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Synthesis of Nitrosourea Derivatives of Sucrose as Central Nervous System Anticancer Agents

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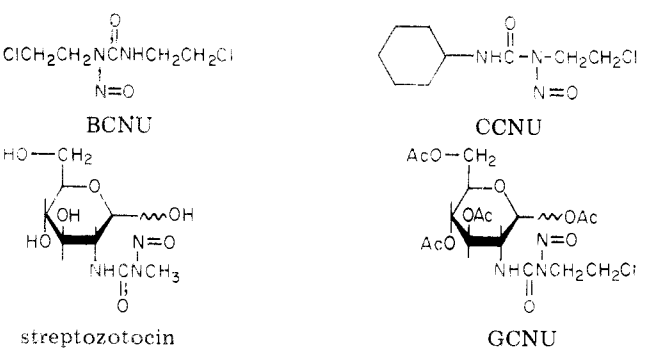
Nitrosourea derivatives of sucrose have been synthesized for the purpose of obtaining anticancer agents with activity against brain cancer. Two such compounds, 6,6′-dideoxy-6,6′-di(3-methyl-3-nitrosoureido)sucrose (**13**) and 1′,-6,6′-trideoxy-1′,6,6′-tri(3-methyl-3-nitrosoureido)sucrose (**14**), and their respective acetylated derivatives **15** and **16** have been prepared from sucrose. Compounds **13** and **14** have demonstrated antitumor activity against both L1210 leukemia and ependymoblastoma brain tumor in mice.

The treatment of human brain tumors by chemotherapy has led to minimal success up to this time. Compounds such as 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) have been used in the clinic,[1,2] but toxic side effects can pose a problem when using these compounds over long periods of time. Physical characteristics such as high lipid solubility, small molecular size, and a low degree of ionization which enable these compounds to penetrate the blood–brain barrier[3] also allow them to easily penetrate into all cells of the body where they might inflict various toxic manifestations.

In 1970, Bakay reported on some studies he had undertaken on sucrose uptake in humans with brain tumors.[4] He found that whereas sucrose did not penetrate into normal brain tissue, the concentration of sucrose found in the tumorous tissue was in direct relation to its concentration in plasma. These results demonstrated that whereas the blood–brain barrier prevents entry of sucrose into the extracellular fluid surrounding normal brain tissue,

