and collidine in acetone[7] or tetraethylammonium chloride and sodium hydrogencarbonate in acetonitrile[8]. Recently, Nashed *et al.*[9] have reported the synthesis of oxazolines by cyclization of 1-propenyl β-glycosides by treatment with mercuric chloride–mercuric oxide in acetonitrile. We decided to reinvestigate the preparation of oxazoline **3** from 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose (**1**), as **1** can be prepared readily in ~90% yield from the commercially available 2-amino-2-deoxy-D-glucose hydrochloride. The present paper describes the synthesis of oxazoline **3** from **1** and **2** by using anhydrous stannic chloride as catalyst in dichloromethane. The ^{1}H- and ^{13}C-n.m.r. data of the oxazoline **3** are recorded and conformational implications discussed.

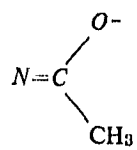
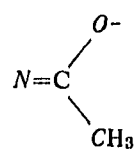
RESULTS AND DISCUSSION

Treatment of **1** with stannic chloride (0.3 equiv.) in dichloromethane for 3 h at room temperature afforded oxazoline **3** in 82% yield as a syrup having $[\alpha]_D^{22}$ +17.2° after chromatographic purification. The ^{13}C-n.m.r. spectrum of **3** (Table I) showed a characteristic downfield shift for C-1 of 8.66 p.p.m. and 13.84 p.p.m. for C-2, indicating oxazoline-ring formation involving C-1 and C-2. Acetamido group carbon resonances disappeared and were replaced by $CH_3\text{-}\overset{O^-}{\overset{|}{C}}{=}N$- signals ($CH_3$ re-

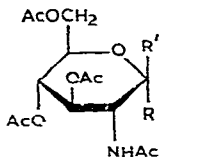
0008-6215/82/0000–0000/S 02.75,

TABLE I

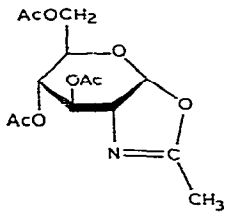
^{13}C-N.M.R. SHIFTS (PROTON DECOUPLED, p.p.m. IN $CDCl_3$)

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C=O*	*CH_3*			
								OAc	*NAc*		
1	91.02	51.36	71.0[a]	70.05[a]	67.95	61.85	171.91, 170.91, 170.27, 169.36, 168.87	20.91 20.71	23.01		
3[b]	99.68	65.20	68.65[a]	70.64[a]	67.82[a]	63.52	170.74, 169.91, 169.73	20.83 20.69		166.91	13.89

[a]May be interchanged. [b]Numbering of ring carbon atoms is kept the same for **1** as in **3**.



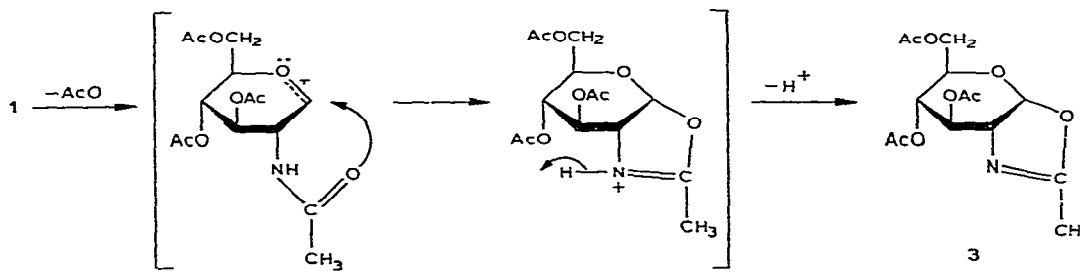
1 R = OAc, R′ = H
2 R = H, R′ = OAc



3

sonated upfield at 13.89 p.p.m. and the tertiary carbon atom resonated at 166.91 p.p.m.). The ^{13}C-n.m.r. data for 3 supported the assignment of an oxazoline ring formation when compared with data for **1**. ^{13}C-N.m.r. data have been recently[10] reported for **1** in trifluoroacetic acid. The ^{1}H-n.m.r. spectrum of 3 was identical to that reported in the literature[9].

