AMINOGLYCOSIDES. V. SYNTHESIS OF GLUCOPYRANOSIDE DERIVATIVES OF NEAMINE MODIFIED IN THE 2-DEOXYSTREPTAMINE RING

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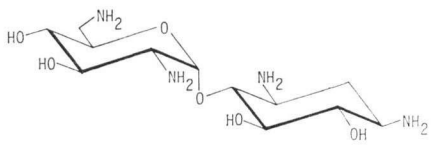
trans-4-Aminocyclohexanol-2′-amino-α-D-glucopyranosides were prepared which are derivatives of neamine having the 3-amino and 5 and 6 hydroxyl groups of the 2-deoxystreptamine ring replaced with hydrogen. The 2′-amino-α-glycosides were synthesized by the method of LEMIEUX using a chloro nitroso dimer of a glucal and appropriately substituted cyclohexanols. Reductive deblocking of the intermediate 2-oximino derivatives afforded paromamine and neamine analogues. Two examples of 2′-amino-α-glycosides with ring-opened variations of the 2-deoxystreptamine aglycone are described. None of the compounds exhibited better *in vitro* antibacterial activity than neamine when compared against Gram-positive and Gram-negative bacteria.

In connection with our earlier studies to determine the effects of structural modifications on the antibacterial activity of aminoglycosides of the amino cyclitol class,[1~3] we have synthesized additional neamine derivatives modified in the 2-deoxystreptamine ring. Although neamine (**1**) exhibits only weak antibacterial activity, it displays lower toxicity than clinically useful pseudotrisaccharides[4~6].

This study was aimed at synthesizing neamine derivatives for biological evaluation in order to improve overall bioactivity or to enhance activity against resistant bacterial strains. Aminoglycosides related to the clinically useful compounds would then be prepared from these neamine derivatives[3,7,8].



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The paromamine analogue (**2**) and the neamine derivatives (**3**~**5**) were prepared from the *trans*-4-aminocyclohexanols (**6**, **10** and **11**). These compounds have the 3-amino and 5- and 6-hydroxyl groups of the 2-deoxystreptamine ring replaced by hydrogen. Using the method of LEMIEUX[9,10] the dimeric 2-nitroso α-D-hexopyranosyl chlorides (**12** and **13**), which were prepared from the requisite glucals[11], were condensed with the protected cyclohexanols in DMF to afford the 2-oximino α-D-hexopyranosides (**14**~**17**). Reductive deblocking of **14**~**17** with palladium and hydrogen in aqueous hydrazine removed the acetyl and carbobenzyloxy groups and gave predominantly the α-D-glucopyranosides (**2**~**5**)[12] as determined by PMR of the crude reaction products. Chromatography over silica gel with the lower phase of chloroform-methanol-concentrated ammonium hydroxide mixtures afforded the pure amino glycosides (**2**~**5**) which were converted to the sulfates.

Access to the *trans*-4-aminocyclohexanols was provided through the catalytic reduction of *p*-acetamidophenol[13] by a modification using rhodium as the catalyst to give *trans*-4-acetamidocyclohexanol

