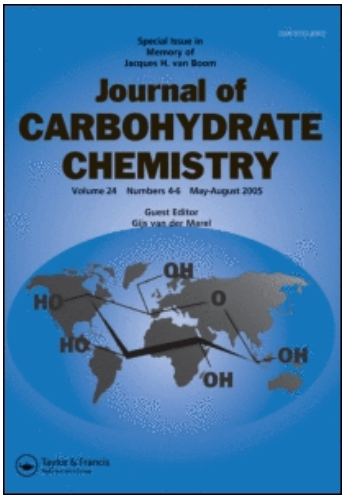

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Synthesis and Preliminary Evaluation of 2-Chloroethylnitrosourea Derivatives of Sucrose

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ABSTRACT

2-Chloroethylnitrosourea derivatives of sucrose have been synthesized as potential antineoplastic agents. Two compounds: 6-[[[(2-chloroethyl)nitrosoamino]carbonyl]amino]-6-deoxysucrose and 6'-[[[(2-chloroethyl)nitrosoamino]carbonyl]amino]-6'-deoxysucrose exhibited significant antitumor activity against experimental leukemia L1210 in mice. Their chemical decomposition rates ($T_{0.5}$) have been determined.

INTRODUCTION

According to an observation of Bakay,[1] normal human cells will not absorb sucrose and sucrose does not penetrate into normal brain tissue. In contrast, sucrose has been found in tumorous brain tissue.[1] Consequently, methylnitrosourea derivatives of sucrose have been synthesized by Almquist and Reist for the purpose of obtaining antitumor agents with activity against brain tumors.[2] Two compounds: 6,6'-di-[[methyl(nitrosoamino)carbonyl]-amino]-6,6'-dideoxysucrose and 1',6,6'-trideoxysucrose showed statistically significant antitumor activity against not only leukemia L1210 but also ependymoblastoma brain tumor in transplanted mice.[2]

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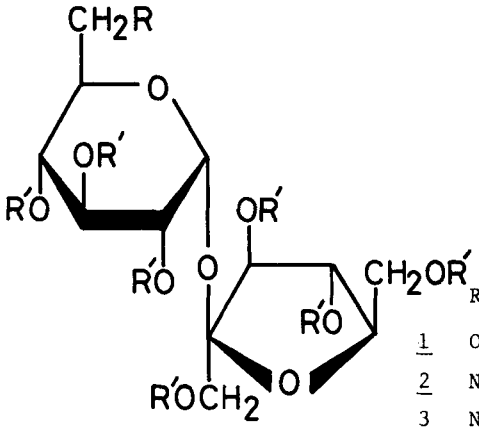
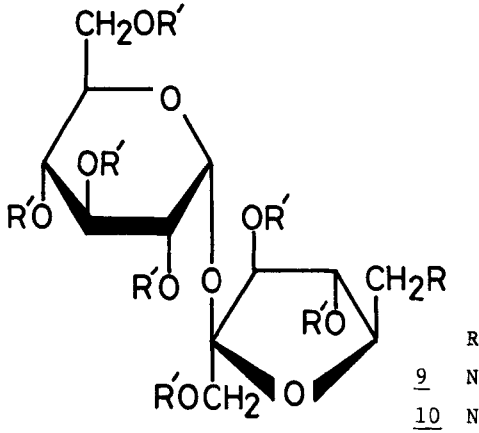


	R	R'
1	$OSO_2C_6H_2(CH_3)_3$	$COCH_3$
2	N_3	$COCH_3$
3	NH_2	H
4	$NHCOCH_3$	$COCH_3$
5	$NHCONHCH_2CH_2Cl$	H
6	$NHCONHCH_2CH_2Cl$	$COCH_3$
7	$NHCON(NO)CH_2CH_2Cl$	H
8	$NHCON(NO)CH_2CH_2Cl$	$COCH_3$