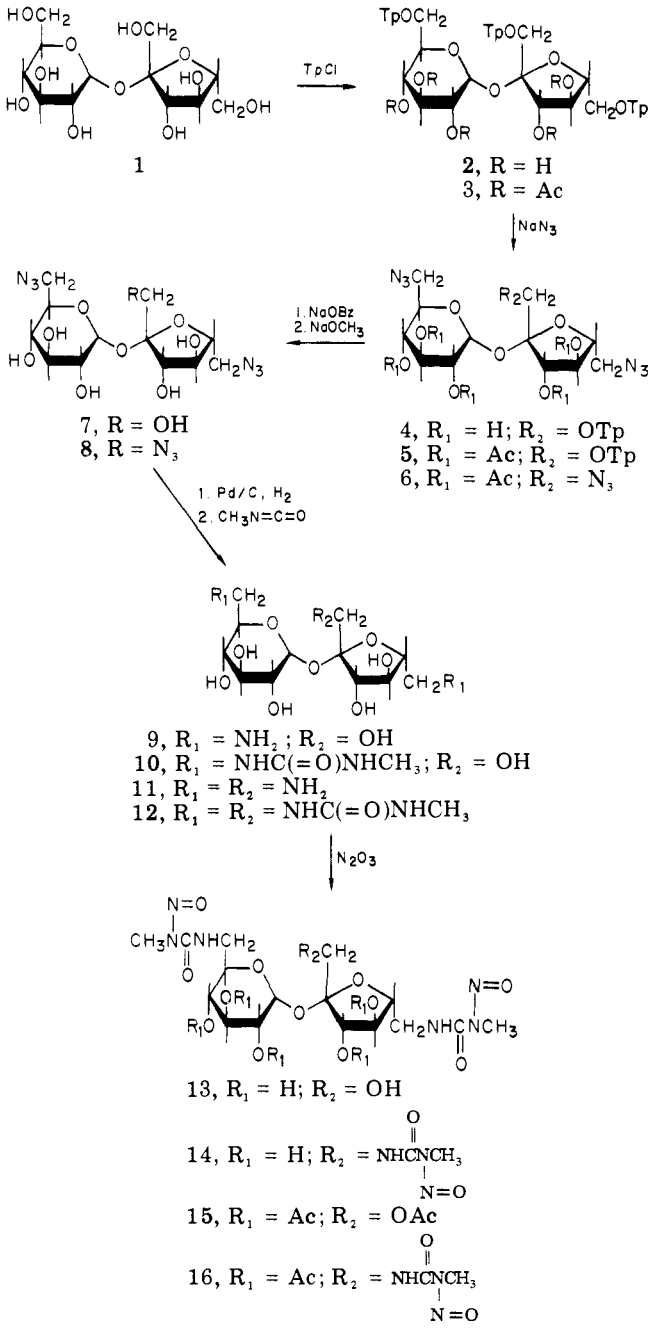
Chart I



there was a complete absence of this barrier to sucrose in brain tumors. Bakay's data further indicated that sucrose penetrated the cell membranes of human brain tumor cells.

The penetration of sucrose through cell membranes is

Scheme I



unusual. Normally human cells will not absorb sucrose.[5,6] It is too polar to pass through cell membranes by passive diffusion, and its large molecular radius of 4.5 Å prevents its passage through cell pores. Since sucrose is also not actively transported into cells, it appears to be a very selective agent for absorption into brain tumor cells.

Based on this observation it seemed that a brain antitumor agent would be a sucrose analogue with similar physical characteristics to sucrose but with the ability to kill cells. Considering the cytotoxic abilities of such nitrosourea derivatives as BCNU, CCNU, and streptozotocin[7] (Chart I), nitrosourea derivatives of sucrose appeared to be good candidates for brain antitumor drugs. The synthesis of 6,6′-dideoxy-6,6′-di(3-methyl-3-nitrosoureido)sucrose (**13**) and 1′,6,6′-trideoxy-1′,6,6′-tri(3-methyl-3-nitrosoureido)sucrose (**14**) was begun in hopes of obtaining such a drug.

In addition, the acetylated derivatives of **13** and **14** were synthesized since the acetylated derivative of chlorozotocin (GCNU) has shown good antitumor activity.[8]

Table I. Test Results against L1210 Leukemia in CDF_1 Mice

Compd no.	NSC[b] no.	Dose,[c] mg/kg	T/C,[a] %	Diluent
13	244265	50	107	Saline
		100	129	
		200	137	
14	263858	50	110	Water
		100	117	
		200	137	
15	263859	50	109	
		100	105	
		200	119	
16	263860	50	104	
		100	102	
		200	120	
Streptozotocin	85998	29	107	Citric acid-sodium citrate buffer
		44	117	
		66	137	
		100	109	

[a] The numerical results (T/C) are ratios of survival times of treated mice over control mice, expressed as a percent. A ratio ≥125 is a positive result denoting activity. [b] Accession number of the National Cancer Institute. [c] Given in nine injections, ip, on days 1-9.

Chemistry. Three different synthetic schemes were used to prepare the intermediate sugar, 6,6′-diazido-6,6′-dideoxysucrose (**7**).[9] The scheme (Scheme I) which gave the best overall yield of **7** from sucrose will be described here.

The synthesis began with the selective tripsylation (2,4,6-triisopropylbenzene sulfonation) of sucrose (**1**) and gave 1,6,6′-tri-*O*-tripsylsucrose (**2**) as a crystalline solid in 54% yield. The tritripsylsucrose **2** was selectively reacted with sodium azide at 70 °C and yielded crude 6,6′-diazido-6,6′-dideoxy-1′-*O*-tripsylsucrose (**4**) which was converted to the pentaacetate **5**. The 1′-tripsyl group of **5** was displaced with sodium benzoate at 110 °C in hexamethylphosphoric triamide (HMPA) and subsequent deesterification with sodium methoxide permitted isolation of the crystalline 6,6′-diazido-6,6′-dideoxysucrose (**7**). The diazide **7** was then reduced using 10% palladium on carbon and 45 psi of hydrogen gas to the diamine **9** which was characterized by reaction with methyl isocyanate as the crystalline 6,6′-dideoxy-6,6′-di(3-methylureido)sucrose (**10**).

