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A New Class of Nitrosoureas. VI.[1] Synthesis and Antitumor Activity of 3-Substituted-1-(2-chloroethyl)-3-(methyl-α-D-glucopyranosid-2-yl)-1-nitrosoureas

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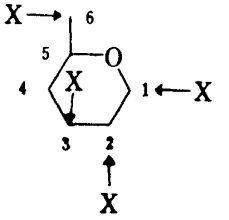
A series of five 3-substituted-1-(2-chloroethyl)-3-(methyl-α-D-glucopyranosid-2-yl)-1-nitrosoureas (**5a**—**e**) was prepared and tested for antitumor activities. The compounds were obtained by the reaction of *N*-substituted methyl-α-D-glucosaminides (**3a**—**e**) with isocyanate followed by nitrosation with dinitrogen tetroxide. All the nitrosoureas obtained were remarkably active against leukemia L1210 and Ehrlich ascites carcinoma and showed greater therapeutic ratios than the positive controls; 1-(2-chloroethyl)-3-(β-D-glucopyranosyl)-1-nitrosourea (GANU) and 1-(2-chloroethyl)-3-(D-glucopyranos-2-yl)-1-nitrosourea (DCNU).

Keywords——chloroethyl nitrosoureas; 3,3-disubstituted nitrosoureas; *N*-substituted glucosaminide derivatives; antitumor activities; leukemia L1210; Ehrlich ascites carcinoma; GANU; DCNU

Many kinds of water-soluble nitrosourea derivatives bearing a sugar moiety, such as 1-(2-chloroethyl)-3-(D-glucopyranos-2-yl)-1-nitrosourea (DCNU),[2] 1-(2-chloroethyl)-3-(β-D-glucopyranosyl)-1-nitrosourea (GANU),[3] 1-(2-chloroethyl)-3-(methyl-α-D-glucopyranosid-6-yl)-1-nitrosourea (MCNU),[4] and 1-(2-chloroethyl)-3-(D-glucopyranos-3-yl)-1-nitrosourea (KCNU,[5] CNUG[6]), have been reported to possess strong antitumor activity with reduced myelotoxicity. These nitrosourea derivatives all have a glucose moiety and differ only in the position to which the *N*-(2-chloroethyl)-*N*-nitrosoureido group is attached (see Fig. 1). The biological results reported for these compounds, however, indicate that these positional isomers appear to differ somewhat in their mode of action, antitumor activity, and toxicity.



Position	Compound
1	GANU
2	DCNU
3	KCNU, CNUG
6	MCNU

X=NHCO–N(NO)–CH_2CH_2Cl

Fig. 1. Glucose-containing Nitrosourea Derivatives

Meanwhile, in previous papers of this series[7b] we reported the synthesis and the potent antitumor activity of a new class of 3,3-disubstituted-1-(2-chloroethyl)-1-nitrosourea derivatives in which the *N*-3 position is substituted by sugar moieties and alkyl groups. In these derivatives, the nitrosoureido groups were invariably attached to the C-1 position of various kinds of sugars. Therefore, it seemed of interest to examine the structure–activity relationships of the positional isomers of the 3,3-disubstituted nitrosourea derivatives with respect to the sugar moiety.

In this paper we will report the synthesis and the antitumor activity of 3,3-disubstituted nitrosoureas in which the nitrosoureido groups are attached to the C-2 position of a methyl

glucoside moiety.

Synthesis of Nitrosoureas and Discussion

The nitrosoureas (**5a**—**e**) were prepared by the sequence outlined in Chart 1. The starting amines, *N*-substituted methyl-α-D-glucosaminides (**3a**—**e**) are not well known. Only the *N*-methyl derivative (**3a**) has been prepared by a rather complicated sequence of reactions.[8] We prepared these amines by reduction of the Schiff bases readily obtained by the reaction of methyl glucosaminide (**1**) with various aldehydes. Because the isolation of these amines in a pure form was difficult, the crude amines were allowed to react with 2-chloroethyl isocyanate, giving the corresponding ureas (**4a**—**e**) which could be purified by column chromatography. The *N*-methylamine (**3a**) could not be obtained by the reaction of **1** with formaldehyde followed by reduction, but could be obtained satisfactorily by the reduction of methyl *N*-benzyloxycarbonyl-α-D-glucosaminide (**2**) with lithium aluminum hydride in tetrahydrofuran. Thus, in a typical procedure, propionaldehyde (1.3 eq mol) was added to an ethanol solution of **1** to give the corresponding Schiff base and the mixture was reduced with sodium borohydride (1.6 eq mol).