	R	R'
9	NH_2	H
10	$NHCON(NO)CH_2CH_2Cl$	H
11	$NHCONHCH_2CH_2Cl$	$COCH_3$
12	$NHCON(NO)CH_2CH_2Cl$	$COCH_3$

Since replacement of the methyl group on the nitrosated nitrogen of a methylnitrosourea by a 2-chloroethyl group gave significantly enhanced antitumor activity, as described by Montgomery and his coworkers,[3-15] a synthesis of 2-chloroethyl nitrosourea derivatives of sucrose was undertaken. Two compounds: 6-[[[(2-chloroethyl)nitrosoamino]carbonyl]amino]-6-deoxysucrose (7) and 6'-[[[(2-chloroethyl)nitrosamino]carbonyl]amino]-6'-deoxysucrose (10) have been synthesized in the present study and evaluated for antitumor activity against leukemia L1210 in mice.

CHEMISTRY

Selective displacement of each of the two primary OH groups in sucrose at C-6 or 6' with an amino group was accomplished. Mesitylenesulfonylation of 1',2,3,3',4,4',6'-hepta-O-acetylsucrose[16] gave 6-O-sulfonate (1), which was converted to a 6-azido derivative (2) with sodium azide. Catalytic hydrogenation of 2 and subsequent de-O-acetylation afforded the 6-amino derivative[17] (3). Carbamoylation of 3 with 2-chloroethyl isocyanate yielded the carbamate (5). Conventional nitrosation of 5 afforded 7 in 41% yield, which was prepared alternatively from 3 and p-nitrophenyl-N-(2-chloroethyl)-N-nitrosocarbamate[18] in 55% yield. Compound 10 was prepared from 6'-amino-6'-deoxysucrose[19] (9) with the same reagent[18] in almost quantitative yield.

A half-life ($T_{0.5}$) of a compound was determined at pH 7.4 in a phosphate buffered solution at 37°C by a literature method.[21] The half-life of 7 and 10 were found to be 57.5 and 58.7 min, respectively.

BIOLOGICAL RESULTS

Compounds 7 and 10 were evaluated for antitumor activity against leukemia L1210 in mice by the established protocol.[20] Compounds 7 and 10 were highly active, and 7 produced >650% ILS (increase of life span) in 100 and 150 mg/kg doses, and cured all mice by day-60 in a 100 mg/kg dose. Also, 10 produced >650% ILS between 100 and 200 mg/kg.

Table I. Antitumor Activity of (2-Chloroethyl)nitrosourea Derivatives of Sucrose against Mouse Leukemia L1210[a]

Compound NO.	Dosage (mg/kg/day)	Median survival days (T/C)	ILS[b] (%)	60-Day suvivors	Half-life $T_{0.5}$(min)
	150	>60.0 / 8.0	>650	4 / 5	
	100	>60.0 / 8.0	>650	5 / 5	
7	50	>18.0 / 8.0	>125	2 / 5	58.7
	20	11.0 / 8.0	38	0 / 5	
	10	11.0 / 8.0	38	0 / 5	
	200	>60.0 / 8.0	>650	6 / 7	
	150	>60.0 / 8.0	>650	5 / 7	
10	100	>60.0 / 8.0	>650	5 / 7	57.5
	50	>14.0 / 7.0	>100	1 / 4	
	20	14.0 / 8.0	75	0 / 5	
	10	12.0 / 8.0	50	0 / 5	

a Male BDF_1 hybrid mice were inoculated interperitoneally with 10^5 cells of lymphoid leukemia L1210. Treatment: single dose, day 1 administered ip.

b Percentage increase in life span of treated animals compared with control tumor bearers: [(T/C)-1] x 100%

EXPERIMENTAL

General Procedures. Melting points were determined in capillary tubes and uncorrected. Solutions were concentrated under reduced pressure below 40°C. Optical rotations were mesured with a Japan Spectroscopic DIS-SL polarimeter. ^{1}H NMR spectra were recorded with a Varian EM-390 spectrometer at 90 MHz.