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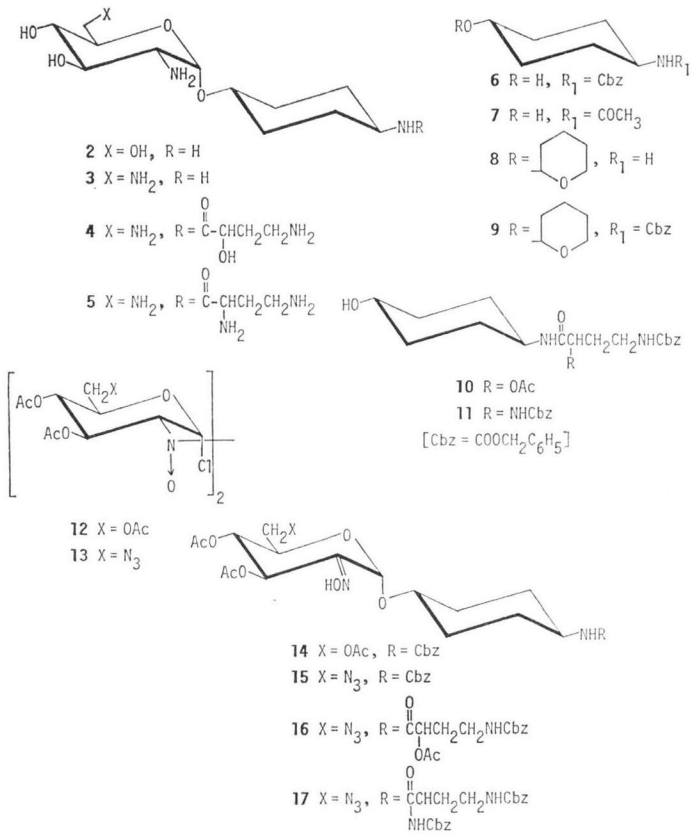
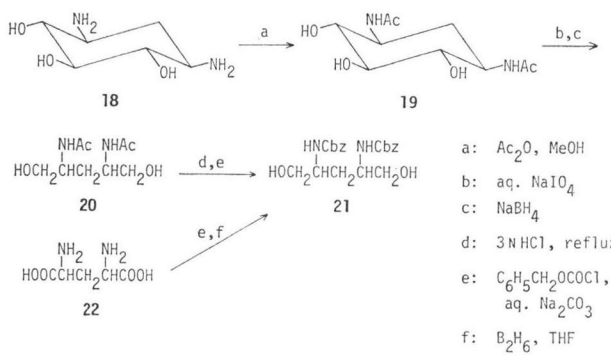
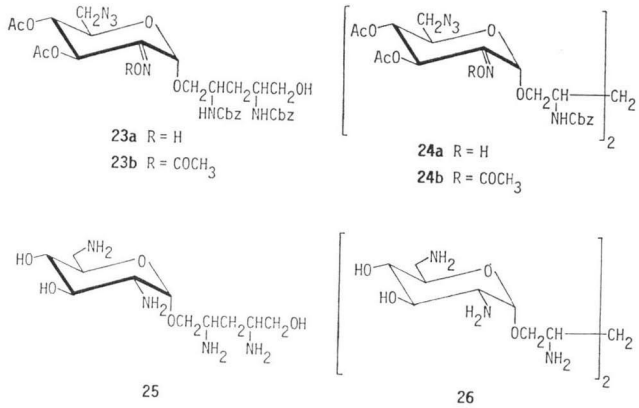


(**7**). The derived (**8**) was treated with L-2,4-N,N′-dicarbobenzyloxyaminobutyric acid and 2-acetoxy-4-carbobenzyloxyaminobutyric acid in the presence of dicyclohexylcarbodiimide, and acid hydrolysis provided the cyclohexanols (**10** and **11**).

Examples of α-glycosides with ring-opened variants of the 2-deoxystreptamine (**18**) aglycone were prepared. Oxidative cleavage of 1,3-bis N,N′-acetyl-2-deoxystreptamine (**19**)[14] with aqueous sodium periodate[15] followed by sodium borohydride reduction of the dialdehyde gave the diol **20** (Scheme **1**) which was converted to the dicarbobenzyloxyamino derivative (**21**).

Scheme 1.





An alternative route to **21** was also successful. 2,4-Diamino glutaric acid (**22**) was obtained from two condensations employing diethyl N-acetyl malonate[16] followed by acid hydrolysis. Diborane reduction of the desired dicarbobenzyloxyamino derivative gave **21**, but the overall yield was lower when compared to the route using 2-deoxystreptamine. When one equivalent of the dimer **13** was reacted with a 50% molar excess of the diol **21**, a 37% yield of the mono adduct **23a** was obtained along with 3.2% of the bis oxime (**24a**). The bis adduct **24a** could be obtained in good yield (58%) by the reaction of 3 equivalents of **13** with 2 equivalents of **21**. Compounds **23a** and **24a** were converted to the 2-oximino acetates (**23b** and **24b**) and reduced first with diborane in THF then with palladium and hydrogen to give the α-D-glucopyranosides (**25** and **26**) in at least 95% configurational purity[12] and in 51% and 39% yield, respectively, after chromatography and purification of the sulfates.