The formation of oxazoline 3 from **1** must require the formation of an exo-carbonium ion at C-1, which then undergoes intramolecular attack by the acetamido group to generate the oxazolinium ion (**5**). The ready elimination of a proton from the NH group stabilizes the oxazoline ring. Nucleophilic displacement of a *trans* substituent on the neighboring carbon atom[8,11] is not operative in this case. Treatment of **1** with anhydrous ferric chloride gave no reaction, and **1** was recovered unchanged. It appears that a strong Lewis acid is required to remove the α-acetate group to generate the carbonium ion at C-1.



4 5

Treatment of the β acetate **2** with stannic chloride for 30 min afforded oxazoline 3 in 88% yield. The ^{1}H-n.m.r., i.r., and optical-rotation data were identical with those of 3 obtained from **1**. The reaction is much faster, as would be predicted.

Conformational analysis of oxazoline 3. — ^{1}H-N.m.r. data (400 MHz) for 3 are given in Table II and the approximate dihedral angles (degrees) of the vicinal protons and the coupling constants (in parentheses) for different possible conformations are given in Table III. Variations in coupling constants are often observed and may be attributed to the effect of substituent electronegativity, the adoption of a favored, lower energy conformation, and the incidence of conformational equilibria[12,13].

Nashed *et al.*[9] concluded earlier that oxazoline 3 adopts a modified $^{O}S_{2}$

TABLE II

^{1}H-N.M.R. CHEMICAL SHIFTS (δ) AND FIRST-ORDER COUPLING CONSTANTS (Hz) FOR OXAZOLINE 3

H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6,H-6'*	*C-CH$_3$*	*COCH$_3$*
5.98(d)	4.14m	5.27dd	4.94dq	3.61dt	4.18d	2.1d	2.13, 2.11, 2.09
$J_{1,2}$ 7.3	$J_{2,3}$ 2.4	$J_{3,4}$ 2.8	$J_{4,5}$ 9.6	$(J_{5,6} + J_{5,6'})/2$ 4.0		J_{2,CH_3} 2.0	
	$J_{2,4}$ 1.5	$J_{2,3}$ 2.4	$J_{2,4}$ 1.5				

TABLE III

BOND ANGLES (DEGREES) FOR DIFFERENT POSSIBLE CONFORMATIONS OF 3

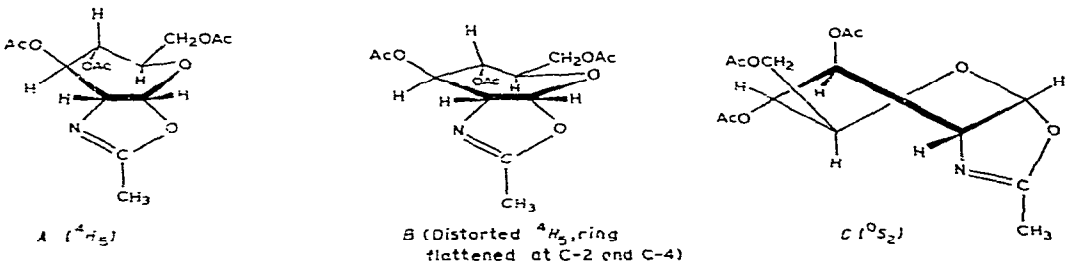
Conformation	$\phi_{1,2}$	$\phi_{2,3}$	$\phi_{3,4}$	$\phi_{4,5}$
From coupling constants[a]	19 or 153	55 or 121	52 or 124	~0 or ~180
From coupling constants[a] reported by Nashed *et al.*[9]	19 or 153	54 or 123	56 or 120	~0 or ~180
Angles (ϕ) as reported by Nashed *et al.*[9]	20–30	50–60	110–120	>160
	(7.2–6.0)[b]	(3.1–1.7)	(0.9–2.2)	(<8.1)
Distorted half-chair[c] $^4H_5$	45	170	170	180
	(3.9)[b]	(8.9)	(8.9)	(9.2)
Boat[c] ^{0,3}B	12	70	60	135
	(7.8)[b]	(0.6)	(1.7)	(4.6)
Skew[c] $^0S_2$	22	60	80	150
	(7.0)[b]	(1.7)	(−0.1)	(6.9)
Distorted[c] $^4H_5$	19	117	122	180
C-2 and C-4 flattened[d]	(7.3)[b]	(1.8)	(2.5)	(9.2)

[a]Calculated from observed coupling constants (Table II), using the standard Karplus equation[14]. [b]Coupling constants in parentheses calculated from the Karplus equation[14]. [c]Bond angles from Dreiding models. [d]Obtained by optimal ring-flattening at C-2 and C-4.

