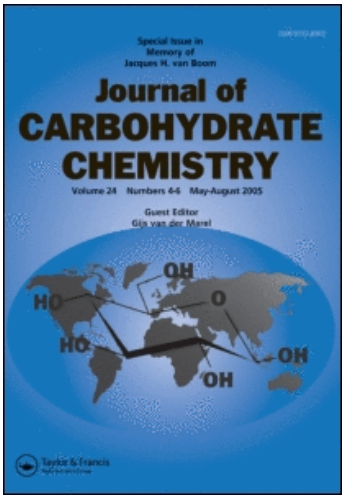

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SYNTHESIS OF GENTAMINE C_{1a} FROM NEAMINE USING IONIC DISPLACEMENT AND RADICAL ELIMINATION METHODS

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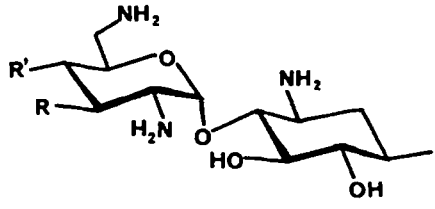
ABSTRACT

The conversion of tetra-N-benzyloxycarbonyl-5,6-O-cyclohexylidene neamine (8) into the corresponding olefin 13 has been investigated by three methods. Application of the Tipson-Cohen procedure via the dimesylate 10 gave a low yield (22%), as did the reaction of the diol 8 with triphenylphosphine-iodine-imidazole reagent (42%). Contrastingly, reductive radical elimination via the dixanthate 11 gave a synthetically useful yield (64%) without any chromatographic purification.

INTRODUCTION

The pseudodisaccharides neamine (1), gentamine C_{1a} (2) and tobramine (3) are subunits of the clinically most useful naturally occurring aminocyclitol glycoside antibiotics,[1] which themselves are weaker antimicrobial agents,[2] but less toxic than the typical pseudotrisaccharides. The recently isolated fortimicins[3] and related naturally occurring pseudodisaccharides,[3,4] however, exhibit highly desirable and promising biological properties.



1 Neamine R = R'=OH

2 Gentamine C_{1a} R=R'=H

3 Tobramine R=H, R'=OH

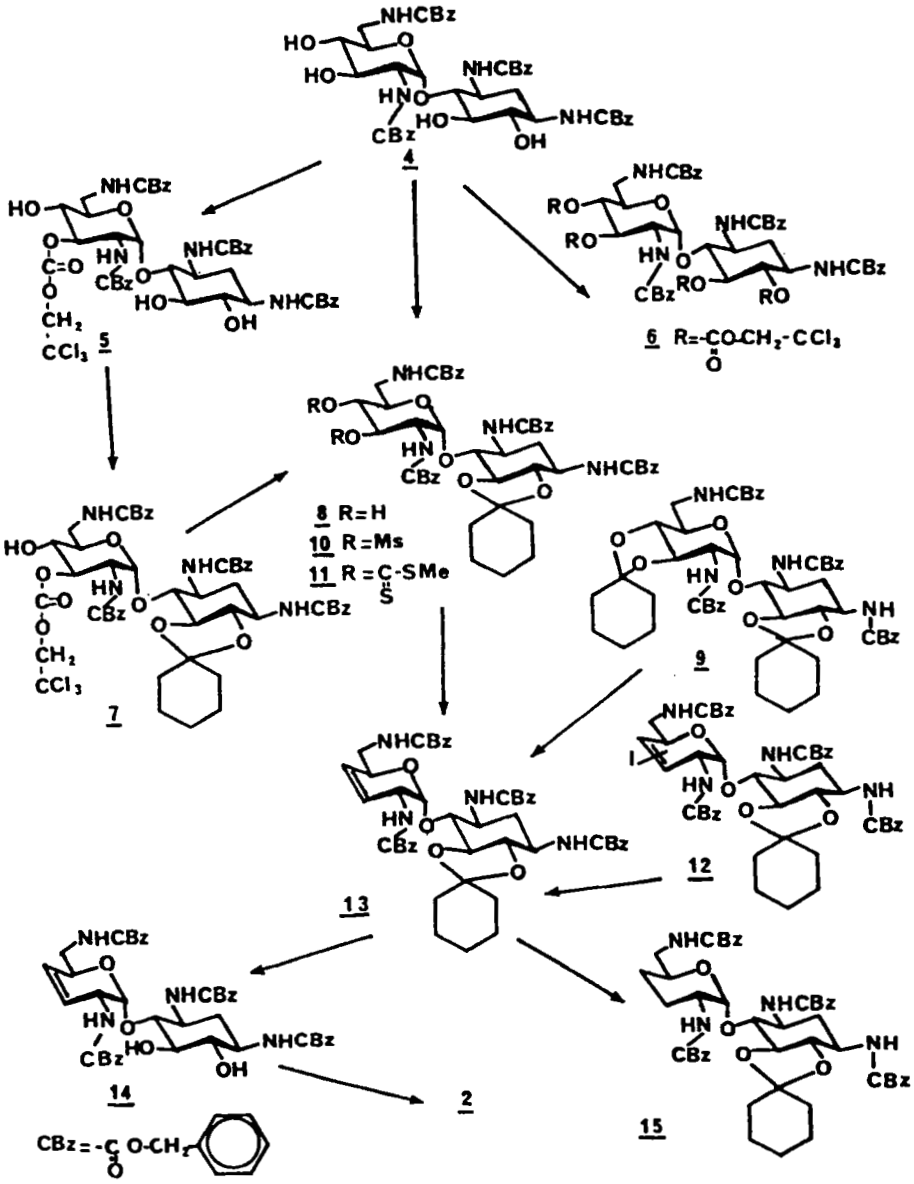
Neamine is readily available from the neomycin and paromomycin type antibiotics; however, gentamine, an ideal starting molecule for further structural modification, is not easily accessible.