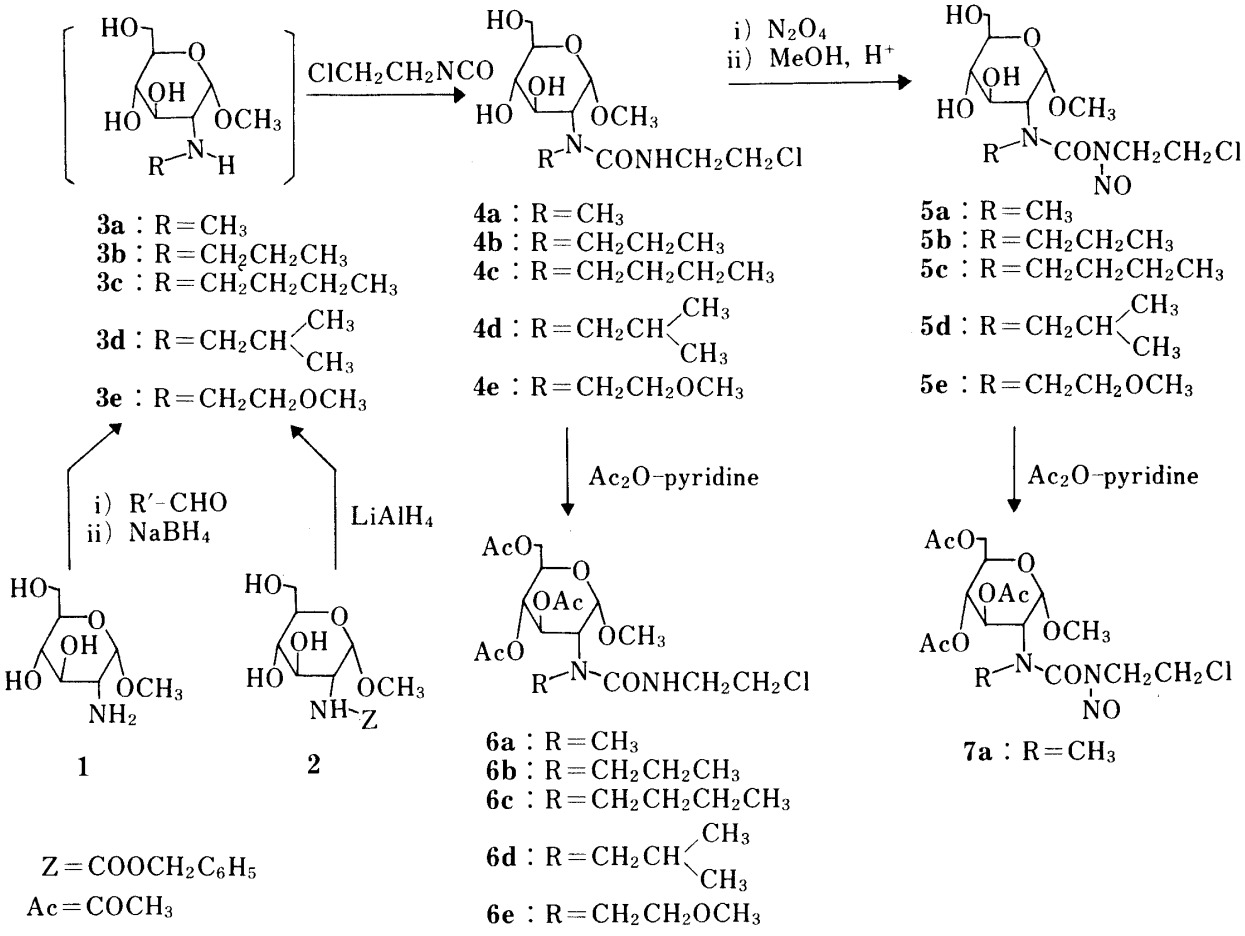


Chart 1

After the usual work-up, the crude amine (**3b**) was dissolved in methanol and 2-chloroethyl isocyanate (1.5 eq mol) was added. The urea (**4b**) was separated by silica gel chromatography in 66% yield from **1** as a colorless powder and showed infrared (IR) signals due to the ureido group at 1670 and 1520 cm^{-1}. Its nuclear magnetic resonance (NMR) signals were also compatible with the assigned structure. Five 3-substituted-1-(2-chloroethyl)-3-(methyl-α-D-glucopyranosid-2-yl)ureas (**4a**—**e**) were thus obtained and their physical data are listed in

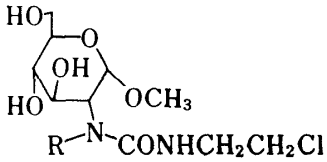
Table I. Acetylation of these ureas with acetic anhydride in pyridine gave the corresponding triacetates (**6a**—**e**) (see Table II).

The nitrosation of the ureas was carried out by the use of dinitrogen tetroxide as described in our previous paper.[7b] Thus, four equivalents of dinitrogen tetroxide was introduced into a mixture of the urea (**4a**) and anhydrous sodium acetate in tetrahydrofuran, and then methanol was added to decompose the nitrous ester groups in the glucoside moiety. After purification by silica gel chromatography, the nitrosourea (**5a**) was obtained in 72% yield. It showed the IR signals due to the nitrosoureido group at 1690 cm^{-1} and NMR signals due to the NCH_3, OCH_3, and β-anomeric protons at δ 3.09, 3.30, and 4.77, respectively. Acetylation of **5a** gave the