Carbohydrate Research, 126 (1984) 303–307
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

The formation and crystal structure of methyl 3-*C*-acetamidomethyl-3-chloro-2,3,6-trideoxy-4-*O*-methoxymethyl-α-L-*arabino*-hexopyranoside

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(Received August 2nd, 1983; accepted for publication, September 1st, 1983)

The reduction of carbohydrate cyanomesylates with lithium aluminium hydride is a well-established procedure for preparing spiro-aziridines, which, in turn, may be converted into branched-chain amino sugars[1–3]. We recently reported[3] that treatment of the cyanomesylate **1**[4] with lithium aluminium hydride in ether at room temperature gave, after *N*-acetylation and chromatography, a crystalline compound that was not the expected spiro-*N*-acetylaziridine **2**. Subsequent investigations have revealed that this compound contains *chlorine* and, in fact, has the structure **3**, namely methyl 3-*C*-acetamidomethyl-3-chloro-2,3,6-trideoxy-4-*O*-methoxymethyl-α-L-*arabino*-hexopyranoside. The principal structural features of **3** were deduced from its 360-MHz ^{1}H-n.m.r. spectrum, but a single-crystal X-ray analysis was required to define the stereochemistry at the branch-point. The X-ray crystallographic analysis leading to structure **3** was straightforward (see Experimental for details), and interatomic distances and bond angles (see Table II) in **3** are unexceptional.

On reviewing the experimental procedures resulting in the formation of **3**, we concluded that chlorine must have been introduced into the molecule during processing of a chloroform solution of the *N*-acetylated products, which was washed with dilute hydrochloric acid to free it from pyridine. This was readily confirmed, since **3** was not obtained when dilute sulphuric acid was used for this purpose. It was also established[5] that the spiro-aziridine **4** is one of the products formed on reduction of the cyanomesylate **1** at room temperature, since hydrogenolysis of the reduction products over Raney nickel gave, after *N*-acetylation, methyl 3-acetamido-2,3,6-trideoxy-4-*O*-methoxymethyl-3-*C*-methyl-α-L-*ribo*-hexopyranoside (**5**) in ~28% overall yield. However, all attempts to prepare the spiro-*N*-acetylaziridine **2** from the mixture containing **4**, using our original procedure, were unsuccessful.

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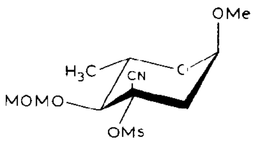
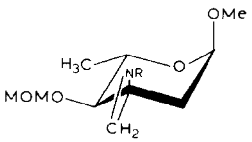
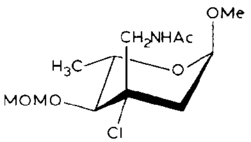


1 MOM = CH_2OMe



2 R = Ac
4 R = H



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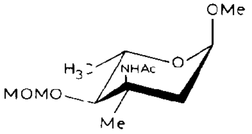

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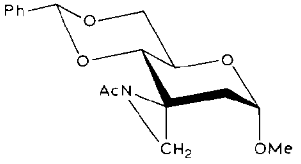

6

Our failure to isolate **2** may be significant, insofar as electrophilic addition of hydrogen chloride to **2**, with opening of the aziridine ring, would furnish **3**. This process presumably involves *O*-(or *N*-)protonation of the acetamido group, rupture of the axial C-N bond, and equatorial attack by chloride ion on the resulting tertiary carbocation. Breaking of the C-N bond would afford relief of the strain in the three-membered ring and of the 1,3-diaxial interaction with the glycosidic methoxyl group. The axial disposition of the C-N bond may facilitate ring-opening, since the related spiro-*N*-acetylaziridine **6**, in which the C-N bond is equatorial, was prepared[2] without difficulty. By whatever process **3** is formed, it must occur very readily, since the reactants are brought together in different phases that are in contact for a relatively short time.