In connection with our earlier studies[6] to determine the effects of structural modification on the antibacterial activity of pseudodisaccharides, we report here the preparation of gentamine C_{1a} from neamine.

RESULTS AND DISCUSSION

Protection of the four free amino groups present in neamine (1), using benzylchloroformate and sodium bicarbonate in 70% aqueous methanol, gave[7] tetra-N-benzyloxycarbonyl neamine (4) in 88% yield.

Two approaches were then examined to obtain tetra-N-benzyloxycarbonyl-5,6-O-cyclohexylideneneamine (8). In the first method, selective protection of the 3'-hydroxy group present in 4 was considered. Application of the literature procedure,[8] i.e. trichloroethyl chloroformate (5 equiv.) in dry pyridine at -5 °C for 7 hours led to the fully protected compound, tetra-N-benzyloxy -tetra-O-trichloroethoxycarbonylneamine (6), in 69% yield. However, a smaller excess of trichloroethyl chloroformate (1.3 equiv.) provided the desired tetra-N-benzyloxycarbonyl-3'-O-trichloroethoxycarbonylneamine (5) in a yield of 60%. Treatment of 5 with 1,1-



dimethoxycyclohexane in dry DMF in the presence of catalytic quantity of p-toluenesulphonic acid (80 °C under reduced pressure for 2 h) gave tetra-N-benzyloxycarbonyl-3'-O-trichloroethoxycarbonyl-5,6-O-cyclohexylideneneamine (7) in 83% yield. Subsequent reaction of 7 with ammonia in aqueous methanol yielded 8 in 95% yield. The second route to 8 employed selective acetalization of the 5,6-diol present in 4. When 4 was reacted with 1,1-dimethoxycyclohexane under the same conditions as those previously mentioned, followed by reaction with methanol at 40 °C for one hour, 8 was obtained directly as the major product in 61% yield. In addition, a small amount of tetra-N-benzyloxycarbonyl-3',4'-5,6-di-O-cyclohexylideneneamine (9) was also obtained which could be readily removed by trituration with ether.

It was envisaged that the remaining transformation could be achieved via the key intermediate, tetra-N-benzyloxycarbonyl-3',4'-dideoxy-3'-eno-5,6-O-cyclohexylideneneamine (13). For its preparation three methods were investigated, starting with the diol 8.

The strategies examined were that of Tipson and Cohen,[9] reductive radical elimination[10-12] and the procedure of Garegg and Samuelsson,[13] which had been previously used for the introduction of unsaturation in the monosaccharide and antibiotics field.