None of six analogues exhibited minimum inhibitory concentrations below 200 μg/ml when tested *in vitro* against four strains of Gram-positive (*Staphylococcus aureus, Streptococcus faecalis*) and eleven strains of Gram-negative bacteria (*Escherichia coli, Klebsiella pneumoniae, Salmonella paratyphi, Shigella paradysenteriae, Pseudomonas aeruginosa, Serratia marcescens, Proteus morganii, Enterobacter aerogenes, Enterobacter cloacae*).

Experimental Section

Column chromatography was carried out on J. T. Baker silica gel (60~200 mesh) and Florisil (Floridin Co., Tallahassee, Florida). Proton magnetic spectra were run on a Varian T-60 instrument using TMS and DSS as standards. Infrared spectra were run on Perkin-Elmer Infracord Model 137. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Thin layer chromatography were run on Uniplate precoated silica gel plates, 250 micron (Analtech, Inc., Newark, Delaware). Solvents were dried over magnesium sulfate. Antibacterial activities were obtained on sulfates by an agar dilution method in Panassay seed medium at pH 8.0.

trans-4-Acetamidocyclohexanol (**7**)

A mixture of 265 g (1.76 mole) of *p*-acetamidophenol, 750 ml of absolute EtOH and 7.5 g of 10% of rhodium on carbon was shaken in an autoclave for 2 hours at 4,000 psi of hydrogen held at 135°C. After 110% of theoretical hydrogen was absorbed, the filtered mixture gave a white solid on evaporation. The crude mixture of *cis* and *trans* isomers was dissolved in 4.5 liters of acetone, concentrated to 2 liters and allowed to stand at 25°C for 18 hours. The white crystals were separated to give 130 g, m.p. 160~163°C. Three additional crystallizations from acetone afforded 81.0 g (29.3%) of **7**, m.p. 161~163°C (Lit.[18] m.p. 165~167°C).

trans-4-Carbobenzyloxyaminocyclohexanol (**6**)

A solution of 9.2 g (0.059 mole) of **7**, 11.3 g (0.059 mole) of *p*-toluenesulfonic acid hydrate[17] and 10 ml of H_2O was refluxed (oil bath at 130°C) for 18 hours. The mixture was cooled, basified to pH 7.5~8.0 with 20% NaOH solution, sodium carbonate (15 g) was added, the solution was cooled to 0°C and a solution of 15 ml (18 g, 0.11 mole) of benzyl chloroformate in 25 ml of acetone was added. In a short time a precipitate appeared. The suspension was stirred at 0°C for 1 hour, an additional 3 ml of benzyl chloroformate was added and stirring was continued for 1 hour at 25°C. After cooling the solid was collected, dissolved in acetone - H_2O (9: 1) and diluted to the cloud point with H_2O to give 11.2 g (69%) of **6**, m.p. 158~160°C. An analytical sample was prepared from acetone, m.p. 159~160.5°C.

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62.
Found: C, 67.57; H, 7.92; N, 5.67.

trans-N-Carbobenzyloxy-4-tetrahydropyranyloxycyclohexylamine (**9**)

A suspension of 8.9 g (0.036 mole) of **6** in 100 ml of dry THF and 25 ml of dihydropyran with 200mg of *p*-toluenesulfonic acid hydrate was stirred for 4 hours. The resulting clear solution was treated with powdered K_2CO_3 (10 g), stirred for 10 minutes and partitioned between H_2O and $CHCl_3$. The organic layer was dried and evaporated to a white solid (9.4 g, 79%). A crystallization from EtOH (containing a few drops of pyridine) followed by a recrystallization from acetone gave **9**, m.p. 106~108°C.

