Carbohydrate Research, 46 (1976) 133–137

Note

Synthesis of some long-chain acylamidoalkyl glucosides

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(Received June 5th, 1975; accepted for publication, June 30th, 1975)

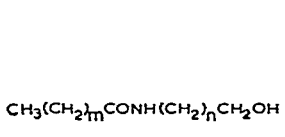
Only a few amidoalkyl glycosides have been described previously. Derivatives of 2-aminoethyl β-D-glucopyranoside were prepared in poor yield[1] by treatment of arylamidoalcohols with tetra-*O*-acetyl-α-D-glucopyranosyl bromide, and 4-chlorobutyl β-D-glucopyranoside was converted[2] into the aminobutyl glycoside by treatment with methanolic ammonia. Recently, 6-aminohexyl 2-acetamido-2-deoxy-β(and α)-D-glucopyranosides were synthesized starting from 6-trifluoroacetamidohexanol[3]. A number of glycosides of sphingenine (*trans*-D-*erythro*-2-amino-4-octadecene-1,3-diol) have also been synthesized, including the β-D-glucopyranoside[4], but similar α-D-glucopyranosides have not been described.

Methods have been developed in recent years for the sterospecific synthesis of α- and β-linked glycosides[5–7] with special emphasis on the effect of the reacting halide on the anomeric configuration of the product[6,7], but less attention has been paid to the effect of substituents in the aglycon on the steric course of the Koenigs–Knorr reaction.

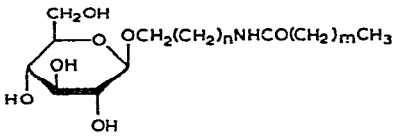
Long-chain acylamidoalkyl glycosides of the type described in this work may also have practical value as intermediates for further conversion and as amphipathic molecules that could serve as model compounds in studies on the role of glycolipids in membranes.

RESULTS AND DISCUSSION

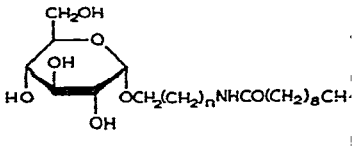
Several *N*-acyl derivatives (**1**–**8**) of 2-aminoethanol, 3-aminopropanol, and 5-aminopentanol were prepared by reaction of equimolar quantities of the requisite acyl chloride with the amino alcohol in aqueous sodium carbonate solution. Yields were usually excellent and the products were crystalline (Table I). Reaction of the acylamido alcohol with tetra-*O*-acetyl-α-D-glucopyranosyl bromide in nitromethane–benzene in the presence of mercuric cyanide, followed by catalytic deacetylation, afforded the crystalline β-D-glucopyranosides in reasonable overall yield (Table II). The optical rotations of the products (low, negative) indicated the β-D anomeric configuration.



	m	n
1	8	1
2	10	1
3	12	1
4	14	1
5	8	2
6	10	2
7	12	2
8	14	4



	m	n
9	8	1
10	10	1
11	12	1
12	14	1
13	8	2
14	10	2
15	12	2
16	14	4



17 n = 1
18 n = 2

TABLE I

ACYLAMIDO ALCOHOLS

Compound	*M.p.* (°)	*Yield* (%)	Anal.					
			Calc.			*Found*		
			C	*H*	*N*	*C*	*H*	*N*
2-Decanamidoethanol (1)	87–89	87	69.09	12.01	5.76	69.24	11.78	5.77
2-Dodecanamidoethanol (2)	91–93	74	70.80	12.26	5.16	70.98	12.12	5.03
2-Tetradecanamidoethanol (3)	99–100	98	72.19	12.45	4.68	71.93	12.33	4.50
2-Hexadecanamidoethanol (4)	98–100	96	73.38	12.71	4.27	73.21	12.95	4.16
3-Decanamidopropanol (5)	75–77	80	69.99	12.14	5.44	70.08	12.01	5.20
3-Dodecanamidopropanol (6)	83–85	99	71.51	12.39	4.90	71.35	12.10	4.65
3-Tetradecanamidopropanol (7)	91–93	92	72.79	12.54	4.47	72.86	12.33	4.42
5-Hexadecanamidopentanol (8)	98–100	97	74.74	12.79	3.79	74.48	12.65	3.91

Two glucosides were also synthesized by reaction of 2-decanamidoethanol (**1**) and 3-decanamidopropanol (**5**), respectively, with 2-*O*-benzyl-3,4,6-tri-*O*-*p*-nitrobenzoyl-β-D-glucopyranosyl bromide[6,8], followed by deblocking and purification. The high, positive optical rotations indicated the α-D-glycosidic configuration of these glucosides (**17** and **18**). P.m.r. spectral analysis in dimethyl sulfoxide solution showed marked differences between the two series of glycosides (**9–16**, on the one hand, and **17** and **18** on the other). Disappearance of the hydroxyl-group resonances on addition of deuterium oxide enabled the unequivocal assignment of the anomeric proton, which corresponded to a doublet at δ 4.1–4.2 (J 7.5 Hz) in the former series of compounds, and at δ 4.6–4.7 (J 3 Hz), in the latter. No resonances were observed at δ 4.6–4.7 for compounds **9–16** or at δ 4.1–4.2 for compounds **17** and **18**. Investigation of the mother liquors obtained from the recrystallization of the synthetic glycosides failed to reveal the presence of any of the other anomers in the products of each of the series of glycosylations. An examination of the sensitivity of measurement of the n.m.r. anomeric proton peaks showed that contamination of one anomer by 2–4% of the other would be detected under the conditions employed. It was concluded, therefore,

TABLE II

β- (9–16) AND α-D-GLUCOPYRANOSIDES (17, 18)