The ionic displacement route based upon the method of Tipson and Cohen, began with the mesylation of 8 to give tetra-N-benzyloxycarbonyl-3',4'-di-O-mesyl-5,6-O-cyclohexylideneneamine (10) in 93% yield. This compound was heated with anhydrous sodium iodide and zinc dust in dry DMF (130 °C, 6 hours), and after chromatographic purification, 13 was obtained in 21% yield. We cannot, of course, exclude the possibility that a diffe-

rent specimen of zinc dust might give much better results.

The method of reductive radical elimination[10-12] involved the preparation of an intermediate, tetra-N-benzyloxycarbonyl-3',4'-O-[(methylthio)thiocarbonyl]-neamine (11), available in 91% yield from 8 by treatment with a mixture of carbon disulphide, aqueous sodium hydroxide and methyl iodide in DMSO at 15 °C. After reduction of 11 with tri-n-butyltin hydride in the presence of azobis(acetonitrile) in refluxing dry toluene or xylene for 3 hours, olefin 13 crystallized from the reaction mixture in 64% yield.

Finally, another ionic displacement procedure originally described by Garegg and Samuelsson[13] was investigated. When 8 was treated with triphenylphosphine (4 equiv.), imidazole (4 equiv.) and iodine (2.55 equiv.) in refluxing dry toluene for 1.5 hours, 13 was obtained in 42% yield. In addition to this compound, a second minor product, monoiodotetra-N-benzyloxycarbonyl-3',4'-dideoxy-3'-eno-5,6-O-cyclohexylideneneamine (12), was also isolated in 22% yield. Whilst the position of iodine substitution has not been determined, confirmation of the identity of 12 was made by its conversion to 13 upon treatment with tri-n-butyltin hydride.

Deprotection of 13 was accomplished using 80% acetic acid-water at 60 °C for 2 hours to afford tetra-N-benzyloxycarbonyl-3',4'-dideoxy-3'-eno-neamine (14) in 95% yield.

Low-pressure catalytic hydrogenation of 13 using platinum oxide as catalyst provided tetra-N-benzyloxycarbonyl-5,6-O-cyclohexylidene gentamine (15) in 61% yield. The simultaneous hydrogenation and hydrogenolysis of 13 and 14 were achieved using excess, 5% palla-

dium/charcoal as catalyst for 40 hours, which on subsequent acetal deprotection gave the free base 2. When 2 was treated with sulphuric acid, a hydroscopic gentamine C_{1a} sulphate was obtained in good yield, identical in all respects with authentic material obtained by methanolysis[14] of the gentamincin C complex.

EXPERIMENTAL

Melting points were determined with a Kofler hot stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 257 spectrometer, and ^{1}H NMR spectra were measured in deuterochloroform solution with tetramethylsilane as the internal standard, unless otherwise stated. Mass spectra were recorded with an A.E.I. MS9 instrument. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. All solvents and reagents were purified and dried by standard techniques.

Attempted preparation of tetra-N-benzyloxycarbonyl-3'-trichloroethoxycarbonylneamine (5). The conditions employed were those described in the literature[8] as leading to 5. To a solution of 4 (0.21 g, 0.24 mmol) in dry pyridine (2 mL) trichloroethyl chloroformate (0.25 g, 1.18 mmol) was added at -5 °C with stirring. After 7 h the mixture was poured into water to give a precipitate (0.463 g). Purification by preparative TLC (eluant : EtOAc/hexane 1:1) gave tetra-N-benzyloxycarbonyl-tetra-O-trichloroethoxycarbonylneamine (6) as a white, amorphous solid (0.262 g, 69%): mp 106-8 °C; $[\alpha]_D^{20}$ + 26.06° (c 1.42, $CHCl_3$); NMR ($CDCl_3$) δ 7.25 (20H, 4 x $COOCH_2$-$C_6\underline{H}_5$), 5.03 (8H, 4 x $COOC\underline{H}_2$-C_6H_5), 4.70, 4.57 (4H, 4H, 4 x $COOC\underline{H}_2$-CCl_3).

Anal. Calcd. for $C_{56}H_{54}N_4O_{22}Cl_{12}$: C, 43.02; H, 3.67; N, 3.58; Cl, 27.18. Found: C, 43.00; H, 3.67; N, 3.64; Cl, 27.19.