Anal. Calcd. for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20.
Found: C, 68.84; H, 8.55; N, 4.09.

trans-4-Carbobenzyloxyaminocyclohexyl 3,4,6-tri-O-acetyl-2-oximino-α-D-arabino-hexopyranoside (**14**)

The directions of LEMIEUX[10] were followed to prepare **12**. Into 50 ml of sieve-dried EtOAc was bubbled 6.35 g (0.097 mole) of nitrosyl chloride. This solution was added dropwise over 30 minutes under nitrogen at −50~−40°C to a solution of 24 g (0.097 mole) of 3,4,6-tri-O-acetyl-D-glucal (Aldrich Chem. Co.) in 200 ml of dry EtOAc. After stirring an additional hour at −45°C and then an hour at 25°C, the solvent was evaporated at 25°C to provide a white solid. This was dissolved in 75 ml of $CHCl_3$ (EtOH-free) and hexane was added to precipitate the solid dimeric **12** (22.0 g, 74%), m.p. 128~131°C (Lit.[10] m.p. 129~130°C).

The dimer **12** (6.75 g, 0.01 mole) and 5.54 g (0.02 mole) of **6** in 40 ml of dry DMF was stirred at 40°C for 18 hours and the solvent was evaporated at 45°C (2 mm) to give a brownish syrup. A TLC on silica gel with 10% MeOH in benzene showed one major product. Chromatography on 400 g of Florisil with a 1~5% gradient of MeOH in CH_2Cl_2 gave 7.8 g (71%) of **14**. A crystallization from ether-hexane provided **14** with a m.p. 69~72°C; $[\alpha]_D^{25}$ +64.0° (*c* 1.0, $CHCl_3$).

Anal. Calcd. for $C_{26}H_{34}N_2O_{11}$: C, 56.72; H, 6.22; N, 5.09.
Found: C, 57.11; H, 6.60; N, 5.01.

trans-4-Carbobenzyloxyaminocyclohexyl 3,4-di-O-acetyl-6-azido-2-oximino-6-deoxy-α-D-arabino-hexopyranoside (**15**)

A solution of 0.765 g (3 mmole) of 3,4-di-O-acetyl-6-azido-6-deoxy-D-glucal[11,18] in 5 ml of dry EtOAc was treated first at −78°C with a 10% excess of a 10% solution of nitrosyl chloride in EtOAc and worked up as described above. The crude dimer **13** was dissolved in 10 ml of dry DMF and stirred with 0.6 g (2.4 mmole) of **6** for 18 hours at 25°C. The solvent was evaporated at 35°C under vacuum and the residue chromatographed over Florisil with a cyclohexane - EtOAc gradient to give 0.56 g (44%) of syrupy **15**, $[\alpha]_D^{25}$ +36.7° (*c* 0.5, $CHCl_3$); IR (Nujol) 4.74 μ (N_3).

Anal. Calcd. for $C_{24}H_{31}N_5O_9$: C, 54.03; H, 5.86; N, 13.13.
Found: C, 54.46; H, 6.10; N, 13.06.

trans-4-(2-Acetoxy-4-N-carbobenzyloxyaminobutyroyl)cyclohexyl 3,4di-O-acetyl-6-azido-2-oximino-6-deoxy-α-D-arabino-hexopyranoside (**16**)

A solution of 2.3 g (3.6 mmole) of **13**, 1 g (2.6 mmole) of *trans*-4-(2-acetoxy-4-N-carbobenzyloxy-aminobutyroyl)cyclohexanol (**10**) and 20 ml of dry DMF was stirred at 25°C for 18 hours. The mixture was diluted with 250 ml of ice H_2O, extracted with EtOAc, and the organic extracts were washed with brine, dried and concentrated to 4.1 g of syrup. Chromatography over 120 g of Florisil with a gradient

from 8 to 1 of cyclohexane-EtOAc to 100% EtOAc gave 1.51 g (67%) of **16**. A precipitation from EtOAc-hexane gave a m.p. 83~88°C; $[\alpha]_D^{25}$ +24.9° (*c* 1, $CHCl_3$); IR (Nujol) 4.74 μ (N_3).