Conversion of the diurea **10** to the dinitrosourea **13** was accomplished with considerable difficulty. In order to prevent acid hydrolysis[11] of the sucrose (**1**) glycosidic linkage, nitrosation was carried out using only 2 equiv of gaseous nitrogen trioxide at 0 °C. Rapid lyophilization removed most of the remaining nitrogen trioxide and nitrous acid that had been generated and minimized product hydrolysis. Crystallization of the product obtained yielded 64% of pure, 6,6′-dideoxy-6,6′-di(3-methyl-3-nitrosoureido)sucrose (**13**).

The synthesis of 1′,6,6′-trideoxy-1′,6,6′-tri(3-methyl-3-nitrosoureido)sucrose (**14**) required the preparation of the triaminosucrose intermediate **11** (Scheme I).

Khan et al.[12] have reported the synthesis of 1′,6,6′-triamino-1′,6,6′-trideoxysucrose (**11**) from 1′,6,6′-tri-*O*-tosylsucrose pentabenzoate. We prepared **11** from the acetylated tritripsylsucrose **4** using similar procedures. We were unable to obtain the triaminosucrose **11** in an analytically pure state; therefore, **11** was converted directly to the more easily purified triurea **12** by reaction with methyl isocyanate. Reaction of **12** with nitrogen trioxide as described for the preparation of **13** gave 1′,6,6′-trideoxy-1′,6,6′-tri(3-methyl-3-nitrosoureido)sucrose (**14**) in 77% yield.

Both **13** and **14** were acetylated in acetic anhydride and pyridine to high yields of the hexaacetate **15** and pentaacetate **16**, respectively.

Biological Results and Discussion. Compounds **13–16** were evaluated by Drug Research and Development, National Cancer Institute, according to published protocols.[13] Test results against L1210 leukemia in mice are listed in Table I. Both compounds **13** and **14** showed statistically significant (T/C ≥ 125) antitumor activity at a dose of 200 mg/kg. The acetylated sucrose nitrosoureas **15** and **16** showed no significant activity at the doses tested. Compounds **13** and **14** have also been tested against ependymoblastoma which is a brain tumor (Table II). At a dose of 200 mg/kg both nitrosoureas showed statistically significant antitumor activity. Toxicity was seen with compound **13** against ependymoblastoma at 400 mg/kg but not with the trinitrosourea **14**.

Compounds **13** and **14** are currently being evaluated more closely by the National Cancer Institute. Based on the evaluation of these first two nitrosourea derivatives of sucrose, additional sucrose derivatives will be designed and synthesized. The synthesis of the mononitrosourea, 6-deoxy-6-(3-methyl-3-nitrosoureido)sucrose, has been attempted, but this compound has proven to be too unstable to be used effectively as a drug.

An attempt has also been made to synthesize an *N*-(2-chloroethyl)-*N*-nitrosourea derivative of sucrose, 6,6′-dideoxy-6,6′-di[3-(2-chloroethyl)-3-nitrosoureido]sucrose. Unfortunately, nitration of the intermediate urea, 6,6′-dideoxy-6,6′-di[3-(2-chloroethyl)ureido]sucrose, requires strongly acid conditions as described by Johnson et al.[15] in their synthesis of chlorozotocin, the 2-chloroethyl analogue of streptozotocin. As explained previously the glycosidic linkage in the sucrose molecule will hydrolyze under even weakly acid conditions. This acid-sensitive linkage prevented the synthesis of an *N*-(2-chloroethyl)-*N*-nitrosourea derivative of sucrose.

The low acute toxicity seen with **13** and **14** at the doses tested indicates that the nitrosourea functionality is a good cytotoxic group to attach to sucrose. A group was desired that would give sucrose cytotoxic ability but would not significantly alter its polarity. Such a compound should retain sucrose's low penetrability of normal cell membranes and would hopefully have the same ability as sucrose to enter cancerous tissue in the brain. Whether nitrosourea derivatives of sucrose will ever be useful as CNS antitumor agents in man will require more extensive biological study.