Aglycon	*M.p.* (°)	$[\alpha]_D^{24}$[a] (°)	*Yield*[b] (%)	Anal.					
				Calc.			*Found*		
				C	*H*	*N*	*C*	*H*	*N*
2-Decanamidoethyl (9)	107–109	−8.1	35	59.23	9.69	3.45	59.05	9.74	3.30
2-Dodecanamidoethyl (10)	108–110	−7.1	35	60.94	10.00	3.22	60.99	10.08	3.10
2-Tetradecanamidoethyl (11)	110–112	−7.5	30	62.44	10.26	3.03	62.30	10.13	3.00
2-Hexadecanamidoethyl (12)	110–112	−7.4	40	64.14	10.49	2.86	64.25	10.36	2.70
3-Decanamidopropyl (13)	113–115	−21.0	32	60.11	9.85	3.34	60.02	9.69	3.15
3-Dodecanamidopropyl (14)	113–115	−19.1	30	61.49	10.13	3.15	61.29	10.26	3.02
3-Tetradecanamidopropyl (15)	115–117	−17.1	32	63.12	10.38	2.94	63.25	10.25	2.89
5-Hexadecanamidopentyl (16)	134–136	−9.4	20	65.50	10.81	2.63	65.76	10.64	2.50
2-Decanamidoethyl (17)	103–105	+68.0	35	59.23	9.69	3.45	59.15	9.85	3.25
3-Decanamidopropyl (18)	105–107	+70.0	40	60.11	9.85	3.34	60.27	10.01	3.40

[a]*C* 1, methanol. [b]Calculated from the aglycon.

that reaction of the aglycons with the peracetylglucosyl bromide gave β-D-glucosides, whereas the 2-*O*-benzylglycosyl bromide led to α-D-glucosides, both processes being essentially stereospecific. The glucosides were only partially soluble in chloroform, but dissolved readily in 4:1 chloroform–methanol; they were insoluble in water.

EXPERIMENTAL

For general methods, see Ref. 6, except for n.m.r. spectra which were recorded with a Bruker MFX-10 90-MHz spectrometer.

Acyl chlorides. — Palmitoyl and stearoyl chlorides were technical products (B.D.H., Poole, England). Other acyl chlorides were prepared from the corresponding acid (purum, Fluka AG, CH-9470 Buchs, Switzerland) by stirring a hot solution in boiling, dry benzene with excess thionyl chloride for 2 h, followed by removal of volatile products by evaporation *in vacuo* at 50°, addition of several portions of dry benzene, and subsequent re-evaporation. It was found to be unnecessary to purify the resulting residual acyl chlorides before use.

Acylation of amino alcohols. — A solution of the amino alcohol (4 g) in aqueous sodium carbonate (500 ml of a 1% solution) was stirred vigorously at room temperature, while a solution of the acyl chloride (1.0 mole) in absolute ether (25 ml) was added dropwise during ~30 min. A white precipitate formed almost immediately that, after stirring for an additional 1 h, was separated by filtration, washed thoroughly with water, dried, and recrystallized from methanol. The product was usually homogeneous (t.l.c. in 14:14:1, v/v, benzene–ether–methanol) and was recrystallized, for analytical purposes, from ethyl acetate.

Glycosylation. — To a solution of the aglycon in 2:1 (v/v) nitromethane–benzene at 40–45°, dried as described previously[6], was added, in portions during 2 days, mercuric cyanide and the requisite glycosyl bromide (1.5 mole of each per mole of aglycon). After being processed[6], the syrup was either (a) dissolved in methanol (peracetate) or (b) in 1:1 (v/v) chloroform–methanol (2-*O*-benzyltri-*O*-*p*-nitrobenzoate) and deacylated catalytically with sodium methoxide.

(a) The resulting solution was treated with Dowex 50 (H^+) to remove Na^+, the solvent removed by evaporation, and the crude solid residue dissolved in 9:1 (v/v) chloroform–methanol and purified by chromatography on silica gel. Chloroform–methanol (4:1 v/v) eluted the glucoside which crystallized from methanol–ether or ethyl acetate.

(b) The chloroform–methanol solution of the 2-*O*-benzyl glucoside was washed with water until free of Na^+, and concentrated to a solid that was dissolved in 9:1 (v/v) chloroform–methanol. The solution was passed through a silica gel column. After elution of methyl *p*-nitrobenzoate, the 2-*O*-benzyl ethers of **17** or **18** were obtained, $[\alpha]_D^{24}$ +47° (*c* 1.0, chloroform). Hydrogenolysis of these intermediates in 95% ethanol solution[6] afforded homogeneous products, **17** or **18**, which were crystallized from methanol–ether.

P.m.r. spectra. — The following peaks (δ) were noted: (a) for **11** (in Me_2SO):

0.97 (3 H, CH_3), 1.25 (CH_2 of the long aliphatic chain), 4.13 (d, H, *J* 7.5 Hz, H-1 of β-D-glucopyranoside), 4.53 (t, H, OH-1), 4.90 (m, 3 H, OH). On addition of D_2O, the triplet at 4.53 and the multiplet at 4.80 disappeared (OH resonances) while the doublet at 4.13 was shifted to 4.18 (*J* 7.5 Hz); there was no peak at 4.6–4.7.

(b) For **17** (in Me_2SO): 0.97 (3 H), 1.25, 4.51 (d, H, *J* 6 Hz, OH), 4.62 (d, H, *J* 3.2 Hz, H-1 of α-glucopyranoside), 4.73 (d, H, *J* 3 Hz, OH), 4.87 (d, H, *J* 5 Hz, OH). On addition of D_2O, the peaks at 4.51, 4.73, and 4.87 disappeared while the doublet at 4.62 was shifted to 4.67 (*J* 3.2 Hz); there was no peak at 4.1–4.2.

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