Anal. Calcd. for $C_{30}H_{40}N_6O_{12}\cdot 0.5H_2O$: C, 52.55; H, 6.03; N, 12.26.
Found: C, 52.29; H, 5.79; N, 12.56.

trans-4-(L-2, 4-Bis N, N'-dicarbobenzyloxyaminobutyroyl) cyclohexyl 3, 4-di-O-acetyl-6-azido-2-oximino-6-deoxy-α-D-arabino-hexopyranoside (**17**)

A solution of 3 g (4.7 mmole) of the dimer **13**, 1.62 g (3.35 mmole) of the alcohol **11** and 15 ml of dry DMF was reacted and worked up as described in previous examples. The crude viscous product (5.3 g) was chromatographed over 150 g of Florisil using a gradient of 50~75% of EtOAc in petroleum ether. The homogeneous cuts (1.58 g, 61%) were crystallized from acetone-ether to give the white **17**, m.p. 130~134°C; $[\alpha]_D^{25}$ +21.8° (*c* 1, $CHCl_3$), IR (Nujol) 4.75 μ (N_3).

Anal. Calcd. for $C_{36}H_{45}N_7O_{12}$: C, 56.32; H, 5.91; N, 12.77.
Found: C, 56.71; H, 5.92; N, 12.54.

trans-4-(2-Acetoxy-4-N-carbobenzyloxyaminobutyroyl)cyclohexanol (**10**)

A mixture of 3.7 g (0.0186 mole) of *trans*-4-(2-tetrahydropyranyloxy)cyclohexylamine (**8**) [prepared from *trans*-4-N-carbobenzyloxyamino-1-(2-tetrahydropyranyloxy) cyclohexane (**9**) *via* catalytic hydrogenation with palladium on charcoal in EtOAc containing a trace of pyridine], 5.79 g (0.0186 mole) of crude 2-acetoxy-4-carbobenzyloxyaminobutyric acid [prepared from 4-amino-2-hydroxybutyric acid[19] *via* the 4-carbobenzyloxy derivative, m.p. 89~91°C (from C_6H_6-petroleum ether) followed by Ac_2O-pyridine at 25°C], 3.83 g (0.0186 mole) of dicyclohexylcarbodiimide and 50 ml of dry THF was stirred at 25°C for 18 hours. The solid was filtered, the filtrate evaporated and the residue dissolved in ether and washed with cold dilute HCl, H_2O, 5% $NaHCO_3$ solution and brine. The ether was evaporated and the residue redissolved in 25 ml of 80% acetic acid. The solution was heated on the steam bath for 4 hours, diluted with brine, extracted with EtOAc and washed well with $NaHCO_3$ solution. The dried, concentrated product was chromatographed over 150 g of Florisil with a 1~5% of MeOH in $CHCl_3$ gradient to give 1.05 g (15%) of **10**. An analytical sample was crystallized from acetone-ether-hexane to give a m.p. 164~165°C.

Anal. Calcd. for $C_{20}H_{28}N_2O_6$: C, 61.21; H, 7.19; N, 7.14.
Found: C, 61.14; H, 7.54; N, 6.98.

trans-4-(L-2,4-Dicarbobenzyloxyaminobutyroyl)cyclohexanol (**11**)

A solution of 6.1 g (0.016 mole) of L-2,4-dicarbobenzyloxyaminobutyric acid[20,21], 1.82 g (0.016 mole) of N-hydroxysuccinimide and 75 ml of dry THF was stirred for 2 hours at 25°C, the urea filtered, the filtrate concentrated and the residue dissolved in 20 ml of dry DMF. A solution of 4.6 g (0.023 mole) of crude **8** (prepared as in the procedure for **10**) in 50 ml of THF was added and the mixture was stirred at 25°C for 18 hours, diluted with H_2O and worked up and deblocked by the procedure described for **10**. The crude product (6 g) was an off-white solid. A crystallization from acetone-ether gave 4.3 g (56%) of **11**, m.p. 180~184°C. Another crystallization from acetone gave a m.p. 192~194°C.

Anal. Calcd. for $C_{26}H_{33}N_3O_6$: C, 64.58; H, 6.88; N, 8.69.
Found: C, 64.29; H, 6.71; N, 8.80.