EXPERIMENTAL AND RESULTS

*Methyl 3-*C*-acetamidomethyl-3-chloro-2,3,6-trideoxy-4-*O*-methoxymethyl-α-*L-arabino*-hexopyranoside* (**3**). — Lithium aluminium hydride (0.244 g, ~6.4 mmol) was added gradually to a cooled (0°) suspension of the cyanomesylate **1**[4] (1.2 g, 3.9 mmol) in anhydrous diethyl ether (20 mL), whereafter the reaction mixture was stirred at 0° for 15 min and then at room temperature for 3.5 h. The excess of reagent was decomposed by the addition of wet ethyl acetate, solids were filtered off and washed thoroughly with ethyl acetate, and the combined filtrate and washings were dried ($MgSO_4$) and concentrated under reduced pressure. A solution of the residue in pyridine (12 mL) was treated overnight at room temperature with acetic anhydride (3.2 mL), and then poured into ice–water. The aqueous solution was extracted with chloroform, and the chloroform solution was washed with 5M

TABLE I

FRACTIONAL ATOMIC CO-ORDINATES ($\times 10^4$) AND ANISOTROPIC THERMAL PARAMETERS ($\times 10^3$) FOR 3, WITH STANDARD DEVIATIONS IN PARENTHESES

Atom	x	y	z	U_{eq}
O-1	5263(4)	3289(5)	6387(6)	38(1)
O-4	4118(3)	3939(5)	1885(6)	39(1)
O-5	3577(3)	3599(5)	5669(7)	37(1)
O-7	2612(6)	3951(8)	581(12)	62(3)
O-7A	3501(21)	4083(23)	−300(37)	70(12)
O-8	7728(4)	4548(6)	2031(8)	57(2)
N	6849(4)	4584(5)	4091(7)	33(2)
Cl	5112(2)	6109(2)	3017(3)	56(1)
C-1	4467(6)	4051(7)	6284(10)	36(2)
C-2	4821(6)	5017(6)	5462(11)	35(2)
C-3	4971(5)	4793(5)	3892(9)	30(2)
C-4	3977(5)	4267(6)	3336(9)	29(2)
C-5	3705(5)	3275(6)	4217(10)	33(2)
C-6	2673(7)	2819(9)	3760(13)	61(3)
C-7	5913(5)	4128(7)	3516(9)	36(2)
C-8	5052(8)	2415(8)	7307(13)	63(3)
C-9	3503(8)	4527(9)	889(12)	59(3)
C-10	2762(9)	3008(11)	−250(14)	73(4)
C-11	7686(6)	4780(7)	3297(11)	40(2)
C-12	8564(6)	5219(9)	4093(12)	58(3)

hydrochloric acid (twice), saturated aqueous sodium hydrogencarbonate, and water, and dried ($MgSO_4$). Removal of the solvent and chromatography on silica gel (elution with 2:1 acetone–dichloromethane) gave 3 (0.268 g, 23%), m.p. 100.5–102.5° (from ethyl acetate–hexane), $[\alpha]_D$ −140° (*c* 0.6, chloroform) (Found: C, 49.0; H, 7.7; Cl, 12.2; N, 4.5. $C_{12}H_{22}ClNO_5$ calc.: C, 48.7; H, 7.5; Cl, 12.0; N, 4.7%). ^{1}H-N.m.r.(360 MHz) data: δ 4.83 (ABq, 2 H, J_{AB} 13 Hz, OCH_2O), 4.59 (dd, 1 H, $J_{1,2}$ 1, $J_{1,2'}$ 4 Hz, H-1), 4.02 (dd, 1 H, J_{gem} 15, $J_{3^1\text{-}C\mathit{H}\text{H,NH}}$ 5 Hz, C*H*HNHAc), 3.82–3.73 (m, 2 H, CH*H*NHAc and H-5), 3.53 (d, 1 H, $J_{4,5}$ 10 Hz, H-4), 3.41 and 3.26 (s, 6 H, 2 OMe), 2.36 (dd, 1 H, J_{gem} 14 Hz, H-2), 2.18 (dd, 1 H, H-2′), 1.97 (s, 3 H, NAc), and 1.27 (d, 3 H, $J_{5,6}$ 6 Hz, 5-Me). This material was used for the following single-crystal X-ray analysis.