triacetate (**7a**), which showed IR signals at 1750 ($OCOCH_3$) and 1695 cm^{-1} (NCON) and NMR signals of the three acetoxyl protons at δ 2.00, 2.06, and 2.11 in addition to the NCH_3 (δ 3.11) and the OCH_3 (δ 3.45) signals. Thus, **5a** was determined to be 1-(2-chloroethyl)-3-methyl-3-(methyl-α-D-glucopyranosid-2-yl)-1-nitrosourea. The physical and analytical data for the nitrosoureas (**5a**—**e**) thus obtained are listed in Table III.

Antitumor Activities of Nitrosoureas and Discussion

The nitrosoureas (**5a**—**e**) were tested for antitumor activities against leukemia L1210 and Ehrlich ascites carcinoma by the methods described in the previous paper.[7a] The results

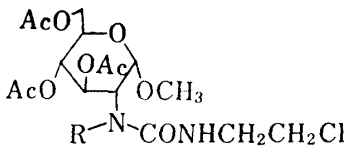
Table I. Yields, Physical Properties, and Analytical Data for Ureas (**4a**—**e**)



Compd. No.	R	mp (°C)	$[\alpha]_D$ deg. (c, °C) in methanol	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	Cl
4a	CH_3	96	+123.7 (1.0, 21)	58	$C_{11}H_{21}ClN_2O_6$	42.24 (42.42	6.72 6.80	8.96 8.73	11.36 11.18)
4b	$CH_2CH_2CH_3$	81	+90.5 (1.1, 18)	66	$C_{13}H_{25}ClN_2O_6$	45.81 (45.92	7.34 7.30	8.22 8.06	10.42 10.29)
4c	$CH_2CH_2CH_2CH_3$	55	+87.6 (1.0, 25)	64	$C_{14}H_{27}ClN_2O_6$	47.39 (47.51	7.61 7.58	7.89 7.69	10.01 9.82)
4d	$CH_2CH(CH_3)_2$	58	+69.8 (1.0, 18)	61	$C_{14}H_{27}ClN_2O_6$	47.39 (47.24	7.61 7.52	7.89 7.71	10.01 9.84)
4e	$CH_2CH_2OCH_3$	52	+101.2 (1.1, 18)	55	$C_{13}H_{25}ClN_2O_7$	43.75 (43.69	7.01 7.08	7.85 7.72	9.95 9.77)

