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Note

Synthesis of a sialic acid ketoside by an intramolecular oxymercuration–demercuration reaction

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Oxymercuration–borohydride demercuration of glycal acetates in alcohol solution gives alkyl 2-deoxyglycoside acetates[1–5]. The method has been applied to the synthesis of 2′-deoxy disaccharides[6] and in a synthesis of 4-*O*-methyl-*N*-acetylneuraminic acid[7]. All of these reactions involve intermolecular processes.

It was considered that mercuration of ethyl 5-acetamido-3,5-dideoxy-2-*O*-ethyl-4-*O*-methyl-D-*glycero*-D-*galacto*-non-2-enonate (**1**) in a non-hydroxylic solvent might give, after demercuration, an ethyl glycoside (*e.g.*, **2**) *via* an intramolecular process. Related cyclisation reactions have been reported[8].

Hydrolysis of ethyl 5-acetamido-3,5-dideoxy-2-*O*-ethyl-6,7:8,9-di-*O*-isopropylidene-4-*O*-methyl-D-*glycero*-D-*galacto*-non-2-enonate[7] to give **1** is effected better with toluene-*p*-sulphonic acid in aqueous ethanol than with aqueous trifluoroacetic acid. Treatment of **1** with 2 equiv. of mercury(II) trifluoroacetate in anhydrous tetrahydrofuran followed by demercuration *in situ* with alkaline sodium borohydride gave the ketoside **2** (88%). Compound **2** reacted with acetone or 2-butanone, used as crystallisation solvents, to give variable amounts of ketals **3** or **4**, so that only moderate yields of crystalline **2** were obtained; crystallisation did not occur from non-ketonic solvents. In aqueous solution at room temperature, **3** or **4** was autohydrolysed into **2** within 10 h, and acid hydrolysis of **2** gave the known[7] 4-*O*-methyl-*N*-acetylneuraminic acid.

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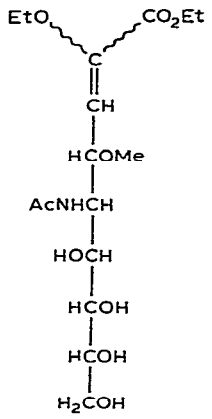

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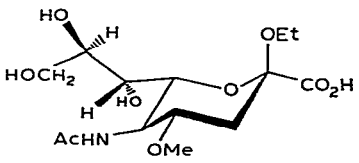

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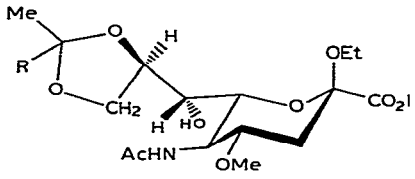

3 R = Me
4 R = Et

^{1}H-N.m.r. data (360 MHz) on **2**, **3**, and the reference compounds NeuAc, 4-*O*-methyl-NeuAc, and methyl α- and β-D-NeuAc, are given in Table I. The coupling constants for **2** are similar to those of NeuAc and 4-*O*-Me-NeuAc, and indicate the *1C*(D) conformation[7]. The chemical shifts of H-3eq and H-4 are strongly indicative of the anomeric configuration[9]. Taking into account the shift increments due to alkyl glycoside formation and methylation of HO-4, the chemical shifts for H-3eq (2.158 p.p.m.) and H-4 (3.820 p.p.m.) of **2** indicate the configuration. The n.m.r. parameters of **2** and **3** are similar, except for the chemical shifts of H-6,7,8,9,9′ and the values of $J_{7,8}$, $J_{8,9}$, and $J_{9,9'}$, which reflect the effect of the 8,9-acetal in **3**.

The stereospecificity in the formation of the above glycoside is noteworthy and the scope of this reaction is being explored.