1',2,3,3',4,4',6'-Hepta-O-acetyl-6-O-mesitylenesulfonyl-sucrose (1). To a stirred solution of 1',2,3,3',4,4',6'-hepta-O-acetylsucrose[16] (5.70 g, 9.0 mmol) in dry pyridine (100 ml), mesitylenesulfonyl chloride (5.70 g, 26.0 mmol) was added. After 42 h, the solution was poured into ice cold water (1 l) and extracted with chloroform repeatedly. The combined chloroform layer was washed with water, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography using 1:3 (v/v) 2-butanone-toluene. Fractions corresponding to R_f 0.51 on TLC in the same solvent (two developments) were concentrated to give 5.4 g (73 %) of 1 as a glass: mp 42-45°C; $[\alpha]_D^{22}$ +60.6° (c 3.1, chloroform); ^{1}H NMR ($CDCl_3$): δ 2.01 (s, 6, 2 x OAc), 2.08 (s, 3, OAc), 2.11 (s, 9, 3 x OAc), 2.16 (s, 3, OAc), 2.32 (s, 3, CH_3), 2.63 (s, 6, 2 x CH_3), 4.74 (dd, 1, $J_{1,2}$=3.6 Hz, $J_{2,3}$=9.2 Hz, H-2), 5.05 (t, 1, $J_{2,3}$=$J_{3,4}$=9.2 Hz, H-3), 5.64 (d, 1, $J_{1,2}$=3.6 Hz, H-1).

Anal. Calcd for $C_{35}H_{46}O_{20}S$: C, 51.34; H, 5.66; S, 3.92. Found: C, 51.11; H, 5.61; S, 4.18.

1',2,3,3',4,4',6'-Hepta-O-acetyl-6-azido-6-deoxysucrose (2). A solution of 1 (5.00 g, 6.1 mmol) and sodium azide (2.50 g, 38.5 mmol) in 90% aqueous 2-methoxyethanol (100 ml) was heated under reflux. After 17 h, the solution was concentrated and the residue was acetylated with acetic anhydride (25 ml) in pyridine (25 ml). The crude product was purified by column chromatography using 1:9 (v/v) acetone-benzene. Fractions corresponding to R_f 0.55 on TLC in 1:4 (v/v) acetone-benzene were concentrated to give 3.30 g (82 %) of 2 as a syrup: $[\alpha]_D^{25}$ +76.1° (c 2.5, chloroform); IR (neat) 2100 (N_3), 1750 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 2.01 (s, 3, OAc), 2.03 (s, 3, OAc), 2.07 (s, 3, OAc), 2.09 (s, 9, 3 x OAc), 2.16 (s,

3, OAc), 3.40 (m, 2, CH_2-6), 4.82 (dd, 1, $J_{1,2}$=3.4 Hz, $J_{2,3}$=9.4 Hz, H-2), 5.05 (t, 1, $J_{2,3}$=$J_{3,4}$=9.4 Hz, H-3), 5.72 (d, 1, $J_{1,2}$=3.4 Hz, H-1).

Anal. Calcd for $C_{26}H_{35}N_3O_{17}$: C, 47.20; H, 5.33; N, 6.35. Found: C, 47.42; H, 5.43; N, 6.10.

6-Amino-6-deoxysucrose (3). Compound 2 (3.30 g) was dissolved in 0.1 M methanolic sodium methoxide (30 ml). After 12 h, the solution was deionized with Amberlite IR-120B (H^+) and concentrated. A solution of the residue in 50% aqueous ethanol (100 ml) was hydrogenated in the presence of platinum oxide (200 mg) in a H_2 atmosphere (3.4 kg/cm^2) for 5h at 40°C. The catalyst was filtered off and the filtrate was concentrated. The residue was triturated in ethanol to give 1.40 g (78 %) of 3 as an amorphous solid: mp 66-69°C; $[\alpha]_D^{22}$ +53.2° (c 2.5, water); ^{1}H NMR (D_2O): δ 5.06 (d, 1, $J_{1,2}$=3.2 Hz, H-1); R_f 0.28 on TLC in 5:8:10:7 (v/v) 28% ammonia-butanol-ethanol-water.

