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Synthesis of (2-Chloroethyl)-nitrosourea Derivatives of Carbohydrate

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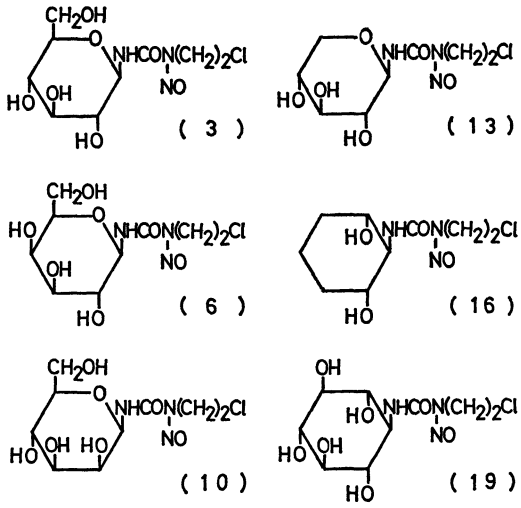
Synopsis. Six antileukemic carbohydrate derivatives which have a (2-chloroethyl)-nitrosoureido group have been prepared by a reaction between amino sugars and 2-chloroethyl isocyanate, followed by nitrosation.

It has been suggested by Johnston *et al.*[1] that the replacement of a methyl group with a 2-chloroethyl group in numerous congeners of methyl-nitrosoureas increased antitumor activities against leukemia L1210, as was demonstrated with BCNU: 1,3-bis(2-chloroethyl)-1-nitrosourea and CCNU: 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea.[1] More recently, two papers[2,3] have described a preparation of 2-chloroethyl analog of antitumor antibiotic streptozotocin.[4] In our laboratory, a synthesis of methyl glycoside of streptozotocin was initiated[5] and afterward, several nitrosourea derivatives of carbohydrate have been prepared by a reaction between amino sugars and alkyl isocyanate, followed by nitrosation.[6–8] In connection with the previous papers, we have attempted to prepare (2-chloroethyl)-nitrosourea derivatives, and in the present note, we wish to report a preparation of the derivatives of D-glycosylamines and polyhydroxycyclohexylamines by the analogous reaction sequence employed in the previous papers.[5–8] The position of the nitroso group in each compound has been established by PMR spectroscopy by demonstrating a spectral symmetry of the $ClCH_2CH_2N(NO)$ group (A_2B_2 system).[1]



All the six compounds showed a remarkable antitumor activity against L1210 leukemia in mice, which will be reported in a near future.

Experimental

Melting points were determined in a capillary tube in a liquid bath and are uncorrected. Solutions were evaporated under diminished pressure. Acetylation was carried out with acetic anhydride and pyridine in the usual manner. Optical rotations were measured on a Japan Spectroscopic

TABLE 1. 1-(2-CHLOROETHYL)UREAS

$$R\text{-}NH\text{-}\underset{\underset{O}{\|}}{C}\text{-}NHCH_2CH_2Cl$$

R	No.	Yield %	Mp °C	$[\alpha]_D$†	Molecular Formula	C% Calcd (Found)	H% Calcd (Found)	N% Calcd (Found)	Cl % Calcd (Found)
A. 1-(2-Chloroethyl)-3-(poly-*O*-acetyl-D-glycosyl)ureas									
Tetra-*O*-acetyl-β-D-glucopyranosyl	**1**	88	154—155	−7*	$C_{17}H_{25}N_2ClO_{10}$	45.09 (45.23)	5.56 (5.56)	6.19 (6.22)	7.83 (7.85)
Tetra-*O*-acetyl-β-D-mannopyranosyl	**8**	80	140—141	−14*	$C_{17}H_{25}N_2ClO_{10}$	45.09 (44.83)	5.56 (5.44)	6.19 (5.95)	7.83 (7.93)
B. 1-(2-Chloroethyl)-3-(D-glycosyl) ureas and -3-(polyhydroxycyclohexyl) ureas									
β-D-Glucopyranosyl	**2**	95	153 (dec)	−8	$C_9H_{17}N_2ClO_6$	37.97 (37.69)	6.02 (5.82)	9.84 (9.62)	12.45 (12.20)
β-D-Galactopyranosyl	**5**	85	116 (dec)	+9.5	$C_9H_{17}N_2ClO_6$	37.97 (37.86)	6.02 (6.18)	9.84 (9.57)	12.45 (12.25)
β-D-Mannopyranosyl	**9**	78	158—159 (dec)	−34	$C_9H_{17}N_2ClO_6$	37.97 (37.96)	6.02 (5.84)	9.84 (9.81)	12.45 (12.21)
β-D-Xylopyranosyl	**12**	47	159—160 (dec)	−13	$C_8H_{15}N_2ClO_5$	37.73 (37.49)	5.94 (6.00)	11.00 (10.79)	13.92 (13.89)
1, 3/2N-Dihydroxycyclohexyl	**15**	66	125—127		$C_9H_{17}N_2ClO_3$	45.67 (45.73)	7.24 (7.11)	11.83 (12.09)	14.98 (15.02)
1N, 3, 5/2, 4, 6-Pentahydroxycyclohexyl	**18**	90	195—197		$C_9H_{17}N_2ClO_6$	37.97 (37.96)	6.02 (5.78)	9.84 (9.76)	12.45 (12.71)

† Opitical rotations were measured at 14—30°C in water and chloroform(*).