In view of the failure of the conditions described in the literature to provide the prescribed compound 5, the preparation was repeated using a smaller excess of trichloroethyl chloroformate (i.e. 1.3 equiv. in place of 5 equiv.).To a solution of 4 (2.0 g, 2.33 mmol) in dry pyridine at -5 °C was added dropwise with stirring trichloroethyl chloroformate (0.64 g, 3.03 mmol). After 2.5 h. at -5 °C, workup as previously described gave a white solid (2.5 g) which was purified by column chromatography on silica gel (eluant : EtOAc/hexane 6:4) to give tetra-N-benzyloxycarbonyl-3'-trichloroethoxycarbonylneamine (5) (1.47 g, 61%): mp 170-2 °C; $[\alpha]_D^{20}$ + 32.3° (c 0.65, $CHCl_3$) [lit.[8] mp 165-8 °C; $[\alpha]_D^{20}$ 33° ($CHCl_3$)]; NMR ($CDCl_3$) δ 7.09 (20H, 4 x $COOCH_2$-C_6H_5), 4.98 (8H, 4 x $COOCH$ -C_6H_5), 4.53 (2H, $COOCH_2$-CCl_3).

Anal. Calcd. for $C_{47}H_{51}N_4O_{16}Cl_3$: C, 54.58; H, 4.97; N, 5.42; Cl, 10.28. Found: C, 54.00; H, 4.89; N, 5.39; Cl, 10.42.

Tetra-N-benzyloxycarbonyl-3'-O-trichloroethoxycarbonyl-5,6-O-cyclohexylideneneamine (7). A solution of 5 (1.01 g, 0.98 mmol) and 1,1-dimethoxycyclohexane (1.2 mL) in dry DMF (10 mL) containing a catalytic quantity of anhydrous p-toluenesulphonic acid (0.077 g) was heated to 80-85 °C under reduced pressure with stirring for 2 h. After cooling the product was precipitated by pouring the solution into sodium bicarbonate solution. The crude material was filtered, washed with water and dried (1.33 g). Purification by chromatography

on silica gel (eluant $CHCl_3$/MeOH/Et_3N 5:0.15:0.031) gave 7 as a white, amorphous solid (0.91 g, 83% yield): mp 96-8 °C; $[\alpha]_D^{20}$ + 15.93° (c 1.13, $CHCl_3$); NMR ($CDCl_3$) δ 7.20 (20H, 4 x $COOCH_2$-C_6H_5), 5.0 (8H, 4 x $COOCH_2$-C_6H_5), 4.63 (2H, $COOCH_2CCl_3$), 1.50 (10H, C_6H_{10}).

Anal. Calcd. for $C_{53}H_{59}N_4O_{16}Cl_3$: C, 57.07; H, 5.33; N, 5.02; Cl, 9.53. Found: C, 56.55, 56.67; H, 5.62,5.45; N, 4.98; Cl, 9.30,9.32.

Tetra-N-benzyloxycarbonyl-5,6-O-cyclohexylidene-neamine (8). Procedure (A). To a solution of 7 (0.5 g, 0.45 mmol) in methanol (5 mL) was added aqueous ammonia solution (0.38 mL, 0.88 S.G.). After 3 h at room temperature, the reaction mixture was poured into water, and the precipitate was filtered, washed with water and dried. Compound 8 was thus obtained as a chromatographically homogeneous, white, amorphous solid (0.4 g, 95%): mp 184-6 °C; $[\alpha]_D^{20}$ + 26.37° (c 1.10, dioxane); NMR ($CDCl_3$) δ 7.20 (20H, 4 x $COOCH_2C_6H_5$), 4.99 (8H, 4 x $COOCH_2C_6H_5$), 1.5 (10H, C_6H_{10}). Procedure (B). A solution of 4 (10 g, 11.64 mmol), 1,1-dimethoxycyclohexane (12 mL) and anhydrous p-toluenesulphonic acid (0.8 g) in dry DMF (80 mL) was heated to 80-85 °C under reduced pressure with stirring for 2 h. After cooling methanol (3 mL) was added, and the mixture was warmed to 40 °C for 1 h. Workup as previously described gave a crude solid which was dissolved in hot chloroform, filtered and evaporated to give a white solid. The residue was triturated carefully with ether to give 8 (6.55 g, 61%): mp 182-4 °C. Purification by preparative TLC (eluant: $CHCl_3$/MeOH/Et_3N 100:6:0.5) gave a white, amorphous solid: mp 183-5 °C; $[\alpha]_D^{20}$ + 26.67° (c 0.90, dioxane); NMR ($CDCl_3$) δ 7.14 (20H, 4 x $COOCH_2C_6H_5$), 4.97 (8H, 4 x $COOCH_2C_6H_5$), 1.5 (10H, C_6H_{10}).

