

Synthesis of Sugar Derivatives of *N*-Alkyl-*N*-nitrosourea

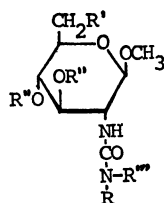
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Synopsis. Thirteen sugar derivatives of *N*-alkyl-*N*-nitrosourea have been prepared as follows. The reaction of a sugar amine with alkyl isocyanate gives a sugar derivative of *N*-alkylurea. When the product is treated with sodium nitrite in aqueous acetic acid, it gives the *N*-alkyl-*N*-nitrosourea derivative.

Streptozotocin is a broad spectrum antibiotic and possesses antitumor¹⁾ and mutagenic activities.²⁾ The antibiotic was isolated from a fermentation broth of *Streptomyces achromogenes* var. *streptozotocin* by the Upjohn research group³⁾ and its structure was established to be *N*-carbamoyl-*N'*-methyl-*N'*-nitroso-D-glucosamine.⁴⁾ An undesirable side effect of the antibiotic, its diabetogenic property, was removed by methylating an anomeric hydroxyl group of the D-glucosamine moiety.⁵⁾ Later an attempt was made to prepare its analogs,⁶⁾ since the nitrosoureido group seems to be an essential group for the appearance of an antitumor activity.⁷⁾

Derivatives of methyl β -D-glucosaminide

We have been working on the preparation of carbohydrate derivatives of *N*-alkyl-*N*-nitrosourea, and we

wish to report a synthesis of methyl glycosides of *N*-alkyl analogs of the antibiotic and *N'*-alkyl-*N*-carbamoyl-*N'*-nitroso derivatives of glycosylamines. All the compounds show remarkable antitumor activities.

Experimental

Melting points were determined in a capillary tube in a liquid bath and are uncorrected. Optical rotations were measured on a JASCO DIP-SL polarimeter. IR spectra were measured on potassium bromide disks with a JASCO IR-E spectrometer. PMR spectra were determined at 60 MHz on a Varian A-60D spectrometer in deuteriochloroform with reference to tetramethylsilane as an internal standard. Solutions were evaporated under reduced pressure at 25–30 °C. Catalytic hydrogenation was carried out under hydrogen atmosphere (3.4 kg/cm²) with a Parr apparatus in the presence of Raney nickel. Acetylation was carried out in a mixture of acetic anhydride and pyridine in the usual manner. De-O-acylation was performed by dissolving a compound in methanolic ammonia or in 0.01–0.06 M methanolic sodium methoxide.

General Procedure for *N*-Alkylurea Derivatives. Alkyl isocyanate was added to a solution of carbohydrate amine in methanol and the mixture was stirred for 20 min at 10 °C to give crystalline precipitates. The mixture was settled in a refrigerator and the crystals were collected by filtration.

General Procedure for *N*-Alkyl-*N*-nitrosourea Derivatives. The carbamoyl derivative was dissolved in aqueous acetic acid. Sodium nitrite was added to the solution under ice cooling with agitation to give crystals. The crystals were