(*a*) *Crystal data.* $C_{12}H_{22}ClNO_5$; M = 295.8, orthorhombic, space group $P2_12_12_1$, $a = 13.135(14)$, $b = 12.306(10)$, $c = 9.392(10)$ Å, volume = 1518 Å^3, $D_c = 1.294$ g.cm^{-3}, $Z = 4$, $F(000) = 632$, λ(CuKα) = 1.5418 Å, μ_λ (for CuKα) = 22.6 cm^{-1}.

(*b*) *Data collection.* Data were collected from prismatic crystals elongated along the *c*-axis. Equi-inclination, multi-film Weissenberg photographs (levels *h*0-3*l* and *hk*0-6) were scanned by using a microdensitometer (SERC Microdensito-

TABLE II

MOLECULAR DIMENSIONS FOR **3**, WITH STANDARD DEVIATIONS IN PARENTHESES

Bond lengths (Å)			
C-1–C-2	1.492(11)	C-5–O-5	1.430(11)
C-2–C-3	1.513(13)	C-8–O-1	1.406(11)
C-3–C-4	1.548(9)	C-9–O-4	1.433(11)
C-3–C-7	1.525(10)	C-9–O-7	1.399(13)
C-4–C-5	1.518(10)	C-10–O-7	1.412(15)
C-5–C-6	1.528(11)	C-11–O-8	1.224(12)
C-11–C-12	1.476(12)	C-3–Cl	1.826(7)
C-1–O-1	1.407(9)	C-7–N	1.455 (9)
C-1–O-5	1.418(9)	C-11–N	1.350(10)
C-4–O-4	1.433(10)		

Bond angles (degrees)			
C-1–O-1–C-8	113.9(6)	C-2–C-3–C-7	115.4(7)
C-4–O-4–C-9	113.9(7)	C-4–C-3–C-7	112.5(6)
C-1–O-5–C-5	113.6(5)	C-3–C-4–O-4	109.2(6)
C-9–O-7–C-10	114.5(9)	C-5–C-4–O-4	108.8(6)
C-7–N–C-11	123.5(7)	C-3–C-4–C-5	110.5(6)
O-1–C-1–O-5	112.3(6)	C-4–C-5–O-5	108.9(6)
C-2–C-1–O-1	109.6(6)	C-6–C-5–O-5	105.4(7)
C-2–C-1–O-5	111.0(7)	C-4–C-5–C-6	110.5(8)
C-1–C-2–C-3	113.6(6)	C-3–C-7–N	113.1(6)
C-2–C-3–Cl	106.9(5)	O-4–C-9–O-7	110.6(8)
C-4–C-3–Cl	107.7(5)	O-8–C-11–N	122.1(8)
C-2–C-3–C-4	107.2(6)	C-12–C-11–O-8	122.8(8)
C-7–C-3–Cl	106.8(5)	C-12–C-11–N	114.9(8)

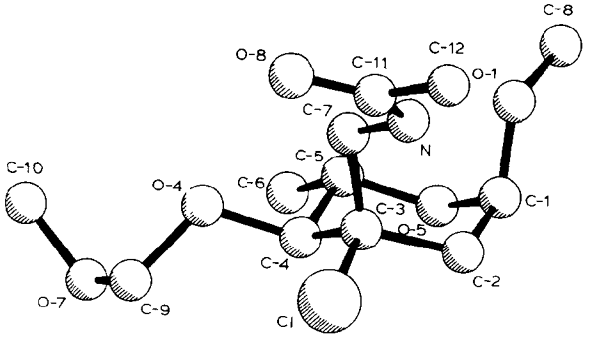

Fig. 1. Stereoview of methyl 3-*C*-acetamidomethyl-3-chloro-2,3,6-trideoxy-4-*O*-methoxymethyl-α-L-*arabino*-hexopyranoside (**3**).

meter Service, Daresbury Laboratory), and 896 independent reflections were classified as statistically significant.