2,4-Bis (carbobenzyloxyamino)pentane-1,5-diol (**21**)

2-Deoxystreptamine (18 g, 0.11 mole) was suspended in 200 ml of MeOH and 40 ml of acetic anhydride was added at 25°C. After a short time the neamine went into solution and then the acetylated product began to separate. The suspension was stirred for 2 hours, 300 ml of ether was added and after cooling 1,3-di-N-acetyl-2-deoxystreptamine (**19**)[14] was filtered to give 23.5 g (87%), m.p. 295°C.

To a solution of 1.71 g (8 mmole) of sodium periodate in 50 ml of H_2O was added portionwise 0.98 g (4 mmole) of **19** at 25°C. The reaction was monitored with a pH meter and showed a rapid drop from pH 4.5 to 3.2. The pH was maintained at 3.5~4.0 by the periodic addition of saturated aqueous Na_2CO_3 solution. After 3 hours at 25°C a saturated solution of barium chloride was added until no more solid precipitated. The barium salts were filtered and the aqueous filtrate was adjusted to pH 6.5 with 10% NaOH solution. Then 1 g of $NaBH_4$ was added in portions (precipitate) and after 1 hour an additional 0.5 g of $NaBH_4$ was added. The mixture was stirred an additional 2 hours, adjusted to pH 6

with acetic acid and the solution was concentrated *in vacuo* to give crude, syrupy 2,4-bis(N-acetylamino) pentane-1,5-diol (**20**). This syrup was dissolved in 50 ml of 3 N HCl, refluxed for 3 hours, concentrated to a small volume *in vacuo* and adjusted to pH 7 with 20% NaOH solution. Then 1.8 g of Na_2CO_3 was added, the mixture cooled in ice H_2O and a solution of 1.7 g (0.01 mole) of benzyl chloroformate in 10 ml of dioxane was added. After 0.5 hour the cooling bath was removed and the mixture was stirred at 25°C for 4 hours. The suspension was adjusted to pH 6 with acetic acid and extracted with 5% of MeOH in EtOAc. The organic extracts were washed with 5% $NaHCO_3$ solution and brine, dried and concentrated to a white solid. A crystallization from EtOAc gave 950 mg (59%) of **21**, m.p. 132~134°C.

Anal. Calcd. for $C_{21}H_{26}N_2O_6$: C, 62.67; H, 6.51; N, 6.96.
Found: C, 62.50; H, 6.72; N, 6.98.

1-(2,4-Biscarbobenzyloxyamino-5-hydroxy)pentyl 3,4-di-O-acetyl-6-azido-2-oximino-6-deoxy-α-D-arabino-hexopyranoside (**23a**)

A solution of 0.01 mole of **13**, 6.03 g (0.015 mole) of **21** and 50 ml of dry DMF (distilled from P_2O_5) was stirred for 18 hours at room temperature and worked up as described above. TLC (3:2, EtOAc-cyclohexane) of the crude product showed a major and a minor component and the excess **21**. This mixture was suspended in 50 ml of warm EtOAc and 2.1 g of the diol **21** was filtered off. The concentrated filtrate was chromatographed over 400 g of Florisil with a petroleum ether - EtOAc gradient. In the early cuts with 1:1 petroleum ether - EtOAc the bis product **24a** (310 mg, 3.2%) was obtained. With 2:3 petroleum ether - EtOAc the major product **23a** (2.52 g, 37%) was isolated as a foam, $[\alpha]_D^{25}+41.8°$ (*c* 1, $CHCl_3$); IR (Nujol) 4.74 μ (N_3); NMR ($CDCl_3$) δ 5.91 (s, 1, H-1).

Anal. Calcd. for $C_{31}H_{33}N_6O_{12}$: C, 54.22; H, 5.58; N, 12.24.
Found: C, 53.98; H, 5.64; N, 12.08.