Experimental Section

General Methods. Melting points were determined on a Thomas-Hoover Uni-melt and are corrected. Optical rotations were measured using a Perkin-Elmer 141 automatic polarimeter. Infrared spectra were taken on a Perkin-Elmer 137 spectrometer. ^{1}H NMR spectra were taken using a Varian T-60 spectrometer. ^{13}C NMR spectra were taken on a Varian XL-100FT (25.17 MHz) NMR spectrometer. Evaporations were carried out at 40 °C under aspirator vacuum on a Büchi Rotavapor unless otherwise stated. Thin-layer chromatography was carried out on Eastman Chromagram Sheets No. 6060 with silica gel and fluorescent indicator unless stated otherwise. Amberlite IRC 50 acid resin was obtained from Mallinckrodt. Elemental analyses were conducted by Ms. Betty McCarthy at SRI and by Mr. Eric Meier, Stanford University, Palo Alto, Calif. Gallard Schlesinger silica gel (90–200 mesh) was used for column chromatography.

1′,6,6′-Tri-*O*-tripsylsucrose Pentaacetate (3). A solution of 1′,6,6′-tri-*O*-tripsylsucrose[10] (**2**, 5.00 g, 4.38 mmol) in dry pyridine (40 mL) was stirred and acetic anhydride (4.13 mL, 43.8 mmol) was added. The mixture was stirred at room temperature for 15 h and then was evaporated at 50 °C to a yellow oil. This oil was refluxed with MeOH (50 mL) for 15 min and then was evaporated (azeotroping with toluene) to a light yellow syrup. This syrup was dissolved in $CHCl_3$ and washed with cold 2 N HCl, saturated $NaHCO_3$, and water. The organic layer was dried (Drierite) and evaporated to a white solid foam, **3**: 5.92 g (100%); mp softens at 75–78 °C and melts at 125–127 °C; IR (KBr) 1770 (C=O), 1600 (aromatics C=C), 1370, 1180 cm^{-1} (SO_2). Anal. ($C_{67}H_{98}S_3O_{22}$) C, H, S.

6,6′-Diazido-6,6′-dideoxy-1′-*O*-tripsylsucrose (4). A mixture of 1′,6,6′-tri-*O*-tripsylsucrose (**2**)[10] (1.00 g, 0.876 mmol), sodium azide (0.569 g, 8.76 mmol), and dry HMPA (5.0 mL) was stirred at 70 °C for 5 days. The mixture was then poured into a stirring mixture of ice and saturated NaCl solution (250 mL). The resulting aqueous mixture was extracted twice with $CHCl_3$ (100 and 50 mL successively). The $CHCl_3$ layers were combined, washed with H_2O, and evaporated to a light yellow oil. This oil was poured into a stirring mixture of ice and saturated NaCl solution (250 mL). The aqueous mixture was extracted with EtOAc. The EtOAc layer was washed with 20% NaCl solution and evaporated to a waxy off-white solid. This solid was dissolved in acetone (10 mL) and filtered through Celite. The filtrate was evaporated to crude **4** as an off-white foam: 0.466 g (80.8%); IR (KBr) 2110 cm^{-1} (N_3); ^{1}H NMR (acetone-d_6) δ 7.33 (s, 2, H-3 and H-5 of tripsyl), 5.27 (d, 1, J = 3.5 Hz, H-1), 1.24 (d. 12, J = 7.0 Hz, *o*-CH_3 of tripsyl), 1.26 (d, 6, J = 7.0 Hz, *p*-CH_3 of tripsyl). This material was acetylated without further purification to the pentaacetate **5**.

6,6′-Diazido-6,6′-dideoxy-1′-*O*-tripsylsucrose Pentaacetate (5). A solution of crude 6,6′-diazido-6,6′-dideoxy-1′-*O*-tripsylsucrose (**4**, 1.63 g, 2.47 mmol) and dry pyridine (18 mL) was stirred at room temperature and acetic anhydride (2.33 mL, 24.7 mmol) was added. The reaction mixture was stirred at room temperature for 16 h and was evaporated at 50 °C to a yellow oil. This oil was refluxed with MeOH for 15 min and then was evaporated (azeotroping with toluene) to a yellow syrup. This syrup was dissolved in $CHCl_3$ and washed with cold 2 N HCl, saturated $NaHCO_3$, and H_2O. The $CHCl_3$ layer was dried (Drierite) and evaporated to crude **5** as an off-white solid foam: 2.01 g (93.9%); IR (KBr) 2110 (N_3), 1730 cm^{-1} (OAc); ^{1}H NMR ($CDCl_3$) δ 7.25 (s, 2, H-3 and H-5 of tripsyl), 5.63 (d, 1, J = 3.5 Hz, H-1), 1.29 (d, 18, J = 7.0 Hz, CH_3 of tripsyl). Crude **5** was converted to crystalline **7** without further purification.