Compd. No.	IR ν_{max}^{Nujol} cm^{-1}	NMR δ (ppm, in d_6-DMSO) (J=Hz)
4a	3300 (br, NH, OH), 1630 (CO) 1530 (CNH), 1020 (–O–)	2.80 (3H, s, NCH_3), 3.25 (3H, s, OCH_3), 4.51 (1H, d, J=3, H-1), 6.68 (1H, br, NH)
4b	3300 (br, NH, OH), 1670 (CO) 1520 (CNH), 1030 (–O–)	0.85 (3H, br, t, CH_2CH_3), 1.2—1.8 (2H, m, CH_2CH_3), 3.29 (3H, s, OCH_3), 4.46 (1H, d, J=2.7, H-1), 6.41 (1H, br, NH)
4c	3300 (br, NH, OH), 1660 (CO) 1510 (CNH), 1030 (–O–)	0.89—1.8 (7H, m, $CH_2CH_2CH_3$), 3.29 (3H, s, OCH_3), 4.47 (1H, d, J=3, H-1), 6.37 (1H, br, NH)
4d	3300 (br, NH, OH), 1660 (CO) 1510 (CNH), 1025 (–O–)	0.87 (6H, dd, J=6 and 3, $CH(CH_3)_2$), 3.32 (3H, s, OCH_3), 4.55 (1H, d, J=2.4, H-1)
4e	3330 (br, NH, OH), 1670 (CO) 1530 (CNH), 1030 (–O)–	3.24 (3H, s, OCH_3), 3.28 (3H, s, OCH_3), 4.53 (1H, d, J=2.9, H-1), 6.75 (1H, br, NH)

Table II. Physical Properties of Acetylated Ureas (**6a—e**)

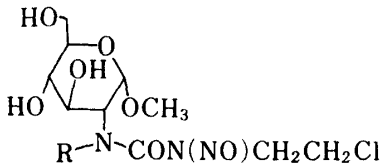


Compd. No.	R	mp (°C)	IR $\nu_{max}^{CHCl_3}$ cm^{-1}	NMR δ (ppm, in $CDCl_3$) (J=Hz)
6a	CH_3	62	3460 (NH), 1745 (CO) 1650 (CO), 1520 (CNH) 1230, 1035 (–O–)	1.98 (3H, s, Ac), 2.01 (3H, s, Ac), 2.09 (3H, s, Ac), 2.82 (3H, s, NCH_3), 3.36 (3H, s, OCH_3)
6b	$CH_2CH_2CH_3$	51	3370 (NH), 1745 (CO) 1640 (CO), 1520 (CNH) 1230, 1035 (–O–)	0.87 (3H, t, J=6.9, $CH_2C\underline{H}_3$), 1.2—1.8 (2H, m, $C\underline{H}_2CH_3$), 1.96 (3H, s, Ac), 2.01 (3H, s, Ac), 2.08 (3H, s, Ac), 3.41 (3H, s, OCH_3), 4.71 (1H, d, J=2.5, H-1)
6c	$CH_2CH_2CH_2CH_3$	Caramel	3380 (NH), 1745 (CO) 1645 (CO), 1520 (CNH)	0.9—1.8 (7H, m, $CH_2CH_2CH_3$), 1.97 (3H, s, Ac), 2.01 (3H, s, Ac), 2.09 (3H, s, Ac), 3.42 (3H, s, OCH_3) 4.75 (1H, d, J=3, H-1)
6d	$CH_2CH\langle^{CH_3}_{CH_3}$	Caramel	3380 (NH), 1745 (CO) 1645 (CO), 1530 (CNH) 1230, 1035 (–O–)	0.89 (6H, dd, J=6.6 and 2.1, $CH(C\underline{H}_3)_2$), 1.97 (3H, s, Ac), 2.01 (3H, s, Ac), 2.09 (3H, s, Ac), 3.45 (3H, s, OCH_3), 4.81 (1H, d, J=3, H-1), 6.07 (1H, br, NH)
6e	$CH_2CH_2OCH_3$	Oil	3380 (NH), 1750 (CO) 1650 (CO), 1540 (CNH) 1230, 1040 (–O–)	1.97 (3H, s, Ac), 2.00 (3H, s, Ac), 2.08 (3H, s, Ac), 3.37 (3H, s, OCH_3), 3.43 (3H, s, OCH_3), 4.73 (1H, d, J=3, H-1), 6.91 (1H, br, NH)

are summarized in Table IV together with the comparative data for positive controls; GANU and DCNU. The data for the glucopyranosyl nitrosoureas **8**, **9**, and **10**),[7b] the positional isomers of **5a**, **5b**, and **5d**, are also included in the table for comparison.