1,5-Bis[2,4-bis (carbobenzyloxyamino) pentyl 3,4-di-O-acetyl-6-azido-2-oximino-6-deoxy-α-D-arabino-hexopyranoside (**24a**)

The procedure for the preparation of **23a** was followed except the proportions of reactants were changed. From 4.3 g (0.0168 mole) of **13** and 2.26 g (0.0056 mole) of **21a** in 60 ml of DMF there was obtained, after chromatography over 200 g of Florisil with a solvent system of 2:1 to 1:1 of petroleum ether - EtOAc, 3.13 g (58%) of **24a** as an amorphous solid, m.p. 85~90°C; $[\alpha]_D^{25}+68.9°$ (*c* 1, $CHCl_3$); IR (film) 4.75 μ (N_3); NMR ($CDCl_3$) δ 5.90 (d, 2, H-1, H-1').

Anal. Calcd. for $C_{41}H_{50}N_{10}O_{18}$: C, 50.72; H, 5.19; N, 14.43.
Found: C, 50.56; H, 5.30; N, 14.76.

trans-4-Aminocyclohexyl 2-amino-2-deoxy-α-D-glucopyranoside (**2**)

The oximino derivative **14** (550 mg, 1 mmole) was dissolved in 30 ml of 95% EtOH containing 1 ml of 64% aqueous hydrazine[12] and was shaken on the Parr apparatus with 0.5 g of 10% palladium/carbon for 18 hours under 3 atmospheres of hydrogen. The filtered, concentrated residue was chromatographed over 20 g of silica gel with the lower layer of a 2:1:1 $CHCl_3$ - MeOH - conc.NH_4OH mixture taking 10 ml cuts. The homogeneous fractions afforded 80 mg (21%) of **2**. This was dissolved in a minimum amount of H_2O, acidified with dil.H_2SO_4 to pH 3.5 and diluted with acetone to give the powdery sulfate of **2**, m.p. 239~241°C; $[\alpha]_D^{25}+84.2°$ (*c* 0.5, H_2O); NMR (D_2O) δ 5.25 (d, 1, J=4 Hz, H-1).

Anal. Calcd. for $C_{12}H_{24}N_2O_5 \cdot H_2SO_4 \cdot H_2O$: C, 37.59; H, 7.10; N, 7.31.
Found: C, 37.95; H, 7.59; N, 7.00.

trans-4-Aminocyclohexyl 2,6-diamino-2,6-dideoxy-α-D-glucopyranoside (**3**)

Compound **15** was deblocked, reduced and purified by the procedure used for the preparation of **2**. From 1 mmole of **15** and after column chromatography over silica gel there was obtained 46 mg (10%) of **3** which was converted to the sulfate and precipitated from H_2O - EtOH with acetone-ether to give m.p. 245~248°C; $[\alpha]_D^{25}+53.4°$ (*c* 0.5, H_2O); NMR (D_2O) δ 5.24 (d, 1, J=4.0 Hz, H-1).

Anal. Calcd. for $C_{12}H_{25}N_3O_4 \cdot 1.5\ H_2SO_4 \cdot H_2O \cdot 0.5\ C_2H_5OH$: C, 33.69; H, 2.18; N, 9.07; S, 10.38.
Found: C, 33.99; H, 6.78; N, 8.98; S, 10.21.

trans-4-(4-Amino-2-hydroxybutyroyl)cyclohexyl 2,6-diamino-2,6-dideoxy-α-D-glucopyranoside (**4**)

Using the procedure described for **2**, from 1.15 g (1.7 mmole) of **16** and after chromatography over

40 g of silica gel with the lower phase of 1:1:1 $CHCl_3$ - MeOH - conc.NH_4OH 210 mg (24%) of **4** was isolated. A precipitation of the derived sulfate from H_2O - EtOH - acetone gave m.p. 230~240°C; $[\alpha]_D^{25}$ +35° (*c* 0.5, H_2O); NMR (D_2O) δ 5.29 (d, 1, J=3.5 Hz, H-1).