Anal. Calcd for $C_{12}H_{23}NO_{10}$ $1/8H_2CO_3$: C, 41.72; H, 6.71; N, 4.01. Found: C, 41.75; H, 6.64; N, 3.62.

1',2,3,3',4,4',6'-Hepta-O-acetyl-6-acetamido-6-deoxysucrose (4). Compound 3 (0.22 g) was acetylated with acetic anhydride (2 ml) in pyridine (2 ml) overnight. The reaction solution was poured into ice cold water and extracted with chloroform repeatedly. The combined chloroform layer was washed with water, dried over Na_2SO_4 and concentrated to give 0.39 g (96 %) of 4 as a glass: mp 50-54°C; $[\alpha]_D^{22}$ +63.0° (c 2.3, chloroform); IR (KBr) 1750 (C=O), 1680 (C=O), 1540 cm^{-1} (NH); ^{1}H NMR ($CDCl_3$): δ 1.98 (s, 6, NAc, OAc), 2.07 (s, 6, 2 x OAc), 2.10 (s, 9, 3 x OAc), 2.15 (s, 3, OAc), 4.78 (dd, 1, $J_{1,2}$=4.0 Hz, $J_{2,3}$=9.4 Hz, H-2), 4.84 (t, 1, $J_{2,3}$=$J_{3,4}$=9.4 Hz, H-3), 5.59 (d, 1, $J_{1,2}$=4.0 Hz, H-1), 6.34 (t, 1, J= 5.0 Hz, NH).

Anal. Calcd for $C_{28}H_{39}NO_{18}$: C, 49.63; H, 5.80; N, 2.07. Found: C, 49.54; H, 5.85; N, 1.93.

6-[[[(2-chloroethyl)amino]carbonyl]amino]-6-deoxysucrose (5). To a solution of 3 (0.30 g) in 50% aqueous methanol (5 ml),

2-chloroethyl isocyanate (0.2 ml, 2.3 mmol) was added under ice cooling. After 1 h, the solution was diluted with water (5 ml) and washed with ethyl acetate. The aqueous layer was concentrated to give 0.35 g (89 %) of 5 as a glass: mp 104-106°C (dec.); $[\alpha]_D^{22}$ +25.2° (c 2.3, ethanol); IR (KBr) 1640 (C=O), 1560 cm^{-1} (NH).

Anal. Calcd for $C_{15}H_{27}N_2ClO_{11}$: C, 40.32; H, 6.09; N, 6.27; Cl, 7.93. Found: C, 40.00; H, 6.12; N, 5.99; Cl, 7.71.

1',2,3,3',4,4',6'-Hepta-O-acetyl-6-[[[(2-chloroethyl)amino]-carbonyl]amino]-6-deoxysucrose (6). To a solution of 5 (0.20 g) in pyridine (1 ml), acetic anhydride (1 ml) was added. After 12 h, the solution was concentrated and the residue was purified by column chromatography using 1:5 (v/v) acetone-benzene. Fractions corresponding to R_f 0.37 on TLC in 1:3 (v/v) acetone-benzene were concentrated to give 0.24 g (72 %) of 6 as a glass: mp 57-60°C; $[\alpha]_D^{21}$ +63.3° (c 1.5, chloroform); IR (KBr) 1750 (C=O), 1650 (C=O), 1560 cm^{-1} (NH); ^1H NMR ($CDCl_3$): δ 2.00 (s, 3, OAc), 2.07 (s, 6, 2 x OAc), 2.14 (s, 12, 4 x OAc), 4.80 (dd, 1, $J_{1,2}$=3.6 Hz, $J_{2,3}$=9.4 Hz, H-2), 4.85 (t, 1, $J_{2,3}$=$J_{3,4}$=9.4 Hz, H-3), 5.77 (d, 1, $J_{1,2}$=3.6 Hz, H-1).

Anal. Calcd for $C_{29}H_{41}N_2ClO_{18}$: C, 47.00; H, 5.58; N, 3.78; Cl, 4.78. Found: C, 47.10; H, 5.50; N, 3.78; Cl, 4.72.