EXPERIMENTAL

General methods. — Melting points were determined in capillary tubes with a Büchi apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer Model 141 polarimeter and i.r. spectra with a Perkin–Elmer Model 457 spectrophotometer. ^{1}H-N.m.r. (360-MHz) spectra were obtained for solutions in neutral D_2O at 25° with a Bruker HX-360 spectrometer operating in the Fourier-transform mode. Chemical shifts are given relative to that of sodium 2,2-dimethyl-2-silapentane-5-sulphonate. Methyl α- and β-NeuAc were prepared by saponification of the corresponding methyl esters[10] at 40° in D_2O at pD ~11 in the presence of triethylamine. The reaction was monitored by n.m.r. spectroscopy; after disappearance of the ester methyl signal, the solution was lyophilised. Purity of products was determined by t.l.c., either on Silica Gel 60 F 254 (Merck) with detection by charring with sulphuric acid–methanol (1:1) or on cellulose (Merck) with detection of sialic acid by staining with the Bial reagent[11]. Solvent systems: *A*, chloroform–methanol (85:15); *B*, ethyl acetate–acetic acid–water (5:2:2); *C*, 1-butanol–acetic acid–water (5:2:3); *D*, 1-

TABLE I

^{1}H-N.M.R. DATA (360 MHz) FOR **2** AND **3** AND REFERENCE SUBSTANCES[a]

Compound	*H-3eq*	*H-3ax*	*H-4*	*H-5*	*H-6*	*H-7*	*H-8*	*H-9*	*H-9′*	*NAc*	*Aglycon*			
											CH_2	*Me*	*4-OMe*	*Me-C*
2	2.518	1.514	~3.820	3.931	~3.834	3.525	3.859	~3.834	3.653	2.041	3.332; 3.585[c]	1.175	3.383	—
3	2.512	1.516	3.809	3.914	3.705	3.587	4.352	4.165	3.990	2.037	3.340; 3.543[c]	1.191	3.380	1.367; 1.426
NeuAc	2.208	1.827	4.024	3.899	3.984	3.514	3.753	3.835	3.608	2.050	— —	—	—	—
	(2.730)[b]	(1.621)[b]								(2.030)[b]				
Methyl β-D-NeuAc	2.337	1.645	4.009	~3.88	3.785	3.532	~3.88	~3.85	3.662	2.047	—	3.200	—	—
Methyl α-D-NeuAc	2.718	1.626	3.675	3.803	3.689	3.586	3.886	3.869	3.641	2.033	—	3.341	—	—
4-*O*-Me-NeuAc	2.382	1.711	~3.77	~3.96	~3.99	3.505	3.756	3.835	3.608	2.039	—	—	3.386	—
	(2.901)[b]	(1.507)[b]								(2.023)[b]				

	$J_{3ax,3eq}$	$J_{3ax,4}$	$J_{3eq,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7}$	$J_{7,8}$	$J_{8,9}$	$J_{8,9'}$	$J_{9,9'}$	*Aglycon*	
											J_{vic}	J_{gem}
2	−12.9	11.6	4.6	10.4	10.4	~1.0	9.6	2.7	6.0	−12.3	7.0	−9.0
3	−13.0	11.2	4.6	10.4	10.5	⩽1.0	8.1	6.0	5.9	−8.7	7.1	−9.1
NeuAc	−13.2	11.8	5.0	10.4	10.7	1.2	9.4	2.8	6.4	−12.4	—	—
4-*O*-Me-NeuAc	−13.1	11.7	4.7	10.6	10.6	~1.0	9.1	2.6	6.5	−12.0	—	—

[a]Neutral solutions in D_2O at 25°, p.p.m. relative to the signal for sodium 2,2-dimethyl-2-silapentane-5-sulphonate. [b]Signals for α anomer, which represents 7% of the anomeric mixture. [c]The methylene protons of the ethoxyl group are not equivalent.

propanol–1-butanol–0.1M HCl (2:1:1). Column chromatography was performed on Silica Gel 60 (Merck 0.063–0.200 mm).

*Ethyl 5-acetamido-3,5-dideoxy-4-O-methyl-*D-glycero-*β*-D-galacto-*2-nonulopyranosidonic acid* (**2**). — A solution of ethyl 5-acetamido-3,5-dideoxy-2-*O*-ethyl-6,7:8,9-di-*O*-isopropylidene-4-*O*-methyl-D-*glycero*-D-*galacto*-non-2-enonate[7] (505 mg) in ethanol–water (7:1, 25 ml) containing toluene-*p*-sulphonic acid (620 mg) was heated for 2 h at 80°, and then cooled to 0°, neutralised ($PbCO_3$), filtered, and concentrated. The residue was extracted with ethanol–ethyl acetate (1:1, 30 ml), and the extracted material was eluted from a column of silica gel (15 g) with chloroform–methanol (9:1), to give ethyl 5-acetamido-3,5-dideoxy-2-*O*-ethyl-4-*O*-methyl-D-*glycero*-D-*galacto*-non-2-enonate[7] (**1**; 292 mg, 70%), m.p. 136°, $[\alpha]_D^{20}$ −9° (*c* 0.6, methanol–water, 4:1, v/v).

