BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 48(12), 3761—3762 (1975)

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

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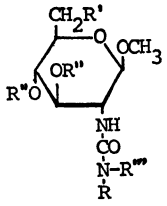
(Received May 29, 1975)

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 antitumor[1] and mutagenic activities.[2] The antibiotic was isolated from a fermentation broth of Streptomyces achromogenes var. streptozoticus by the Upjohn research group[3] 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 atomosphere (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 metoxide.

General Procedure for N-*Alkylurea Derivatives.* Alky 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	$[\alpha]_D^a$	Molecular Formula	C % Calcd	C % Found	H % Calcd	H % Found	N % Calcd	N % Found
A. Derivatives of Methyl β-D-glucosaminide R"=OH, R"'=H												
Ethyl	OH	1	98	239-240	-29	$C_{10}H_{20}N_2O_6$	45.44	45.68	7.63	7.46	10.60	10.65
Propyl	OH	4	95	227-229	-29	$C_{11}H_{22}N_2O_6$	47.47	47.23	7.97	7.73	10.09	10.13
Butyl	OH	7	89	227-228	-26	$C_{12}H_{24}N_2O_6$	49.30	49.50	8.28	8.17	9.58	9.56
Methyl	OMs	10	52	178-179	-34	$C_{10}H_{20}N_2O_8S$[b]	36.58	36.81	6.13	6.18	8.53	8.29
Methyl	H	13	67	237(dec)	-55	$C_9H_{18}N_2O_5$	46.14	45.98	7.74	7.43	11.96	11.75
Methyl	$-NHCONHCH_3$	16	37	265-266	-24	$C_{11}H_{22}N_4O_6$	43.13	42.96	7.24	6.98	18.29	17.99
B. N-Alkyl-N'-(poly-O-acyl-D-glycosyl)ureas RNH-CO-NHR'												
Tetra-O-acetyl-β-D-glucopyranosyl	Ethyl	21	90	171-172	+5*	$C_{17}H_{26}N_2O_{10}$	48.80	48.88	6.26	6.25	6.70	6.56
Tetra-O-acetyl-β-D-glucopyranosyl	Propyl	24	81	144-145	+1*	$C_{18}H_{28}N_2O_{10}$	49.99	49.87	6.53	6.46	6.48	6.35
Tetra-O-acetyl-β-D-glucopyranosyl	Butyl	28	95	109-110	+2*	$C_{19}H_{30}N_2O_{10}$	51.11	50.85	6.79	6.83	6.09	6.09
Tetra-O-acetyl-β-D-mannopyranosyl	Methyl	31	86	210-211	-24*	$C_{16}H_{24}N_2O_{10}$	47.52	47.54	5.98	5.92	6.93	6.85
Tri-O-acetyl-β-D-xylopyranosyl	Methyl	34	71	170-172	+4*	$C_{13}H_{20}N_2O_8$	46.98	47.08	6.07	6.15	8.43	8.22
Tri-O-benzoyl-β-D-ribofuranosyl	Methyl	38	29	168-169	-31*	$C_{28}H_{26}N_2O_8$	64.86	64.58	5.05	5.06	5.40	5.09
C. N-Alkyl-N'-(D-glycosyl)ureas RNH-CO-NHR'												
β-D-Glucopyranosyl	Propyl	25	80	191-193	-26	$C_{10}H_{20}N_2O_6$	45.44	45.47	7.64	7.39	10.60	10.31
β-D-Mannopyranosyl	Methyl	32	88	120-122	-27**	$C_8H_{16}N_2O_6$	40.67	40.90	6.83	6.80	11.86	11.63
β-D-Xylopyranosyl	Methyl	35	62	197-198	-27	$C_7H_{14}N_2O_5$	40.77	40.50	6.84	6.63	13.59	13.26
β-D-Ribofuranosyl	Methyl	39	21	184-185	-26**	$C_7H_{14}N_2O_5$	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'	No.	Yield %	Mp °C	$[\alpha]_D^{\alpha}$	Molecular Formula	C % Calcd	C % Found	H % Calcd	H % Found	N % Calcd	N % Found
D. Derivatives of Methyl β-D-glucosaminide R"=OH, R"'=NO												
Ethyl	OH	2	92	113(dec)	-30	$C_{10}H_{19}N_3O_7$	40.95	40.66	6.53	6.35	14.33	14.04
Propyl	OH	5	90	126(dec)	-26	$C_{11}H_{21}N_3O_7$	42.99	42.55	6.89	6.64	13.67	13.36