Anal. Calcd. for $C_{50}H_{58}N_4O_{14}$: C, 63.95; H, 6.23; N, 5.97. Found: C, 63.31, 63.44; H, 6.25, 6.25; N, 5.97, 6.00.

Evaporation of the ether gave a syrup that was purified by column chromatography on silica-gel (eluant: CH_2Cl_2/EtOAc 8:2). Tetra-N-benzyloxycarbonyl-3',4':5,6-di-O-cyclohexylideneneamine (9) was present in the early fractions: mp 95-7 °C; $[\alpha]_D^{20}$ + 26.15° (c 1.30, $CHCl_3$); NMR ($CDCl_3$) δ 7.20 (20H, 4 x $COOCH_2C_6H_5$), 5.0 (8H, 4 x $COOCH_2C_6H_5$), 1.5 (20H, 2 x C_6H_{10}).

Anal. Calcd. for $C_{56}H_{66}N_4O_{14}$: C, 61.11; H, 6.53; N, 5.50. Found: C, 60.95; H, 6.42; N, 5.43.

Tetra-N-benzyloxycarbonyl-3',4'-di-O-mesyl-5,6-O-cyclohexylideneneamine (10). To a solution of 8 (1.1 g, 1.17 mmol) in dry pyridine (5 mL) was added methanesulphonyl chloride (1 mL), and the mixture was left standing at room temperature overnight. The product was poured into sodium bicarbonate solution to give a precipitate of 10 (1.2 g, 93%): mp 102-5 °C. Purification by preparative TLC (eluant: CH_2Cl_2/MeOH 100:31) gave: mp 104-6 °C; $[\alpha]_D^{20}$ + 14.74° (c 0.95, $CHCl_3$); NMR ($CDCl_3$) δ 7.20 (20H, 4 x $COOCH_2C_6H_5$), 4.94 (8H, 4 x $COOCH_2C_6H_5$), 3.05, 2.72 (3H, 3H, s, 3',4'-di-SO_2CH_3), 1.5 (10H, C_6H_{10}).

Anal. Calcd. for $C_{52}H_{62}N_4O_{18}S_2$: C, 56.82; H, 5.69; N, 5.10; S, 5.83. Found: C, 56.98; H, 5.77; N, 5.21; S, 5.74.

Tetra-N-benzyloxycarbonyl-3',4'-di-O-(methylthio)-thiocarbonyl-5,6-O-cyclohexylideneneamine (11). To a solution of 8 (6.0 g, 6.38 mmol) in carbon disulphide/DMSO (15 mL/30 mL) was added dropwise 5N aqueous sodium hydroxide solution (15 mL) at 15 °C with stirring. After 20 min iodomethane (30 mL) was added portionwise and the mixture was left to stir for 45 min. The sol-

vent was evaporated and the residue was extracted with ethyl acetate. The extract was washed with brine, dried and evaporated to give a yellow oil. Purification by column chromatography (prior elution with hexane/methylene chloride 7:3) to remove a yellow, non-polar impurity, then with methylene dichloride/methanol (100:5) gave the title compound 11 (6.54 g, 92%): mp 91-3 °C; $[\alpha]_D^{20}$ + 38.55° (c 0.83, $CHCl_3$); NMR ($CDCl_3$) δ 7.25 (20H, 4 x $COOCH_2C_6H_5$), 5.04 (8H, 4 x $COOCH_2C_6H_5$), 2.48, 2.40 (3H, 3H, S, 3',4'-diCSSCH$_3$), 1.5 (10H, C_6H_{10}).

Anal. Calcd. for $C_{54}H_{62}N_4O_{14}S$: C, 57.94; H, 5.58; N,5.01; S, 11.46. Found: C, 57.74; H, 5.85; N, 4.99; S, 11.66.