All the nitrosoureas prepared in the present study were remarkably active against both leukemia L1210 and Ehrlich ascites carcinoma and showed greater therapeutic ratios (3—7

Table III. Yields, Physical Properties, and Analytical Data for Nitrosoureas (**5a—e**)



Compd. No.	R	mp (dec.) (°C)	$[\alpha]_D$ deg. (c, °C) in methanol	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	Cl
5a	CH_3	66	+149.5 (1.0, 20)	71	$C_{11}H_{20}ClN_3O_7$	38.65 (38.93	5.85 5.89	12.29 12.10	10.39 10.15)
5b	$CH_2CH_2CH_3$	67	+91.9 (1.2, 17)	73	$C_{13}H_{24}ClN_3O_7$	42.21 (42.45	6.49 6.63	11.36 11.16	9.60 9.42)
5c	$CH_2CH_2CH_2CH_3$	53	+91.5 (0.8, 25)	69	$C_{14}H_{26}ClN_3O_7$	43.80 (43.72	6.77 6.81	10.95 10.72	9.25 9.11)
5d	$CH_2CH\langle^{CH_3}_{CH_3}$	69	+98.8 (1.0, 17)	75	$C_{14}H_{26}ClN_3O_7$	43.80 (43.68	6.77 6.85	10.95 10.79	9.25 9.14)
5e	$CH_2CH_2OCH_3$	55	+99.4 (1.1, 17)	70	$C_{13}H_{24}ClN_3O_8$	40.46 (40.67	6.22 6.32	10.89 10.73	9.20 9.09)

(continued)

Compd. No.	IR ν_{max}^{Nujol} cm^{-1}	NMR δ (ppm, in d_6-DMSO) (J=Hz)
5a	3400 (br, OH), 1690 (CO), 1075, 1020 (–O–)	3.09 (3H, s, NCH_3), 3.30 (3H, s, OCH_3), 4.77 (1H, d, J=2, H-1)
5b	3400 (br, OH), 1690 (CO), 1080, 1020 (–O–)	0.83 (3H, t, J=7, $CH_2C\underline{H}_3$), 1.3—1.8 (2H, m, $CH_2C\underline{H}_2CH_3$), 3.30 (3H, s, OCH_3), 4.62 (1H, d, J=2, H-1)
5c	3400 (br, OH), 1680 (CO), 1080, 1020 (–O–)	0.91—1.8 (7H, m, $CH_2CH_2CH_3$), 3.33 (3H, s, OCH_3), 4.68 (1H, d, J=3, H-1)
5d	3400 (br, OH), 1695 (CO), 1080, 1030 (–O–)	0.88 (6H, d, J=6.3, $CH(C\underline{H}_3)_2$), 3.27 (3H, s, OCH_3), 4.63 (1H, d, J=2, H-1)
5e	3400 (br, OH), 1690 (CO), 1095, 1025 (–O–)	3.22 (3H, s, OCH_3), 3.29 (3H, s, OCH_3), 4.62 (1H, d, J=2, H-1)