6,6′-Diazido-6,6′-dideoxysucrose (7). A mixture of crude 6,6′-diazido-6,6′-dideoxy-1′-*O*-tripsylsucrose pentaacetate (**5**, 2.04 g, 2.35 mmol), sodium benzoate (3.38 g, 23.5 mmol), and HMPA (35 mL) was stirred at 105–110 °C for 16 h. The mixture was then cooled in an ice bath and H_2O was added to dissolve the NaOBz. The resulting thick orange solution was poured into a stirring mixture of ice and 20% NaCl solution (1100 mL). The resulting aqueous mixture was extracted with EtOAc. The EtOAc layer was washed with 4% NaCl solution (twice) and H_2O and dried (Na_2SO_4). The dried EtOAc solution was evaporated to an orange gum, 1.88 g (crude 6,6′-diazido-1′-*O*-benzoylsucrose pentaacetate). This gum was dissolved in dry MeOH (15 mL) with stirring, and the pH of the resulting orange solution was adjusted to pH 9–11 by adding solid sodium methoxide. The reaction was stirred at room temperature for 16 h and then was neutralized by stirring the mixture with IRC 50 (H) (10 mL, 3.5 mequiv/mL) for 1 h. The solution was filtered and evaporated to a yellow solid foam. This foam was dissolved in H_2O (80 mL) and ether and was stirred with IRC 50 (H) resin (washed thoroughly with H_2O, used to convert NaOBz to BzOH) while being continuously extracted with ether for 5 h. The H_2O layer was separated and evaporated at 50 °C to an orange syrup. This syrup was dissolved in absolute EtOH, treated with activated charcoal, and evaporated to a light yellow solid foam, 0.765 g. Crystallization of this foam from acetone yielded 0.305 g of **7**. The mother liquor yielded an additional 0.123 g of **7** for a total yield of 0.428 g (46.4%): mp 168–169 °C; $[\alpha]^{21}_D$ +82° (*c* 1.0, H_2O) [lit.[16] mp 163–164 °C; $[\alpha]_D$ +78.8° (*c* 0.98, H_2O)]. Anal. ($C_{12}H_{20}N_6O_9$) C, H, N.

6,6′-Diamino-6,6′-dideoxysucrose (9). A solution of 6,6′-diazido-6,6′-dideoxysucrose (**7**) (4.42 g, 11.3 mmol) and 10% Pd/C (442 mg) in MeOH (75 mL), water (22 mL), and triethylamine (1.0 mL) was reduced at 45 psi of hydrogen gas in a Parr shaker for 20 h. The mixture was then filtered, and the filtrate was evaporated at 50 °C to a light yellow syrup. This syrup was dissolved in H_2O and filtered through Celite. The filtrate was

Table II. Test Results against Ependymoblastoma in C58BL/6 Mice

Compd no.	Dose,[a] mg/kg	T/C, %
13	50	111
	100	97
	200	148
14	50	97
	100	120
	200	133
Streptozotocin[b]	100	127
	130	144

[a] Given in five injections in saline, ip, on days 1-5. [b] Results from C57BL/6 mice in ref 14.

evaporated to a white solid foam, 4.18 g. The foam was crystallized from H_2O–MeOH to white crystalline **9**: 3.06 g (79.6%); mp 200–201 °C dec; $[\alpha]^{20}_D$ +68° (*c* 0.98, H_2O). Anal. ($C_{12}H_{24}O_9N_2$) C, H, N.