Anal. Calcd. for $C_{16}H_{32}N_4O_6 \cdot 1.5H_2SO_4 \cdot H_2O \cdot C_2H_5OH$: C, 36.79; H, 7.38; N, 9.53.
Found: C, 37.18; H, 7.42; N, 9.52.

trans-4-(L-2,4-Diaminobutyroyl)cyclohexyl 2,6-diamino-2,6-dideoxy-α-D-glucopyranoside (**5**)

From the procedure described above, compound **5** was obtained from **17** in 38% yield. The sulfate of **5** had m.p. 229~233°C (from H_2O - EtOH - acetone); $[\alpha]_D^{25}$ +52° (*c* 0.7, H_2O); NMR (D_2O) δ 5.35 (d, 1, J=3.4 Hz, H-1).

Anal. Calcd. for $C_{16}H_{33}N_5O_5 \cdot 2H_2SO_4 \cdot 0.5H_2O \cdot C_2H_5OH$: C, 34.50; H, 7.08; N, 11.17.
Found: C, 34.48; H, 6.49; N, 10.95.

1-(2,4-Diamino-5-hydroxy)pentyl 2,6-diamino-2,6-dideoxy-α-D-glucopyranoside (**25**)

Compound **23a** (2.3 g) was acetylated with 10 ml of pyridine and 5 ml of acetic anhydride at 25°C for 18 hours. Ice H_2O was added and after 1 hour the mixture was extracted with EtOAc and then washed with cold dil. HCl, H_2O, 5% $NaHCO_3$ solution and brine. The dried solution was concentrated to 2.2 g of the pale yellow, syrupy oximino acetate (**23b**). The NMR spectrum showed the proper ratio of acetate protons to benzylic protons. The crude **23b** was dissolved in 50 ml of dry THF and treated dropwise at 0°C (under nitrogen) with 55 ml of 1 M BH_3[12] in THF. The solution was stirred for 18 hours at 25°C and the excess BH_3 destroyed by careful addition of MeOH. The solvents were evaporated, and the residue was azeotroped three times with additional MeOH containing 3 drops of acetic acid. The residual colorless syrup was dissolved in 50 ml of 9:1 MeOH - acetic acid and shaken for 18 hours on the Parr apparatus at 60 psi of hydrogen with 2.5 g of 10% of palladium on carbon. The filtered mixture was concentrated, and the residue azeotroped several times with toluene to give a clear colorless syrup. This was dissolved in a small amount of H_2O, adjusted to pH 3.5 with dil. H_2SO_4, concentrated to a small volume *in vacuo* and diluted with 1:1 MeOH - acetone. On cooling at −30°C the whitish sulfate of **25** (748 mg, 19%) was isolated and dried at 110°C for 18 hours to give m.p. 260~265°C; $[\alpha]_D^{25}$ +46.2° (*c* 1, H_2O); NMR (D_2O) δ 5.39 (d, 1, J=4.0 Hz, H-1).

Anal. Calcd. for $C_{11}H_{26}N_5O_5 \cdot 2H_2SO_4 \cdot 2CH_3OH$: C, 27.77; H, 6.81; N, 9.96.
Found: C, 27.93; H, 6.44; N, 10.25.

1,5-Bis(2,4-diamino)pentyl 2,6-diamino-2,6-dideoxy-α-D-glucopyranoside (**26**)

The procedure used for the preparation of **25** was followed. Compound **24a** (3.3 g, 3.4 mmole) was converted to the oximino acetate (**24b**) and sequentially reduced to give a crude product whose TLC on silica gel with 1:1 2-propanol-28% NH_4OH showed one major component (Rf 0.41). The sulfate was prepared and fractionally crystallized four times from H_2O - MeOH - acetone to give 1.2 g (49%) of the sulfate of **26** as a white powder, m.p. 260°C d.; $[\alpha]_D^{25}$ +66° (*c* 1, H_2O); NMR (D_2O) δ 5.35 (d, 2, J=3.4 Hz, H-1, H-1′).

Anal. Calcd. for $C_{17}H_{38}N_6O_8 \cdot 3H_2SO_4 \cdot CH_3OH$: C, 27.68; H, 6.19; N, 10.76; S, 10.76.
Found: C, 27.92; H, 6.41; N, 10.44; S, 11.62.

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