TABLE IV. Antitumor Activities of Nitrosoureas

Compd. No.	Anti-L1210 activity[a]				Anti-Ehrlich activity[b]		
	ILS_{30}[c] (mg/kg/d)	OD[d] (mg/kg/d)	ILS_{max} (%)	Therapeutic[e] ratio	MED[f] (mg/kg/d)	MTD[g] (mg/kg/d)	Therapeutic[h] ratio
GANU	0.8	6.25	>198.6	7.8	0.39	12.5	32
DCNU	1.4	12.5	>240.0	8.9	0.78	12.5	16
5a	1.9	50	>700.0[i]	26.3	0.78	100	128
5b	1.6	50	>650.0[i]	31.3	0.78	50	64
5c	1.5	50	>745.1[i]	33.3	1.56	100	64
5d	1.4	50	>689.5[i]	35.7	0.78	50	64
5e	0.45	25	>650.0[i]	55.6	0.39	50	128
8[j]	4.3	50	>689.5[i]	11.5	6.25	100	16
9[k]	1.25	25	>710.8[i]	20.0	1.56	50	32
10[l]	0.73	25	>669.2[i]	34.2	0.78	50	64

a) Leukemic cells (10^5) were inoculated *i.p.* into male BDF_1 mice and *i.p.* administration was begun 24 h after the inoculation and performed once daily for 5 d.
b) The ascites cells (10^6) were inoculated *i.p.* into female ICR mice and *i.p.* administration was begun 24 h after the inoculation and performed once daily for 5 d.
c) Daily dose providing 30% increase in life-span over the control. ILS(%)=(T/C−1)×100.
d) Optimal dose: the daily dose providing the maximum increase in life-span.
e) Therapeutic ratio=OD/ILS_{30}.
f) Minimum effective dose: the minimum dose which shows 100% inhibition of the growth of the tumor.
g) Maximum tolerated dose: the maximum dose which shows 100% inhibition of the growth of the tumor without causing the death of mice.
h) Therapeutic ratio=MTD/MED.
i) All treated mice survived for more than sixty d.
j) 1-(2-Chloroethyl)-3-β-D-glucopyranosyl-3-methyl-1-nitrosourea.
k) 1-(2-Chloroethyl)-3-β-D-glucopyranosyl-1-nitroso-3-*n*-propylurea.
l) 1-(2-Chloroethyl)-3-β-D-glucopyranosyl-3-isobutyl-1-nitrosourea.

times larger against leukemia L1210 and 2—8 times larger against Ehrlich ascites tumor) than the two positive controls. Sixty-day survivors with leukemia L1210 were found at the optimal dose for all these nitrosoureas. On the other hand, none were obtained with the positive controls. It appears that the presence of alkyl groups on the *N*-3 position of this class of nitrosoureas is necessary for significant antitumor activity. With regard to the effect of alkyl groups, methoxyethyl substitution is most preferable, since the compound (**5e**) showed excellent antitumor activity. Comparison of the positional isomers (**5a**, **5b**, **5d**, and **8**, **9**, **10**) showed that the effect of positional change in a glucose moiety is not significant, though some advantage was observed for compounds in which the nitrosoureido groups are attached to the C-2 position of the glucoside moiety.

Further studies on the synthesis and antitumor activity of this new class of nitrosoureas bearing a glucose moiety are in progress.

Experimental

IR spectra were recorded with a Hitachi IR-215 spectrometer, and NMR spectra with a JEOL PMX-60 spectrometer using tetramethylsilane (TMS) as an internal standard in d_6-DMSO. The optical rotations were measured in a 0.5-dm tube with a Jasco DIP-180 polarimeter. Column chromatography was carried out on Merck silica gel 60. Organic solutions were commonly dried over $MgSO_4$ and concentrated by evaporation *in vacuo*.

General Procedure for the Preparation of 3-Substituted-1-(2-chloroethyl)-3-(methyl-α-D-glucopyranosid-2-yl)ureas (4b—e)——Methyl glucosaminide hydrochloride[9] (2.3 g, 0.01 mol) was stirred in the solution of sodium methoxide (0.01 mol) in 20 ml of methanol at room temperature for 2 h. After filtration, the filtrate was concentrated and the residue was dissolved in 20 ml of ethanol. An appropriate aldehyde (0.013 mol) was added to the solution at room temperature and the mixture was stirred for 5 min. Sodium borohydride (0.61 g, 0.016 mol) was added to the reaction mixture under cooling and the mixture was stirred at room temperature for 2 h. After addition of methanol (15 ml), concentrated hydrochloric acid was added dropwise to the reaction mixture until the pH of the mixture reached about 4. After being stirred for 10 min, the mixture was basified with 20% potassium carbonate solution, filtered, and concentrated. The residue was dissolved in 40 ml of methanol and 2-chloroethyl isocyanate (2.0 g, 0.019 mol) was added dropwise at 5°C, then the mixture was stirred for 1.5 h at room temperature and concentrated. The residue was chromatographed on silica gel (solvent: chloroform–benzene–methanol). The ureas obtained were generally colorless powders and are listed in Table I with the yields and physical properties.