(skew *C*) conformation having $\phi_{1,2}$ smaller than that in the "theoretical" skew form. The dihedral angle $\phi_{2,3}$ of 50–60° reported by these workers appears to be in question, as this would require a $\phi_{3,4}$ dihedral angle equal to ~80°, and not 110–120°. This consideration suggested the possibility of another conformation for 3 which would permit a much better fit of the observed ^{1}H-n.m.r. data.

A Dreiding model of 3 in the $^0S_2$ conformation *C* suggested by Nashed *et al.*[9] gave $\phi_{2,3}$ ~60° and $\phi_{3,4}$ ~80°, which would result in very low $J_{2,3}$ and $J_{3,4}$ values (see Table III). If $\phi_{3,4}$ were increased to give the $\phi_{3,4}$ angle reported[9], $\phi_{2,3}$ would approach ~75° and again would result in a lower $J_{2,3}$ value (<0.5 Hz) than that observed ($J_{2,3}$ 2.4 Hz). Thus, the favored conformation for 3 appears not to be a modified $^0S_2$.

The oxazoline ring is not planar, and appears to be slightly puckered as shown by a Dreiding model, and $\phi_{1,2}$ (calculated from $J_{1,2}$ by using the Karplus equation[14])



A ($^4H_5$) *B* (Distorted $^4H_5$, ring flattened at C-2 and C-4) *C* ($^0S_2$)

is 19°. This puckering would certainly shift the conformation of the pyranose ring towards a distorted half-chair *A* (the two possibilities are $^4H_5$ or $^5H_4$). These may be distinguished unequivocally on the basis of the $J_{4,5}$ value, whose large magnitude (9.6 Hz) clearly indicates the $^4H_5$ conformation and not the $^5H_4$. Examination of the Dreiding model (as a distorted half-chair) shows two 1,3-diaxial steric interactions between H-2 and H-4, and H-3 and H-5. These steric interactions are expected to change the basic geometry of the distorted half-chair (*A*). Relief of this steric strain demands the opening of bond angles, that is, the reflex effect[15] will operate and several torsion angles in the ring may be affected. Ring flattening at C-2 and C-4 would decrease these steric interactions (H-3 and H-4 become quasiaxial). Because of ring flattening at C-2, $\phi_{1,2}$ is decreased and, because of ring flattening at C-4, $J_{2,3}$ and $J_{3,4}$ are also decreased and the conformation of **3** may best be depicted as a distorted half-chair (*B*) having $\phi_{1,2}$, $\phi_{2,3}$, $\phi_{3,4}$ smaller than in the distorted half-chair (Dreiding model, Table III). A distorted half-chair with the ring flattened at C-2 and C-4 shows a better fit of the observed ^{1}H-n.m.r. data than a modified $^0S_2$ conformation for **3**, as the C-3 substituent is quasiaxial in conformation *B*, whereas the $^0S_2$ conformation has it axially disposed.

EXPERIMENTAL

General methods. — ^{1}H-N.m.r. spectra were obtained with a Bruker 400-MHz n.m.r. spectrometer operating in the pulsed Fourier-transform mode, in chloroform-*d*, with tetramethylsilane as internal reference. The accuracy of the coupling constants is ~0.25 Hz. ^{13}C-N.m.r. spectra were determined with a Varian XL-100-15 spectrometer in the pulsed Fourier-transform, proton-noise-decoupled mode for similar solutions. Chemical shifts are downfield from Me_4Si. Individual protons were assigned by sequentially irradiating H-1, H-2, H-3, H-4, and H-5. Optical rotations were determined with a Perkin–Elmer 141 polarimeter in jacketed, 1-dm cells. I.r. spectra were recorded with a Perkin–Elmer 137 spectrometer for solutions in chloroform. T.l.c. was performed on plates (2.5 × 7.5 cm) of "Baker-flex" silica gel 1B-F. Column chromatography was performed with silica gel (Baker 60–200 mesh) and 1:1 (v/v) ethyl acetate–hexane as eluant. Anhydrous stannic chloride ($SnCl_4$) was purchased from the Fisher Scientific Company.

2-Acetamido-1,3,4,6-tetra-O-*acetyl-2-deoxy-α*-D-*glucopyranose* (**1**) was pre-

pared in 90% yield by acetylation of 2-amino-2-deoxy-D-glucose hydrochloride in pyridine with acetic anhydride[16]. The β-anomer **2** was prepared by the method of Bergmann and Zervas[17].