6,6′-Dideoxy-6,6′-di(3-methylureido)sucrose (10). A solution of 6,6′-diamino-6,6′-dideoxysucrose (**9**, 3.06 g, 8.99 mmol) in H_2O (40 mL) was stirred at 0 °C. Methyl isocyanate (1.75 mL, 28.2 mmol) was added and the mixture was stirred at 0 °C for 1 h. Then the mixture was allowed to warm to room temperature (20 min) and was evaporated to a white solid foam. This foam was crystallized from MeOH to white crystalline **10** (MeOH solvate): 4.69 g (85.6% based on 1); mp 207–208 °C dec; $[\alpha]^{21}_D$ +63° (*c* 0.96, H_2O); IR (KBr) 1655 (C=O), 1610 cm^{-1} (CNH); ^1H NMR (D_2O) δ 5.40 (d, 1, J = 3.5 Hz, H-1), 3.38 (s, 3, MeOH CH_3), 2.73 (s, 6, urea CH_3). Anal. ($C_{16}H_{30}N_4O_{11}$·MeOH) C, H, N.

1′,6,6′-Trideoxy-1′,6,6′-tri(3-methylureido)sucrose (12). Crude 1′,6,6′-triamino-1′,6,6′-trideoxysucrose (**11**, 6.92 g, 20.4 mmol) was dissolved in water (50 mL) and cooled with stirring in an ice bath as methyl isocyanate (4.5 mL, 73.4 mmol) was added. The mixture was stirred at ice bath temperature for 1 h and then was allowed to warm to room temperature (1.5 h). Evaporation of the mixture gave an off-white solid foam, 10.9 g. This foam was eluted through a silica gel column (450 g) with MeOH–$CHCl_3$–NH_4OH (2:2:1). Fractions shown by TLC [Analtech silica gel GF on Prescored plates, R_f 0.50, MeOH–$CHCl_3$–NH_4OH (2:2:1) + H_2SO_4 spray and heat] to be pure product were combined and evaporated to a white solid foam, **12**: 6.33 g (60.8%); IR (KBr) 1655 (C=O), 1575 cm^{-1} (CNH); ^1H NMR (D_2O) δ 5.41 (br s, 1, H-1), 2.73 (s, 9, urea CH_3). Anal. ($C_{18}H_{34}N_6O_{11}$·2.5H_2O) C, H, N.

6,6′-Dideoxy-6,6′-di(3-methyl-3-nitrosoureido)sucrose (13). A solution of 6,6′-dideoxy-6,6′-di(3-methylureido)sucrose MeOH solvate (**10**, 1.00 g, 2.05 mmol) was dissolved in ice–water (20 mL) and 0.31 g (4.1 mmol) of nitrogen trioxide was bubbled into the solution. The yellow solution was stirred in an ice bath for 2 h and then was lyophilized for 5 h. The yellow residue was mixed with ice-cold H_2O (10 mL) and relyophilized for 18 h to a light yellow solid. This solid was mixed with acetone (15 mL) and cooled at −20 °C, and crude yellow product was collected by filtration. The filtrate was concentrated in vacuo without heating to approximately 5 mL. This solution was eluted through a silica gel column (100 g) with acetone–MeOH (10:1). Fractions determined by TLC to have pure product [R_f 0.48, acetone–MeOH (10:1)] were combined and evaporated to a yellow syrup. This syrup was dissolved along with the solid product obtained previously in MeOH and evaporated to a yellow, gummy solid. This gummy solid crystallized from acetone to yellow crystalline **13**, 0.580 g. Seeding of other fractions from the column yielded an additional 0.093 g of **13** (total yield 64.1%): mp 220–260 °C, slow decomposition; $[\alpha]^{22}_D$ +52° (*c* 0.97, H_2O); IR (KBr) 1730 (C=O), 1550 (CNH), 1490 cm^{-1} (NN=O); ^1H NMR (MeOH-d_4) δ 5.45 (d, 1, J = 4.0 Hz, H-1), 3.20 (s, 6, nitrosourea CH_3). Anal. ($C_{16}H_{28}N_6O_{13}$) C, H, N.