6-[[[(2-chloroethyl)nitrosoamino]carbonyl]amino]-6-deoxy-sucrose (7). (a). To a stirred solution of 5 (173 mg, 0.4 mmol) in 99% formic acid (2 ml), sodium nitrite (45 mg, 0.65 mmol) was added under ice cooling. After 30 min, the solution was treated with Amberlite IR-120B (H^+) and concentrated. The residue was purified by column chromatography using 5:2 (v/v) benzene-methanol. Fractions corresponding to R_f 0.56 on TLC in 1:1 (v/v) benzene-methanol were collected and concentrated to give 76 mg (41 %) of 7 as an amorphous powder: mp 85-87°C; $[\alpha]_D^{18}$ +36.1° (c 0.36, methanol); IR (KBr) 1720 (C=O), 1540 (NH), 1495 cm^{-1} (NO); ^1H NMR (D_2O): δ 5.31 (d, 1, $J_{1,2}$=3.2 Hz, H-1); $T_{0.5}$=58.7 min.

Anal. Calcd for $C_{15}H_{26}N_3ClO_{12}$: C, 37.86; H, 5.51; N, 8.83; Cl, 7.45. Found: C, 37.59; H, 5.45; N, 8.61; Cl, 7.14.

(b). To a stirred solution of 3 (2.00 g, 5.7 mmol) in methanol (150 ml) containing triethylamine (4 ml), a solution of p-nitrophenyl-N-(2-chloroethyl)-N-nitrosocarbamate[18] (4.40 g, 16.1 mmol) in tetrahydrofuran (100 ml) was added. After 3 h, the solution was concentrated and the residue was purified by column chromatography as was described in (a) to give 1.52 g (55 %) of 7.

1',2,3,3',4,4',6'-Hepta-O-acetyl-6-[[[(2-chloroethyl)nitrosoamino]carbonyl]amino]-6-deoxysucrose (8). To a solution of 7 (0.31 g, 0.7 mmol) in pyridine (3 ml), acetic anhydride (3 ml) was added. The crude product was purified by column chromatography using 1:9 (v/v) acetone-benzene. Fractions corresponding to R_f 0.77 on TLC in 1:3 (v/v) acetone-benzene were concentrated to give 0.29 g (57 %) of 8: mp 46-48°C; $[\alpha]_D^{17}$ +48.4° (c 1.8, chloroform); IR (KBr) 1740 (C=O), 1530 (NH), 1490 cm^{-1} (NO); ^1H NMR ($CDCl_3$): δ 2.02 (s, 3, OAc), 2.08 (s, 15, 5 x OAc), 2.16 (s, 3, OAc), 3.44 (t, 2, J=6.0 Hz, $CH_2\underline{CH_2}Cl$), 3.64 (t, 2, J=6.0 Hz, $\underline{CH_2}CH_2Cl$), 4.73 (dd, 1, $J_{1,2}$=4.0 Hz, $J_{2,3}$=9.6 Hz, H-3), 5.61 (d, 1, $J_{1,2}$=4.0 Hz, H-1).

Anal. Calcd for $C_{29}H_{40}N_3ClO_{19}$: C, 45.23; H, 5.24; N, 5.46; Cl, 4.60. Found: C, 45.25; H, 5.20; N, 5.33; Cl, 4.84.

6'-[[[(2-chloroethyl)nitrosoamino]carbonyl]amino]-6'-deoxysucrose (10). To a stirred suspension of 6'-amino-6'-deoxysucrose (9) (0.11 g, 0.3 mmol) in methanol (6 ml) containing triethylamine (37 mg), a solution of p-nitrophenyl-N-(2-chloroethyl)-N-nitrosocarbamate[18] (0.23 g, 0.9 mmol) in THF (6 ml) was added. After 12 h, the solution was concentrated and the residue was dissolved in methanol. To the solution, isopropyl ether was added and the suppernatant solution was decanted. The syrupy precipitate was washed with isopropyl ether. This treatment was repeated three times and the precipitate was dried in vacuo to give 0.13 g (97 %) of 10: mp 61-65°C (dec.); $[\alpha]_D^{23}$ +39.5° (c 0.38, water); IR (KBr) 1725 (C=O), 1530 (NH), 1495 cm^{-1} (NO); $T_{0.5}$=57.5 min.