TABLE 1. *N*-ALKYLUREAS

R	R'	No.	Yield %	Mp °C	$[\alpha]_D^{25}$	Molecular Formula	C % Calcd Found	H % Calcd Found	N % Calcd Found
A. Derivatives of Methyl β -D-glucosaminide						R''=OH, R'''=H			
Ethyl	OH	<u>1</u>	98	239–240	–29	C ₁₀ H ₂₀ N ₂ O ₆	45.44 45.68	7.63 7.46	10.60 10.65
Propyl	OH	<u>4</u>	95	227–229	–29	C ₁₁ H ₂₂ N ₂ O ₆	47.47 47.23	7.97 7.73	10.09 10.13
Butyl	OH	<u>7</u>	89	227–228	–26	C ₁₂ H ₂₄ N ₂ O ₆	49.30 49.50	8.28 8.17	9.58 9.56
Methyl	OMe	<u>10</u>	52	178–179	–34	C ₁₀ H ₂₀ N ₂ O ₈ ^b	36.58 36.81	6.13 6.18	8.53 8.29
Methyl	H	<u>13</u>	67	237(dec)	–55	C ₉ H ₁₈ N ₂ O ₅	46.14 45.98	7.74 7.43	11.96 11.75
Methyl	–NHCONHCH ₃	<u>16</u>	37	265–266	–24	C ₁₁ H ₂₂ N ₄ O ₆	43.13 42.96	7.24 6.98	18.29 17.99
B. <i>N</i> -Alkyl- <i>N'</i> -(poly-O-acyl-D-glycosyl)ureas						RNH-CO-NHR'			
Tetra-O-acetyl- β -D-glucopyranosyl	Ethyl	<u>21</u>	90	171–172	+5*	C ₁₇ H ₂₆ N ₂ O ₁₀	48.80 48.88	6.26 6.25	6.70 6.56
Tetra-O-acetyl- β -D-glucopyranosyl	Propyl	<u>24</u>	81	144–145	+1*	C ₁₈ H ₂₈ N ₂ O ₁₀	49.99 49.87	6.53 6.46	6.48 6.35
Tetra-O-acetyl- β -D-glucopyranosyl	Butyl	<u>28</u>	95	109–110	+2*	C ₁₉ H ₃₀ N ₂ O ₁₀	51.11 50.85	6.79 6.83	6.09 6.09
Tetra-O-acetyl- β -D-mannopyranosyl	Methyl	<u>31</u>	86	210–211	–24*	C ₁₆ H ₂₄ N ₂ O ₁₀	47.52 47.54	5.98 5.92	6.93 6.85
Tri-O-acetyl- β -D-xylopyranosyl	Methyl	<u>34</u>	71	170–172	+4*	C ₁₃ H ₂₀ N ₂ O ₈	46.98 47.08	6.07 6.15	8.43 8.22
Tri-O-benzoyl- β -D-ribofuranosyl	Methyl	<u>38</u>	29	168–169	–31*	C ₂₈ H ₂₆ N ₂ O ₈	64.86 64.58	5.05 5.06	5.40 5.09
C. <i>N</i> -Alkyl- <i>N'</i> -(D-glycosyl)ureas						RNH-CO-NHR'			
β -D-Glucopyranosyl	Propyl	<u>25</u>	80	191–193	–26	C ₁₀ H ₂₀ N ₂ O ₆	45.44 45.47	7.64 7.39	10.60 10.31
β -D-Mannopyranosyl	Methyl	<u>32</u>	88	120–122	–27**	C ₈ H ₁₆ N ₂ O ₆	40.67 40.90	6.83 6.80	11.86 11.63
β -D-Xylopyranosyl	Methyl	<u>35</u>	62	197–198	–27	C ₇ H ₁₄ N ₂ O ₅	40.77 40.50	6.84 6.63	13.59 13.26
β -D-Ribofuranosyl	Methyl	<u>39</u>	21	184–185	–26**	C ₇ H ₁₄ N ₂ O ₅	40.77 40.83	6.84 6.73	13.59 13.32

^a Optical rotation was measured at 20–33 °C in water, chloroform(*) and methanol(**). ^b Compound 10: Found: S, 9.45%. Calcd: S, 9.76%.