Butyl	OH	8	93	125(dec)	-26	$C_{12}H_{23}N_3O_7$	44.85	44.60	7.21	6.99	13.08	12.83
Methyl	OMs	11	80	129(dec)	-14	$C_{10}H_{19}N_3O_9S$[c]	33.61	33.87	5.35	5.36	11.75	11.44
Methyl	H	14	90	135(dec)	-13	$C_9H_{17}N_3O_6$	41.06	41.03	6.51	6.42	15.96	16.00
Methyl	-NHCON(NO)CH_3	17	80	159(dec)	-14	$C_{11}H_{20}N_6O_8$	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	3	92	130-131	+39*	$C_{16}H_{25}N_3O_{10}$	45.82	45.92	6.01	5.98	10.02	10.02
Propyl	OAc	6	89	112-114	+19*	$C_{17}H_{27}N_3O_{10}$	47.11	47.16	6.28	6.50	9.70	10.04
Butyl	OAc	9	80	126-127	+18*	$C_{18}H_{29}N_3O_{10}$	48.32	48.46	6.53	6.54	9.39	9.49
Methyl	OMs	12	80	136-137	+35*	$C_{14}H_{23}N_3O_{11}S$[d]	38.09	38.29	5.25	5.31	9.52	9.27
Methyl	H	15	76	115-117	+65*	$C_{13}H_{21}N_3O_8$	44.96	45.12	6.28	6.41	12.10	11.98
Methyl	-NHCON(NO)CH_3	18	76	121	+22*	$C_{15}H_{24}N_6O_{10}$	40.18	40.05	5.40	5.34	18.74	18.40
F. N-Alkyl-N'-(D-glycosyl)-N-nitrosoureas RNH-CO-N(NO)R'												
β-D-Glucopyranosyl	Methyl	19[e]	90	184(dec)	-19	$C_8H_{15}N_3O_7$	36.23	36.12	5.70	5.69	15.84	15.46
β-D-Glucopyranosyl	Ethyl	22	96	hygroscopic	-2	$C_9H_{17}N_3O_7$[f]						
β-D-Glucopyranosyl	Propyl	26	80	112(dec)	-6	$C_{10}H_{19}N_3O_7$	40.95	40.77	6.54	6.69	14.33	13.93
β-D-Glucopyranosyl	Butyl	29	90	hygroscopic	-1.5	$C_{11}H_{21}N_3O_7$[f]						
β-D-Mannopyranosyl	Methyl	33	78	103(dec)	-13	$C_8H_{15}N_3O_7$	36.23	35.92	5.70	5.70	15.84	15.67
β-D-Xylopyranosyl	Methyl	36	63	109(dec)	-27	$C_7H_{13}N_3O_6$	35.74	35.92	5.57	5.54	17.87	17.65
β-D-Ribofuranosyl	Methyl	40	75	105(dec)	-31	$C_7H_{13}N_3O_6$	35.74	36.04	5.57	5.56	17.87	18.14
G. N-Alkyl-N'-(poly-O-acetyl-D-glycosyl)-N-nitrosoureas RNH-CO-N(NO)R'												
Tetra-O-acetyl-β-D-glucopyranosyl	Methyl	20[g]	89	125-126	-13*	$C_{16}H_{23}N_3O_{11}$	44.34	44.50	5.35	5.18	9.70	9.58
Tetra-O-acetyl-β-D-glucopyranosyl	Ethyl	23	65	118-120	-8*	$C_{17}H_{25}N_3O_{11}$	45.63	45.89	5.64	5.60	9.39	9.34
Tetra-O-acetyl-β-D-glucopyranosyl	Propyl	27	76	111	-10*	$C_{18}H_{27}N_3O_{11}$	46.84	46.66	5.91	5.85	9.11	8.89
Tetra-O-acetyl-β-D-glucopyranosyl	Butyl	30	80	124-125	-12*	$C_{19}H_{29}N_3O_{11}$	47.99	48.17	6.16	6.07	8.84	8.82
Tri-O-acetyl-β-D-xylopyranosyl	Methyl	37	87	127-128	-25*	$C_{13}H_{19}N_3O_9$	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), $[\alpha]_D$ -12° (water). f Compounds did not give correct analyses. g Lit.[11] mp 89-90°C, $[\alpha]_D$ -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-glucosaminide[9] by the four step reaction in 37% yield. Compound **19** was prepared from 1-(β-D-glucopyranosyl)-3-methylurea[10] 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*-nitrosourea derivatives 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.

We wish to express our thanks to Mr. Saburo Nakada for the elemental analyses. We are also indebted to Mr. Shigeru Nishiyama, Mr. Kazuo Kikuchi and Mr. Yasuhiro Nagamatsu for assistance in the preparation of the compounds.

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