To a solution of **1** (207 mg) in anhydrous tetrahydrofuran (20 ml) at 0° was added mercury(II) trifluoroacetate (465 mg) in three portions at intervals of 15 min. After 6 h, the pH of the mixture was adjusted to 10 with M sodium hydroxide, and M sodium borohydride in M sodium hydroxide (0.6 ml) was added. The mixture was stirred at 0° for 1 h, neutralised with M acetic acid, filtered, and concentrated. A solution of the residue in tetrahydrofuran–water (3:2, 10 ml) at 4° was treated with Dowex-50 (H^+) resin (10 ml) and eluted from a column of Dowex-2 X8 (AcO^-) resin (100–200 mesh; 30 ml, equilibrated in water at 4°) with 0.05M pyridinium acetate (pH 6). Bial-positive fractions[11] were combined and concentrated to give the ethyl glycoside (**2**) of 4-*O*-methyl-*β*-D-*N*-acetylneuraminic acid as a colourless syrup (168 mg, 88%). Crystallisation from acetone–1-propanol gave material (45 mg, 23%) having m.p. 156–157°, $[\alpha]_D^{20}$ −31.5° (*c* 0.7, methanol); ν_{max}^{Nujol} 3420–3250 (NH, OH), 1680 (COOH), 1635 (Amide I), and 1570 cm^{-1} (Amide II). N.m.r. data are given in Table I.

Anal. Calc. for $C_{14}H_{25}NO_9 \cdot H_2O$: C, 45.24; H, 6.99; N, 3.54. Found: C, 45.52; H, 7.37; N, 3.79.

Ethyl glycoside (**3**) *of* 8,9-O-*isopropylidene-4-*O-*methyl-β-*D-N-*acetylneuraminic acid.* — (*a*) The mother liquors from the crystallisation of **2** were concentrated and the residue was crystallised from acetone, to give the ketal **3** (94 mg, 44% from **4**), m.p. 191–192°, $[\alpha]_D^{20}$ −23° (*c* 0.2, methanol); ν_{max}^{Nujol} 3265 (NH, OH), 1750 (COOH), 1640 (Amide I), and 1560 cm^{-1} (Amide II). N.m.r. data are given in Table I.

Anal. Calc. for $C_{17}H_{29}NO_9$: C, 52.17; H, 7.47; N, 3.58. Found: C, 52.32; H, 7.60; N, 3.38.

(*b*) To a solution of **2** (3 mg) in acetone (3 ml) at −20° were added a few beads of dried Dowex-50 (H^+) resin. T.l.c. (solvents *B* and *C*) showed reaction to be complete within 15 min. The resin was collected, and washed with acetone, and the combined washings and filtrate were concentrated to give **3**, which was identical with the compound described in (*a*).

Ethyl glycoside (**4**) *of* 8,9-O-sec-*butylidene-4-*O-*methyl-β-*D-N-*acetylneuraminic acid.* — Crystallisation of **2** from 2-butanone–2-propanol–ether gave **4** as small needles (30% from **2**), m.p. 187.5–188.5°, $[\alpha]_D^{20}$ −26° (*c* 0.35, methanol); ν_{max}^{Nujol}

3270 (NH, OH), 1750 (COOH), 1640 (Amide I), and 1560 cm^{-1} (Amide II).

Anal. Calc. for $C_{18}H_{31}NO_9$: C, 52.32; H, 7.71; N, 3.45. Found: C, 52.97; H, 7.36; N, 3.15.

Autohydrolysis of **3** *and* **4**. — When a solution of **3** or **4** (0.5 mg) in water was kept for 10 h at room temperature, t.l.c. (solvents *B* and *C*) showed complete conversion into **2**.

4-O-Methyl-N-acetylneuraminic acid. — A solution of **2** (0.5 mg) in 0.1M hydrochloric acid was heated for 4 h at 80°. Conversion into known 4-*O*-methyl-*N*-acetylneuraminic acid[7] was monitored by t.l.c. on cellulose (solvent *D*) and silica gel (solvent *B*).

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