TABLE 2. *N*-ALKYL-*N*-NITROSOUREAS

R	R'	Yield No. %	Mp °C	[α] _D ^a	Molecular Formula	C % Calcd Found	H % Calcd Found	N % Calcd Found
D. Derivatives of Methyl β-D-glucosaminide					R''=OH, R'''=NO			
Ethyl	OH	<u>2</u>	92	113(dec)	-30	C ₁₀ H ₁₉ N ₃ O ₇	40.95 40.66	6.53 6.35 14.33 14.04
Propyl	OH	<u>5</u>	90	126(dec)	-26	C ₁₁ H ₂₁ N ₃ O ₇	42.99 42.55	6.89 6.64 13.67 13.36
Butyl	OH	<u>8</u>	93	125(dec)	-26	C ₁₂ H ₂₃ N ₃ O ₇	44.85 44.60	7.21 6.99 13.08 12.83
Methyl	OMs	<u>11</u>	80	129(dec)	-14	C ₁₀ H ₁₉ N ₃ O ₉ S ^c	33.61 33.87	5.35 5.36 11.75 11.44
Methyl	H	<u>14</u>	90	135(dec)	-13	C ₉ H ₁₇ N ₃ O ₆	41.06 41.03	6.51 6.42 15.96 16.00
Methyl	-NHCON(NO)CH ₃	<u>17</u>	80	159(dec)	-14	C ₁₁ H ₂₀ N ₃ O ₈	36.26 36.50	5.49 5.58 23.08 22.89
E. Derivatives of Methyl 3,4-di-O-acetyl-β-D-glucosaminide					R''=OAc, R'''=NO			
Ethyl	OAc	<u>3</u>	92	130-131	+39*	C ₁₆ H ₂₅ N ₃ O ₁₀	45.82 45.92	6.01 5.98 10.02 10.02
Propyl	OAc	<u>6</u>	89	112-114	+19*	C ₁₇ H ₂₇ N ₃ O ₁₀	47.11 47.16	6.28 6.50 9.70 10.04
Butyl	OAc	<u>9</u>	80	126-127	+18*	C ₁₈ H ₂₉ N ₃ O ₁₀	48.32 48.46	6.53 6.54 9.39 9.49
Methyl	OMs	<u>12</u>	80	136-137	+35*	C ₁₄ H ₂₃ N ₃ O ₁₁ S ^d	38.09 38.29	5.25 5.31 9.52 9.27
Methyl	H	<u>15</u>	76	115-117	+65*	C ₁₃ H ₂₁ N ₃ O ₈	44.96 45.12	6.28 6.41 12.10 11.98
Methyl	-NHCON(NO)CH ₃	<u>18</u>	76	121	+22*	C ₁₅ H ₂₄ N ₃ O ₁₀	40.18 40.05	5.40 5.34 18.74 18.40
F. <i>N</i> -Alkyl- <i>N'</i> -(D-glycosyl)- <i>N</i> -nitrosoareas					RNH-CO-N(NO)R'			
β-D-Glucopyranosyl	Methyl	<u>19</u> ^e	90	184(dec)	-19	C ₈ H ₁₅ N ₃ O ₇	36.23 36.12	5.70 5.69 15.84 15.46
β-D-Glucopyranosyl	Ethyl	<u>22</u>	96	hygroscopic	-2	C ₉ H ₁₇ N ₃ O ₇ ^g		
β-D-Glucopyranosyl	Propyl	<u>26</u>	80	112(dec)	-6	C ₁₀ H ₁₉ N ₃ O ₇	40.95 40.77	6.54 6.69 14.33 13.93
β-D-Glucopyranosyl	Butyl	<u>29</u>	90	hygroscopic	-1.5	C ₁₁ H ₂₁ N ₃ O ₇ ^g		
β-D-Mannopyranosyl	Methyl	<u>33</u>	78	103(dec)	-13	C ₈ H ₁₅ N ₃ O ₇	36.23 35.92	5.70 5.70 15.84 15.67
β-D-Xylopyranosyl	Methyl	<u>36</u>	63	109(dec)	-27	C ₇ H ₁₃ N ₃ O ₆	35.74 35.92	5.57 5.54 17.87 17.65
β-D-Ribofuranosyl	Methyl	<u>40</u>	75	105(dec)	-31	C ₇ H ₁₃ N ₃ O ₆	35.74 36.04	5.57 5.56 17.87 18.14
G. <i>N</i> -Alkyl- <i>N'</i> -(poly-O-acetyl-D-glycosyl)- <i>N</i> -nitrosoareas					RNH-CO-N(NO)R'			
Tetra-O-acetyl-β-D-glucopyranosyl	Methyl	<u>20</u> ^g	89	125-126	-13*	C ₁₆ H ₂₃ N ₃ O ₁₁	44.34 44.50	5.35 5.18 9.70 9.58
Tetra-O-acetyl-β-D-glucopyranosyl	Ethyl	<u>23</u>	65	118-120	-8*	C ₁₇ H ₂₅ N ₃ O ₁₁	45.63 45.89	5.64 5.60 9.39 9.34
Tetra-O-acetyl-β-D-glucopyranosyl	Propyl	<u>27</u>	76	111	-10*	C ₁₈ H ₂₇ N ₃ O ₁₁	46.84 46.66	5.91 5.85 9.11 8.89
Tetra-O-acetyl-β-D-glucopyranosyl	Butyl	<u>30</u>	80	124-125	-12*	C ₁₉ H ₂₉ N ₃ O ₁₁	47.99 48.17	6.16 6.07 8.84 8.82
Tri-O-acetyl-β-D-xylopyranosyl	Methyl	<u>37</u>	87	127-128	-25*	C ₁₃ H ₁₉ N ₃ O ₉	43.21 42.96	5.26 5.32 11.63 11.51

c Compound 11: Found: S, 8.73%. Calcd: S, 8.97%. d Compound 12: Found: S, 7.08%. Calcd: S, 7.26%. e Lit.¹¹⁾ mp 177-180°C(dec), [α]_D -12° (water). f Compounds did not give correct analyses. g Lit.¹¹⁾ mp 89-90°C, [α]_D -8° (chloroform).

collected by filtration and another crop of the product was obtained from the filtrate by evaporation.

Starting Materials. Compounds: **1**, **4** and **7** were synthesized from methyl β-D-glucosaminide.⁸⁾ Compound **10** was prepared by selective mesylation of methyl 2-deoxy-2-(*N'*-methylureido)-β-D-glucopyranoside.^{6a)} Compound **13** was prepared from **10** by the four step reaction in 70% yield. Compound **16** was synthesized from methyl 2-*N*-benzyloxycarbonyl-β-D-glucosaminide⁹⁾ by the four step reaction in 37% yield. Compound **19** was prepared from 1-(β-D-glucopyranosyl)-3-methylurea¹⁰⁾ in 90% yield. Compounds: **21**, **24** and **28** were synthesized from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine.¹²⁾ Compound **31** was prepared from 2,3,4,6-tetra-*O*-acetyl-β-D-aminopyranosylamine which was obtained by azidolysis and subsequent catalytic hydrogenation of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide.^{13,14)} Compound **34** was prepared from 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl azide.¹⁵⁾ Compound **38** was prepared from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride.^{16,17)}

The *N*-alkyl-*N*-nitrosoareas revealed a characteristic absorption for *N*-nitroso group at 1480-1495 cm⁻¹ in their ir spectra. The position of the nitroso group was deduced from their PMR spectra by ascertaining the absence of a proton on the nitrogen atom possessing an alkyl group.

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