Tetra-N-benzyloxycarbonyl-3',4'-dideoxy-3'-ene-5,6-O-cyclohexylideneneamine (13). Method (A).[9] To a suspension of sodium iodide (3 g) and zinc dust (1.6 g) in dry DMF (8 mL) was added 10 (0.394 g, 0.358 mmol) with stirring. The mixture was heated to 130 °C for 6 h. Upon cooling, chloroform was added and the product was filtered. The filtrate was washed with saturated aqueous sodium bicarbonate solution, then with aqueous sodium thiosulphate solution. After drying, filtration and evaporation gave a crude mixture of products. Purification by preparative TLC (eluant: methylene chloride/methanol 100:6) gave 13 (0.07 g, 22%): mp 192-4 °C; $[\alpha]_D^{22}$ - 24.71° (c 0.85, $CHCl_3$); NMR ($CDCl_3$) δ 7.20 (20H, 4 x $COOCH_2$-C_6H_5), 5.43 (2H, H-3',4'), 4.94 (4 x $COOCH_2$-C_6H_5), 1.5 (10H, C_6H_{10}). Method (B).[12] To a refluxing solution of 11 (0.835 g, 0.75 mmol) and a trace amount of azobis-(dimethylacetonitrile) in dry toluene (5 mL) was added dropwise with stirring over 1.5 h a solution of tri-n-butyltin hydride (1.03 g, 3.54 mmol) in dry toluene (5 mL). After a further 0.5 h reflux the mixture was

cooled, and a white precipitate formed. This was filtered and washed with toluene followed by hexane. Compound 13 was obtained as a white, amorphous solid (0.433 g, 64%): mp 189-191 °C. The material was recrystallized from hot ethanol: mp 192-4 °C; $[\alpha]_D^{22}$ - 25.00° (c 1.20, $CHCl_3$); NMR ($CDCl_3$) δ 7.20 (20H, 4 x $COOCH_2C_6\underline{H}_5$), 5.43 (2H, H-3'4'), 4.94 (8H, 4 x $COOC\underline{H}_2C_6H_5$), 1.5 (10H, C_6H_{10}).

Anal. Calcd. for $C_{50}H_{56}N_4O_{12}$: C, 66.35; H, 6.24; N, 6.19. Found: C, 65.97, 65.89; H, 6.15, 6.30; N, 6.19, 6.14. Method (C).[13] To a suspension of 8 (2.4 g, 2.56 mmol), triphenylphosphine (2.7 g, 10 mmol) and imidazole (0.7 g, 10 mmol) in dry, refluxing toluene was added iodine (1.5 g, 5.9 mmol), portionwise over 0.5 h. After an additional 1 h reflux, the solution was cooled, the supernatant decanted, and the residue extracted with toluene. The extract was washed sequentially with aqueous sodium bicarbonate, aqueous sodium thiosulphate, and water. The solution was dried, filtered and evaporated to give a syrup. Purification by column chromatography on silica gel (eluant: CH_2Cl_2/EtOAc 8.5:1.5) gave 13 as a white, amorphous solid (0.98 g, 42%): mp 193-5 °C; $[\alpha]_D^{22}$ - 25.49° (c 1.02, $CHCl_3$); NMR ($CDCl_3$) δ 7.2 (20H, 4 x $COOCH_2$-$C_6\underline{H}_5$), 5.43 (2H, H-3',4'), 4.94 (4 x $COOC\underline{H}_2$-C_6H_5), 1.5 (10H, $C_6\underline{H}_{10}$).

A monoiodo by-product 12 was also obtained from the early eluted fractions (0.562 g, 22%): mp 130-2 °C; $[\alpha]_D^{22}$ + 8.55 (c 1.52, $CHCl_3$); NMR ($CHCl_3$) δ 7.15 (20H, 4 x $COOCH_2$- $C_6\underline{H}_5$), 6.05 (1H, H-3' or 4'), 4.97 (8H, 4 x $COOC\underline{H}_2$-C_6H_5), 1.44 (10H, $C_6\underline{H}_{10}$).

Anal. Calcd. for $C_{50}H_{55}N_4O_{12}I$: C, 58.25; H, 5.78; N, 5.43; I, 12.31. Found: C, 58.25, 58.07; H, 5.36, 5.30; N, 5.47, 5.30; I, 12.08, 12.23.