(*c*) *Structure analysis* (Tables I and II). The positions of the atoms of the pyranoid ring and those of non-hydrogen atoms bonded directly to the pyranoid ring were located from an *E*-map. The remaining non-hydrogen atoms were located from Fourier and difference-Fourier syntheses. In the later stages of full-matrix, least-squares refinement, chlorine, oxygen, nitrogen, and carbon atoms were allowed anisotropic thermal parameters, and hydrogen atoms were included at calculated positions. A difference-Fourier synthesis showed that O-7 had an alternative position, O-7A, for which the refined site-occupancy factor was 0.26(2); alternative positions for the adjacent atoms, C-9 and C-10, could not be distinguished. Final convergence was reached at R 0.062 and R_w 0.063 {896 reflections, 177 parameters, and a weighting factor of $w = (1 + 0.0109 F^2)^{-1}$ in the last cycle}. All calculations were carried out on the Dundee University DEC 10 computer, using the SHELX-76 program[6]. Observed and calculated structure-factors, anisotropic temperature-factors, and calculated positions of the hydrogen atoms have been submitted as supplementary data*.

The numbering system used (see Fig. 1) is such that carbon and oxygen atoms of the parent hexose are numbered in the normal carbohydrate convention and the remaining atoms are numbered arbitrarily.

ACKNOWLEDGMENTS

We thank the SERC Microdensitometer Service for microdensitometer measurements, and Edinburgh University WH-360 NMR service for recording the ^{1}H-n.m.r. spectrum.

REFERENCES

1 J.-M. Bourgeois, *Helv. Chim. Acta,* 57 (1974) 2553–2557; 59 (1976) 2114–2124; J. Yoshimura, M. Matsuzawa, and M. Funabashi, *Bull. Chem. Soc. Jpn.*, 51 (1978) 2064–2067; J. Yoshimura, M. Matsuzawa, K.-I. Sato, and Y. Nagasawa, *Carbohydr. Res.*, 76 (1979) 67–78; T. That Thang, F. Winternitz, A. Olesker, A. Lagrange, and G. Lukacs, *Chem. Commun.*, (1979) 153–154; J. S. Brimacombe, A. S. Mengech, K. M. M. Rahman, and L. C. N. Tucker, *Carbohydr. Res.*, 110 (1982) 207–215; J. Yoshimura, T. Yasumori, T. Kondo, and K.-I. Sato, *ibid.*, 106 (1982) c1–c3.

2 J. S. Brimacombe, M. S. Saeed, and T. J. R. Weakley, *J. Chem. Soc., Perkin Trans. 1,* (1980) 2061–2064.

3 J. S. Brimacombe, R. Hanna, and L. C. N. Tucker, *Carbohydr. Res.*, 105 (1982) c1–c3.

4 J. S. Brimacombe, R. Hanna, M. S. Saeed, and L. C. N. Tucker, *Carbohydr. Res.*, 100 (1982) c10–c13.

5 J. S. Brimacombe, R. Hanna, and L. C. N. Tucker, *J. Chem. Soc., Perkin Trans. 1,* (1983) 2277–2280.

6 G. M. Sheldrick, *SHELX-76 Program for Crystal Structure Determination,* Cambridge University, 1975.

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*The supplementary data are deposited with, and can be obtained from, Elsevier Scientific Publishing Company, BBA Data Deposition, P.O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/272/*Carbohydr. Res.*, 126 (1984) 303–307.