1′,6,6′-Trideoxy-1′,6,6′-tri(3-methyl-3-nitrosoureido)sucrose (14). A solution of 1′,6,6′-trideoxy-1′,6,6′-tri(3-methylureido)-sucrose (**12**, 1.24 g 2.43 mmol) in ice–water (20 mL) was cooled in an ice bath and nitrogen trioxide (0.55 g, 7.3 mmol) was bubbled into this solution. The yellow mixture was stirred in an ice bath for 2 h and then was lyophilized for 4 h. The yellow solid residue was dissolved in ice–water (15.0 mL) and relyophilized for 17 h. The yellow fluffy solid obtained was crystallized from cold acetone–MeOH to yellow crystalline **14**, 0.470 g. The mother liquor was concentrated at 10 °C to a yellow residue. This residue was eluted through a silica gel (200 g) column with acetone. The fractions containing product [R_f 0.34, acetone–MeOH (2:1)] were combined and evaporated to a yellow solid, 0.874 g. This solid was crystallized from MeOH to more yellow crystalline, **14**: 0.645 g (total yield 76.9%); mp slow dec 200–280 °C; $[\alpha]^{21}_D$ +35° (c 0.98, H_2O); IR (KBr) 1710–1750 (C=O), 1545 (CNH), 1490 cm^{-1} (NN=O); ^1H NMR (D_2O) δ 5.60 (d, 1, J = 3.0 Hz, H-1), 3.26 (s, 9, nitrosourea CH_3). Anal. ($C_{18}H_{31}N_9O_{14}$) C, H, N.

6,6′-Dideoxy-6,6′-di(3-methyl-3-nitrosoureido)sucrose Hexaacetate (15). A solution of 6,6′-dideoxy-6,6′-di(3-methyl-3-nitrosoureido)sucrose (**13**, 2.73 g, 5.33 mmol) was dissolved in dry pyridine (40.0 mL). This solution was stirred in an ice bath and acetic anhydride (5.03 mL, 53.5 mmol) was slowly added. The reaction was left at room temperature for 15 h. Then MeOH was added to the mixture and it was evaporated at 30 °C to a yellow oil. The oil was dissolved in $CHCl_3$ and washed with ice-cold 2 N HCl, ice-cold saturated $NaHCO_3$, and H_2O. The $CHCl_3$ layer was dried (Drierite) and evaporated to a light yellow solid foam, 4.12 g. This foam was crystallized from ether–hexane to yellow solid **15**: 3.56 g (87.5%); mp softens at 72–76 °C and melts at 82–91 °C with gas evolution; $[\alpha]^{20}_D$ +51° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 100 MHz) δ 7.46 (m, 2, NH), 5.66 (d, 1, J = 3.5 Hz, H-1), 3.18 and 3.20 (2 s, 3 each, nitrosourea CH_3), 2.12 (m, 18, acetate CH_3). Anal. ($C_{28}H_{40}N_6O_{19}$) C, H, N.

1′,6,6′-Trideoxy-1′,6,6′-tri(3-methyl-3-nitrosoureido)sucrose Pentaacetate (16). A solution of 1′,6,6′-trideoxy-1′,6,6′-tri(3-methyl-3-nitrosoureido)sucrose (**14**, 2.50 g, 4.18 mmol) was dissolved in dry pyridine (35 mL) and cooled in an ice bath. Acetic anhydride (3.15 mL, 33.4 mmol) was slowly added to this stirring solution. The reaction mixture was left at room temperature for 16 h and then was mixed with MeOH and evaporated at 35 °C to a yellow residue. The residue was dissolved in $CHCl_3$, washed with ice-cold 2 N HCl, ice-cold saturated $NaHCO_3$, and H_2O, dried (Drierite), and evaporated to a yellow solid foam, 3.55 g. The foam was triturated in ether and cooled to −20 °C. The yellow solid which formed was collected by filtration and dried as **16**, 2.22 g. More product was obtained by crystallization of the mother liquor from ether–hexane to give an additional 0.927 g (total yield 93.2%) of **16**: mp softens at 88–89 °C and melts at 98–120 °C with gas evolution; $[\alpha]^{20}_D$ +49° (c 0.98, $CHCl_3$); ^1H NMR ($CDCl_3$, 100 MHz) δ 7.46 (m, 3, NH), 5.66 (d, 1, J = 3.5 Hz, H-1), 3.21 and 3.18 (2 s, 6 and 3, nitrosourea CH_3), 2.09 (m, 15, acetate CH_3). Anal. ($C_{28}H_{41}N_9O_{19}$) C, H, N.