12 was treated with tri-n-butyltin hydride as previously described to give 13: mp 178-180 °C. Purifica-

tion by recrystallization from methanol gave pure 13: mp 192-4 °C; $[\alpha]_D^{22}$ - 25.45° (c 1.10, $CHCl_3$); NMR ($CDCl_3$) δ 7.18 (20H, 4 x $COOCH_2-C_6H_5$) , 5.50 (2H, H-3',4'), 5.0 (8H, 4 x $COOCH_2-C_6H_5$), 1.5 (10H, C_6H_{10}).

Tetra-N-benzyloxycarbonyl-3',4'-dideoxy-3'-eno-neamine (14). 13 (0.983 g, 1.09 mmol) was heated in 80% acetic acid-water at 60 °C for 2 h. The mixture was poured into water, and the precipitate was filtered and washed with water to give 14 (0.88 g, 98%), mp 208-212 °C. Purification by preparative TLC (eluant: methylene chloride/methanol 100:6) gave the title compound: mp 217-9 °C; $[\alpha]_D^{22}$ - 25.26° (c 0.95, dioxane); NMR ($CDCl_3$, 2 drops of DMSO) δ 7.13 (20H, 4 x $COOCH_2-C_6H_5$), 5.53 (2H, H-3',4'), 5.02 (8H, 4 x $COOCH_2-C_6H_5$).

Anal. Calcd. for $C_{44}H_{48}N_4O_{12}\cdot H_2O$: C, 62.70; H, 5.98; N, 6.65. Found: C, 62.65, 62.69; H, 5.79, 5.78; N, 6.52, 6.59.

Tetra-N-benzyloxycarbonyl-5,6-O-cyclohexylidene gentamine C_{1a} (15). 13 (0.453 g, 0.5 mmol) was dissolved in methanol (30 mL) and ethyl acetate (30 mL) and hydrogenated with platinum oxide and hydrogen (50 psi) at room temperature for 3 h. The mixture was filtered, evaporated and purified by preparative TLC (eluant: ethyl acetate/methylene chloride 4.5 : 1.5) to give 15 (0.30 g, 61%): mp 76-8 °C; $[\alpha]_D^{22}$ + 33.13° (c 1.63, $CHCl_3$); NMR ($CDCl_3$) δ 7.13 (20H, 4 x $COOCH_2-C_6H_5$), 5.0 (8H, 4 x $COOCH_2-C_6H_5$), 1.5 (10H, C_6H_{10}).

Anal. Calcd. for $C_{50}H_{58}N_4O_{12}$: C, 66.21; H, 6.45; N, 6.18. Found: C, 66.16; H, 6.35; N, 6.12.

Gentamine C_{1a} (2). Method (A). 14 (1.59 g, 1.93 mmol) in acetic acid (70 mL) was hydrogenated and hydro-

genolysized with palladium/charcoal (2.08 g) and hydrogen (50 psi) at room temperature for 40 h. The mixture was filtered and evaporated under reduced pressure. The residue was dissolved in methanol and treated with Amberlite IR-45 [OH] , filtered and evaporated to give crude 2. This was taken up in methanol, treated with sulphuric acid (in methanol, pH 2-3) to give 2 as the sulphate in quantitative yield. TLC (chloroform/methanol/concentrated ammonia 1:1:1, lower phase) showed one spot (R_f ca. 0.35) which corresponded to gentamine C_{1a} obtained[14] by hydrolysis of gentamincin C_{1a}. MS $^{m+1}$/e : 291 (M Calcd. for $C_{12}H_{26}N_4O_4$), 163 (291-$C_6H_{13}O$), 129 ($C_6H_{13}O$). Method (B). 13 (0.6 g, 0.663 mmol) in acetic acid (20 mL) was hydrogenated and hydrogenolysed with palladium/charcoal (0.8 g) and hydrogen under the same coditions as in method (A) to give an intermediate 5,6-O-cyclohexylidenegentamine C_{1a} which showed a single spot on TLC detection. The intermediate was heated with 80% acetic acid-water (10 mL) at 90 °C for 6 h. Workup as previously described gave a crude product, gentamin C_{1a} (2) sulphate.

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