Anal. Calcd for $C_{15}H_{26}N_3ClO_{12}$: C, 37.86; H, 5.51; N, 8.83; Cl, 7.45. Found: C, 37.52; H, 5.79; N, 8.50; Cl, 7.78.

1',2,3,3',4,4',6-Hepta-O-acetyl-6'-[[[(2-chloroethyl)amino]-carbonyl]amino]-6'-deoxysucrose (11). To a solution of 9 (0.50 g, 1.5 mmol) in 50% aqueous methanol (4 ml), 2-chloroethyl isocyanate (0.3 ml, 3.5 mmol) was added under ice cooling. After 1 h, crystals that appeared in the solution were filtered off and the filtrate was concentrated. The residue was acetylated with acetic anhydride (5 ml) in pyridine (5 ml) overnight. The crude product was purified by column chromatography using 1:5 (v/v) acetone-benzene. Fractions corresponding to R_f 0.21 on TLC in 1:3 (v/v) acetone-benzene were concentrated to give 0.76 g (76 %) of 11 as a glass: mp 61-63°C; $[\alpha]_D^{20}$ +66.0° (c 3.1, chloroform); IR (KBr) 1750 (C=O), 1650 (C=O), 1560 cm^{-1} (NH); ^1H NMR ($CDCl_3$): δ 2.02 (s, 3, OAc), 2.03 (s, 3, OAc), 2.07 (s, 3, OAc), 2.11 (s, 9, 3 x OAc), 2.14 (s, 3, OAc), 4.80 (dd, 1, $J_{1,2}$=3.4 Hz, $J_{2,3}$=9.9 Hz, H-2), 5.64 (d, 1, $J_{1,2}$=3.4 Hz, H-1).

Anal. Calcd for $C_{29}H_{41}N_2ClO_{18}$: C, 47.00; H, 5.58; N, 3.78; Cl, 4.78. Found: C, 47.24; H, 5.57; N, 3.56; Cl, 4.86.

1',2,3,3',4,4',6-Hepta-O-acetyl-6'-[[[(2-chloroethyl)nitroso-amino]carbonyl]amino]-6'-deoxysucrose (12). To a stirred solution of 11 (0.46 g, 0.62 mmol) in 99% formic acid (6 ml), sodium nitrite (64 mg, 0.93 mmol) was added under ice cooling. After 1 h, the solution was poured into ice cold water and extracted with chloroform repeatedly. The combined chloroform layer was washed with water, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography using 1:10 (v/v) acetone-benzene. Fractions corresponding to R_f 0.60 on TLC in 1:3 (v/v) acetone-benzene were concentrated to give 0.37 g (79 %) of 12: mp 50-52°C (dec.); $[\alpha]_D^{20}$ +56.2° (c 1.7, chloroform); IR (KBr) 1750 (C=O), 1540 (NH), 1500 cm^{-1} (NO); ^1H NMR ($CDCl_3$) δ 1.99 (s, 3, OAc), 2.02 (s, 3, OAc), 2.04 (s, 3, OAc), 2.06 (s, 3, OAc), 2.08 (s, 3, OAc), 2.10 (s, 3, OAc), 2.13 (s, 3, OAc), 3.45 (t, 2, J=6.0 Hz, CH_2CH_2Cl), 4.79 (dd, $J_{1,2}$=4.2 Hz, $J_{2,3}$=10.0 Hz, H-2).

Anal. Calcd for $C_{29}H_{40}N_3ClO_{19}$: C, 45.23; H, 5.24; N, 5.46; Cl, 4.60. Found: C, 45.12; H, 5.19; N, 5.30; Cl, 4.80.

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