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Synthesis and Preliminary Pharmacological Activity of Aminoalkoxy Isosteres of Glycolate Ester Anticholinergics

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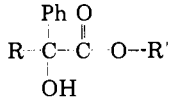
A series of 2-(N-substituted amino)alkoxy-1,1-diphenylethanols was synthesized and evaluated for anticholinergic activity. The compounds differ structurally from the glycolate ester-type anticholinergic compounds by the bioisosteric substitution of a methylene group for the ester carbonyl moiety. The ethers which result from this change have increased lipophilicity compared to their ester isosteres. Compounds in the series have significant anticholinergic activity when tested on isolated rat jejunum or for their ability to inhibit perphenazine-induced catatonia in rats. Structure–activity relationships of the compounds are discussed.

The glycolate esters **1** are a series of agents which have received considerable attention.[1-4] These agents produce a variety of pharmacological effects which are typical of peripheral and central muscarinic receptor blockage.[1,5] As a result of their activities, the glycolates have been reported effective as antispasmodic,[6,7] antidepressant,[8,9] antiparkinsonian,[10] and anticonvulsant[5] drugs.

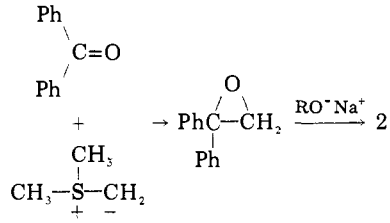


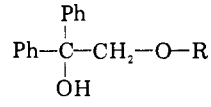
1, R = phenyl or cycloalkyl;
R' = dialkylaminoalkyl or
alkyl heterocyclic amino

Despite their wide variety of activity, the central anticholinergic effects of the glycolates have not been applied clinically. Major problems associated with use of these agents are their unfavorable peripheral to central anticholinergic activity ratios[11] and probably more significant is their potential to produce psychotomimetic episodes.[1] The degree to which useful central activity is associated with the ability of the drugs to block peripheral muscarinic receptors is not clear. Compounds with potent antispasmodic activity will generally produce CNS effects;[12] however, the correlation between the peripheral and central activities is not good.[1,13] Furthermore, there are few studies which attempt to differentiate or separate the different types of CNS effects produced by anticholinergic agents. Thus, in designing new compounds with potentially useful central anticholinergic activity, one should attempt to prepare agents which possess a high degree of central activity compared to their peripheral activity and, if possible, a low degree of psychotomimetic activity.[10]

In an effort to investigate further the structure–activity relationships of anticholinergics we have synthesized and obtained preliminary pharmacological results on a series of substituted aminoalkoxy-1,1-diphenylethanol derivatives **2**. This series differs from the glycolate esters only in the replacement of the ester carbonyl with a methylene moiety. This bioisosteric replacement should result in (1) compounds of greater lipophilicity and thus greater ability to penetrate the blood brain barrier and (2) compounds with a greater duration of action resulting from the inability of serum and tissue esterases to metabolize the ethers. It is conceivable that agents with a longer biological half-life and a greater potential to reach the CNS might result in a favorable shift in their peripheral to central activity ratio.

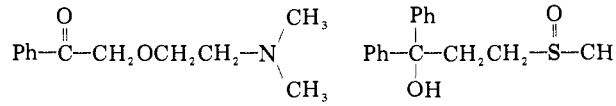
Scheme I





2, R = dialkylaminoalkyl or
alkyl heterocyclic amino

Chemistry. Previous attempts to synthesize these ethers by the classical Williamson method or by addition of phenyllithium to **3**, although partially successful, were tedious and produced poor yields.[14] The alternative route outlined in Scheme I was used to prepare the compounds. The near quantitative yield of 2,2-diphenyloxirane, obtained by reacting trimethylsulfonium ylide[15] with benzophenone, and the commercial availability of a number of amino alcohols made this route extremely attractive. When the alkoxide opening of the oxirane intermediate was carried out at temperatures above 70 °C considerable methylsulfinyl methylide addition occurred to give **4**. The opening of the oxirane to give tertiary alcohols was confirmed by the failure of the products (**2**) to be oxidized by chromic acid[16] and by the singlet carbinol peak observed when the NMR spectra of **2** were determined in anhydrous Me_2SO-d_6.[17]



3 4

Pharmacology. Peripheral anticholinergic (antispasmodic) activity was determined on isolated rat jejunum.