Preparation of 1-(2-Chloroethyl)-3-methyl-3-(methyl-α-D-glucopyranosid-2-yl)urea (4a)——Methyl *N*-benzyloxycarbonyl-α-D-glucosaminide[10] (3.27 g, 0.01 mol) was dissolved in 100 ml of dried tetrahydrofuran, lithium aluminum hydride (2.28 g, 0.06 mol) was added portionwise and then the mixture was refluxed for 5 h. To the mixture, ethyl acetate (15 ml) was added dropwise under cooling and the whole was stirred at room temperature for 15 min and then refluxed for 10 min. It was then cooled, and 30% sulfuric acid was added dropwise untill the pH of the mixture reached about 2. The mixture was filtered. The filtrate was concentrated and the residue was dissolved in 40 ml of methanol. The pH of the solution was adjusted to about 9 by adding saturated aqueous potassium carbonate and the insoluble material was filtered off. The filtrate was concentrated and the residue was dissolved in 50 ml of methanol. 2-Chloroethyl isocyanate (2.0 g, 0.019 mol) was added at 5°C and the whole was stirred for 1.5 h at room temperature, then concentrated. The residue was chromatographed on silica gel (solvent: chloroform–benzene–methanol=5: 2: 1) to give **4a** (1.8 g, 53% yield) as a colorless powder. Physical properties of **4a** are given in Table I.

Preparation of 3-Substituted-1-(2-chloroethyl)-3-(methyl-3,4,6-tri-*O*-acetyl-α-D-glucopyranosid-2-yl)urea (6a—e)——Acetylation of the ureas was done as follows. A mixture of the urea (0.005 mol), acetic anhydride (7 ml) and pyridine (15 ml) was stirred at room temperature overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The extracts were washed with cold aqueous hydrochloric acid, water, aqueous sodium bicarbonate, and aqueous sodium chloride successively. The organic layer was dried, filtered, and concentrated. The residue was chromatographed on silica gel. The yields and physical properties of these acetylated ureas are listed in Table II.

General Procedure for the Preparation of 3-Substituted-1-(2-chloroethyl)-3-(methyl-α-D-glucopyranosid-2-yl)-1-nitrosoureas (5a—e)——The urea (0.01 mol) was dissolved in 40 ml of tetrahydrofuran and then anhydrous sodium acetate (0.04 mol) was added. Dinitrogen tetroxide (0.045 mol) was introduced into the mixture at −5°C for 10 min under stirring. After 10 min, 7 ml of methanol was added to the mixture and the whole was stirred at the same temperature for 10 min. Cold ethyl acetate (40 ml), anhydrous sodium acetate (0.03 mol), and 10 ml of water were then added at −5°C. The whole was stirred vigorously for 10 min and the pH of the mixture was confirmed to be about 5. After filtration, the organic layer was collected, dried, filtered, and concentrated. The residue was purified by silica gel chromatography (solvent: ethyl acetate–benzene–methanol). The nitrosoureas (**5a—e**) thus obtained were usually unstable yellow powders and the yields and physical properties are listed in Table III.

Preparation of 1-(2-Chloroethyl)-3-methyl-3-(methyl-3,4,6-tri-*O*-acetyl-α-D-glucopyranosid-2-yl)-1-nitrosourea (7a)——Acetylation of **5a** was done as described for the preparation of acetylated urea (**6a—e**). **7a** was obtained in 58% yields as a pale yellow oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1750 (CO), 1695 (CO), 1230, 1080, 1040. NMR (in $CDCl_3$) δ: 2.00, 2.06, 2.12 (3H×3, s, OAc), 3.11 (3H, s, NCH_3), 3.45 (3H, s, OCH_3).

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