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Note

2-Deoxy-2-nicotinamido derivatives of some mono-, oligo-, and poly-saccharides

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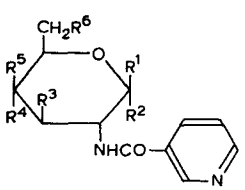
Nicotinamide is one of the B_2 group of vitamins, a vasodilator, a factor which decreases the lipid level in rat blood plasma[1,2], a bifidus factor[3], and a component of nicotinamide adenine dinucleotide (NAD) and its phosphate (NADP).

We now report some novel nicotinamide derivatives produced by the *N*-nicotinoylation of 2-amino-2-deoxy sugars and some oligo- and poly-saccharides containing 2-amino-2-deoxy sugar residues.

2-Deoxy-2-nicotinamido-D-glucose (**1**), ethyl 2-deoxy-2-nicotinamido-α- (**3**) and β-D-glucopyranoside (**4**) were prepared by treatment of the amino compound with nicotinic anhydride in methanol. Formamide was the reaction medium for *N*-nicotinoylchondrosine (**5**) and *N*-nicotinoylheparin (**7**), 10% aqueous acetic acid–methanol for *N*-nicotinoylchitosan (**6**), and pyridine for 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-nicotinamido-D-glucose (**2**). Products **1–4** were isolated crystalline, and **5–7** as amorphous substances, in yields up to 87%. Physical constants and analytical data are given in Table I; **1**, **3–5**, and **7** were soluble in water, but **2** and **6** were insoluble. Compound **2** was identical with the product {m.p. 221–222°, $[\alpha]_D^{19}$ + 21° (*c* 0.48,



Compound	R^1	R^2	R^3	R^4	R^5	R^6
1	H, OH		OH	OH	H	OH
2	H, OAc		OAc	OAc	H	OAc
3	H	OEt	OH	OH	H	OH
4	OEt	H	OH	OH	H	OH
5	H, OH		OH	H	*O*-β-D-GlcA	OH
6	*O*-Glycan	H	OH	*O*-Glycan	H	OH
7	H	*O*-Glycan	OH	*O*-Glycan	H	OSO_3Na

TABLE I

2-DEOXY-2-NICOTINAMIDO DERIVATIVES OF SOME MONO-, OLIGO- AND POLY-SACCHARIDES

Derivative	*Procedure for preparation*[a]	*Yield (%)*	*M.p. (degrees)*	$[\alpha]_D$ *(degrees) (c, solvent, temperature)*	*Formula*	*Calc. (%)*			*Found (%)*		
						C	*H*	*N*	*C*	*H*	*N*
1	*A*	82	235–237	+38 (1.1, water, 21)	$C_{12}H_{16}N_2O_6$	50.70	5.67	9.86	50.98	5.64	9.68
2	*B*	59	219–222	+26 (0.70, chloroform, 19)	$C_{20}H_{24}N_2O_{10}$	53.09	5.35	6.19	52.88	5.33	6.14
3	*A*[b]	85	227	+116 (1.0, water, 22)	$C_{14}H_{20}N_2O_6$	53.84	6.45	8.97	53.67	6.60	8.86
4	*A*[b]	87	251–254	−38 (0.24, water, 20)	$C_{14}H_{20}N_2O_6$	53.84	6.45	8.97	53.86	6.31	8.94
5	*C*[c]	60	—	+4.2 (0.83, water, 19)	$C_{18}H_{24}N_2O_{12}$	46.96	5.25	6.09	46.59	5.51	5.81
6	*D*	72	—	−5.6 (0.9, formic acid, 21)	$[C_6H_{10}NO_4(C_6H_4NO)_{0.88}(C_2H_3O)_{0.12} \cdot 0.70H_2O]_n$	51.00	5.68	9.71	49.58	5.76	9.44
7	*C*[d]	79–83	—	+25 (0.75, water, 18)	$[(C_{24}H_{31}N_2Na_5O_{29}S_3)(C_4H_6O_2)_{0.18}(C_{12}H_8N_2O_2)_{0.82}]_n$			4.21			3.99
7	*E*	77	—	+26 (0.8, water, 17)					Not determined		

[a] *A*, *N*-Acylation with nicotinic anhydride in methanol (Ref. 7). *B*, Peracetylation with acetic anhydride and pyridine. *C*, *N*-Acylation with nicotinic anhydride in formamide (Ref. 5). *D*, *N*-Acylation with nicotinic anhydride in 10% aqueous acetic acid–methanol (Ref. 8). *E*, *N*-Acylation with nicotinic anhydride in the presence of Dowex 1(CO_3^{2-}) resin in water (Ref. 4). **1** was recrystallized from aqueous ethanol, **2** from ethanol, and **3** and **4** from ethanol and ether. [b] The reaction mixture was evaporated *in vacuo* to a syrup. Free nicotinic acid and sodium chloride were crystallized out of the reaction mixture in ethanol. [c] Ethanol was added to the reaction mixture, to afford precipitates that were collected by centrifugation and washed with ethanol and ether. [d] Calc.: SO_4^{2-}, 23.8. Found: SO_4^{2-}, 23.2%.

chloroform)} prepared from 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-D-glucose hydrochloride and nicotinoyl chloride[1,2].

The presence of nicotinamido residue in the various products was reflected by i.r. absorptions at ν_{max}^{KBr} 1650 and 1550 (C = O and NH), and 1600 cm^{-1} (phenyl); by n.m.r. signals at δ 7.2–9.1; and by u.v. absorptions at λ_{max} 256 and 262 nm. The d.s. (degree of substitution) values were calculated on the basis of the ratio of the intensities of signals for (*N*-acyl protons)/(methine and methylene protons of the sugar) in the n.m.r. spectra. The d.s. values of *N*-nicotinoyl group were 1.00 for **1–5**. Compound **6** contained 0.88 *N*-nicotinoyl and 0.12 *N*-acetyl per hexosaminide residue, **7** (prepared in formamide) contained 0.82 *N*-nicotinoyl and 0.18 *N*-acetyl per hexosaminide residue, and **7** (prepared in water[4]) contained only 0.41 *N*-nicotinoyl and 0.18 *N*-acetyl per hexosaminide residue.

The biological properties of these new compounds are under investigation.

EXPERIMENTAL

Melting points were measured with a Yanagimoto SP-2 apparatus and are uncorrected. Other analytical methods have been described previously[5].

Nicotinic anhydride was prepared from nicotinoyl chloride and potassium nicotinate[6]. Ethyl 2-amino-2-deoxy-α- and β-D-glucopyranoside hydrochloride were prepared from ethyl 2-acetamido-2-deoxy-αβ-D-glucopyranoside by *N*-deacetylation followed by chromatography on a cation-exchange resin[7]. *N*-Desulphated heparin[4] was prepared from heparin isolated from porcine intestinal mucosa (Sigma Chemical Company, St. Louis), and chondrosine (Seikagaku Kogyo Company, Ltd., Tokyo) and chitosan (Kyowa Yushi Company Ltd., Tokyo) were commercial products.

N-Nicotinoylation was performed by each of the four established methods[4,5,7,8], as cited in Table I.

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