2-Methyl-(3,4,6-tri-O-acetyl-1,2-dideoxy-α-D-glucopyrano)-[2,1-d]-2-oxazoline (**3**) *from the α anomer* **1** — The α anomer **1** (1.0 g) was dissolved in dichloromethane (20 mL), anhydrous stannic chloride (0.2 g) was added, and the mixture was stirred for 3 h at room temperature. T.l.c. [14:14:1 (v/v) benzene–diethyl ether–methanol] showed complete disappearance of starting material and the formation of a fast-moving (R_F 0.56) product (oxazoline **3**) and an unidentified, slow-moving (R_F 0.18) byproduct. The mixture was made neutral with saturated sodium hydrogencarbonate (~2.0 mL) and filtered through Celite to remove a sticky residue. The organic layer was separated from the filtrate, washed with cold water (3 × 20 mL), dried (magnesium sulfate), and evaporated to a syrup (0.95 g). Chromatographic separation on a column (2.5 × 25 cm) of silica gel (50 mL) afforded a pure, fast-moving fraction as syrup (0.71 g, 82%), $[\alpha]_D^{22}$ +17.2° (*c* 1.6, chloroform), lit.[9] $[\alpha]_D^{25}$ +7.2°, and lit.[8] +16.3°. The ^{13}C- and ^1H-n.m.r. data are given in Tables I and II; $\nu_{max}^{CHCl_3}$ showed no absorption at 1510 (amide II) or 3420 cm^{-1}.

The reaction of the β anomer **2** with stannic chloride was conducted as already described. The reaction was much faster and was complete in 30 min. Isolation as just described gave **3** in 88% yield. An unidentified byproduct was likewise present.

ACKNOWLEDGMENT

This work was supported by grant AI-12509 from National Institute of Allergy and Infectious Diseases, National Institutes of Health. The author thanks Professor C. Schuerch for his help and guidance. The 400-MHz n.m.r. measurements were provided by the Department of Chemistry, University of Rochester, Rochester, NY.

REFERENCES

1 S. E. Zurabyan and A. Ya. Khorlin, *Usp. Khim.*, 43 (1974) 1865–1903; *Russ. Chem. Rev.*, 43 (1974) 887–902.
2 C. D. Warren and R. W. Jeanloz, *Carbohydr. Res.*, 53 (1977) 67–84.
3 W. L. Salo and H. G. Fletcher, Jr., *Biochemistry*, 9 (1970) 878–881.
4 A. Ya. Khorlin, S. E. Zurabyan, and T. S. Antonenko, *Tetrahedron Lett.*, (1970) 4803–4804.
5 C. D. Warren, A. Herscovics, and R. W. Jeanloz, *Carbohydr. Res.*, 61 (1978) 181–186.
6 K. L. Matta and O. P. Bahl, *Carbohydr. Res.*, 21 (1972) 460–464.
7 A. Ya. Khorlin, M. L. Shuman, S. E. Zurabyan, I. M. Privalova, and Y. L. Kopaevich, *Izv. Akad. Nauk S.S.S.R., Ser. Khim.*, 227 (1968) 2094–2098.
8 R. U. Lemieux and H. Driguez, *J. Am. Chem. Soc.*, 97 (1975) 4063–4068.
9 M. A. Nashed, C. W. Slife, M. Kiso, and L. Anderson, *Carbohydr. Res.*, 82 (1980) 237–252.
10 P. Welzel, G. Knupp, F. J. Witteler, Th. Schubert, H. Duddeck, D. Muller, and G. Hofle, *Tetrahedron*, 37 (1981) 97–104.
11 W. L. Salo and H. G. Fletcher, Jr., *J. Org. Chem.*, 33 (1968) 3585–3588.

12 M. BLANC-MUESSER, J. DEFAYE, AND D. HORTON, *Carbohydr. Res.*, 68 (1979) 175–187.
13 R. EBY AND V. K. SRIVASTAVA, *Carbohydr. Res.*, 102 (1982) 1–9.
14 B. COXON, *Carbohydr. Res.*, 13 (1970) 321–330.
15 C. ALTONA AND C. A. G. HAASNOOT, *Org. Magn. Reson.*, 13 (1980) 417–429, and references cited therein.
16 D. HORTON, *J. Org. Chem.*, 29 (1964) 1776–1782.
17 M. BERGMANN AND L. ZERVAS, *Ber.*, 64 (1931) 975–980.