Table 2. 1-(2-Chloroethyl)-1-nitrosoureas

$$R\text{-}NH\text{-}\underset{\underset{O}{\|}}{C}\text{-}\underset{\underset{NO}{|}}{N}\text{-}CH_2CH_2Cl$$

R	No.	Yield %	Mp °C	$[\alpha]_D$†	Molecular Formula	C% Calcd (Found)	H% Calcd (Found)	N% Calcd (Found)	Cl % Calcd (Found)
A. 1-(2-Chloroethyl)-3-(D-glycosyl)-1-nitrosoureas and -3-(polyhydroxycyclohexyl)-1-nitrosoureas									
β-D-Glucopyranosyl	**3**	97	85 (dec)	−14	$C_9H_{16}N_3ClO_7$	34.46 (34.36)	5.14 (5.09)	13.40 (13.20)	11.30 (11.33)
β-D-Galactopyranosyl	**6**	64	145 (dec)	+13	$C_9H_{16}N_3ClO_7$	34.46 (34.58)	5.14 (5.09)	13.40 (13.12)	11.30 (11.22)
β-D-Mannopyranosyl	**10**	67	104 (dec)	−10	$C_9H_{16}N_3ClO_7$††				
β-D-Xylopyranosyl	**13**	76	84—85 (dec)	−8	$C_8H_{14}N_3ClO_6$	33.87 (34.17)	4.97 (5.10)	14.81 (14.44)	12.50 (12.80)
1, 3/2N-Dihydroxycyclohexyl	**16**	58	125—126 (dec)		$C_9H_{16}N_3ClO_4$	40.68 (40.51)	6.07 (5.87)	15.82 (15.70)	13.34 (13.13)
1N, 3, 5/2, 4, 6-Pentahydroxy-cyclohexyl	**19**	78	140—142 (dec)		$C_9H_{16}N_3ClO_7$	34.46 (34.58)	5.14 (5.13)	13.40 (13.10)	11.30 (11.50)
B. 1-(2-Chloroethyl)-3-(poly-*O*-acetyl-D-glycosyl)-1-nitrosoureas and -3-(polyacetoxycyclohexyl)-1-nitrosoureas									
Tetra-*O*-acetyl-β-D-glucopyra-nosyl	**4**	55	88—90	−14*	$C_{17}H_{24}N_3ClO_{11}$	42.38 (42.55)	5.02 (5.06)	8.72 (8.44)	7.36 (7.44)
Tetra-*O*-acetyl-β-D-galactopyra-nosyl	**7**	76	69—70	+5*	$C_{17}H_{24}N_3ClO_{11}$	42.38 (42.59)	5.02 (5.02)	8.72 (8.61)	7.36 (7.38)
Tetra-*O*-acetyl-β-D-mannopyra-nosyl	**11**	87	78 (dec)	−20*	$C_{17}H_{24}N_3ClO_{11}$	42.38 (42.68)	5.02 (5.05)	8.72 (8.47)	7.36 (7.50)
Tri-*O*-acetyl-β-D-xylopyranosyl	**14**	40	124—125	−19*	$C_{14}H_{20}N_3ClO_9$	41.03 (41.32)	4.92 (5.06)	10.25 (10.23)	8.65 (8.80)
1, 3/2N-Diacetoxycyclohexyl	**17**	82	151—152		$C_{13}H_{20}N_3ClO_9$	44.64 (44.52)	5.76 (5.74)	12.01 (11.81)	10.14 (10.09)
1N, 3, 5/2, 4, 6-Pentaacetoxy-cyclohexyl	**20**	85	206—209		$C_{19}H_{26}N_3ClO_{12}$	43.56 (43.58)	5.00 (4.97)	8.02 (7.79)	6.77 (6.75)

† See, Table 1. †† Compound did not give a correct analysis.

DIP-SL polarimeter. Elementary analyses were performed by Mr. Saburo Nakada to whom our thanks are due.

General Procedure for 1-(2-Chloroethyl)-3-(D-glycopyranosyl)urea and -3-(polyhydroxycyclohexyl)urea. *O*-Acetyl-D-glycosylamine or aminocyclitol was treated with 2-chloroethyl isocyanate (1.1—2.2 mol. equiv.) in a solvent. The reaction mixture was agitated for 1—2.5 hr under ice cooling and then evaporated. The residue was recrystallized from an appropriate solvent. The product was de-*O*-acetylated in methanolic ammonia or 0.1 M methanolic sodium methoxide.

General Procedure of Nitrosation. The carbamoyl derivative was treated with sodium nitrite (2 mol. equiv.) in 99% formic acid. After agitated for 1—2 hr under ice cooling, the solution was diluted with ice cold water and deionized with Amberlite IR-120(H^+). The solution was evaporated or lyophilized to give the product.

Starting Materials. Compound **1** was prepared from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine,[9] compound **5** was from 2,3,4,6-tetra-O-acetyl-β-D-galactopyranosylamine,[9] and compound **8** was from 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosylamine.[8] Starting from 2,3,4-tri-*O*-acetyl-1-azido-1-deoxy-β-D-xylopyranose,[10] compound **12** was prepared. Compound **15** was synthesized from 1,3/2N-aminocyclohexanediol[11] and compound **18** was from *scyllo*-inosamine.[12]

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