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## Note

# 5,6-*O*-Cyclohexylidene and 5,6-*O*-cyclohexylidene-1,3-di-*N*-methoxycarbonyl derivatives of 2-deoxystreptamine*

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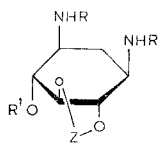
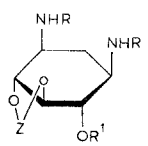
In the published syntheses of aminocyclitol glycosides (kanamycins, neamine, *etc.*)[1], key intermediates are *racemic* derivatives of 2-deoxystreptamine (**1**–**2**) with HO-4 or HO-6 unprotected. Subsequent Koenigs–Knorr glycosylations gave, in poor yields after column chromatography, the 4-*O*-α- and 6-*O*-α-glycosyl derivatives. Syntheses would be more convenient if optically pure, positional isomers (**1** or **2**) were available for glycosylation.

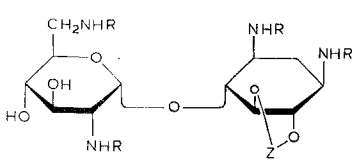



**1**

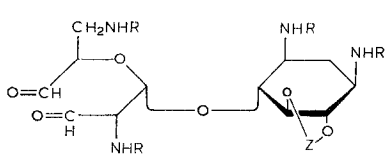



**2**

**1a**, **2a** R = $CO_2Et$, $R^1$ = H, Z = isopropylidene
**1b**, **2b** R = $CO_2CH_2Ph$, $R^1$ = H, Z = isopropylidene
**1c**, **2c** R = $CO_2Et$, $R^1$ = H, Z = cyclohexylidene
**1d** R = $CO_2Me$, $R^1$ = H, Z = cyclohexylidene
**1e** R = $CO_2Me$, $R^1$ = Ac, Z = cyclohexylidene
**1f** R = $R^1$ = H, Z = cyclohexylidene




**3** R = $CO_2Me$, Z = cyclohexylidene




**4** R = $CO_2Me$, Z = cyclohexylidene

*Intermediates in the Synthesis of Aminocyclitol Glycosides: Part I.

We now report an unequivocal synthesis of optically pure 5,6-*O*-cyclohexylidene-1,3-di-*N*-methoxycarbonyl (**1d**) and 5,6-*O*-cyclohexylidene (**1f**) derivatives of 2-deoxystreptamine as potential precursors of the 4-*O*-glycosyl derivatives.

Treatment of tetra-*N*-(methoxycarbonyl)neamine with 1,1-dimethoxycyclohexane gave the known[2] 5,6-*O*-cyclohexylidenetetra-*N*-(methoxycarbonyl)neamine (**3**). The reported, tedious chromatographic purification of **3** was avoided by crystallization of the crude product from tetrahydrofuran–water, which gave pure material in high yield. Oxidation of **3** by sodium periodate in tetrahydrofuran–water and reaction of the resulting dialdehyde (**4**) with triethylamine[3], or with catalytic amounts of sodium methoxide, effected $\beta$-elimination giving 5,6-*O*-cyclohexylidene-2-deoxy-1,3-di-*N*-(methoxycarbonyl)streptamine (**1d**). Compound **1d** was more easily isolated, and in better yields, when the crude reaction mixture was first reduced with sodium borohydride to make the by-products more polar, and then treated with acetic anhydride–pyridine. The resulting 4-acetate (**1e**), isolated by chromatography, was catalytically deacetylated with sodium methoxide to give crystalline **1d** which was a suitable substrate for glycosylations. Under alkaline conditions (barium hydroxide-reflux), both **1d** and **1e** gave 5,6-*O*-cyclohexylidene-2-deoxystreptamine (**1f**).

## EXPERIMENTAL

*General methods.* — Melting points are uncorrected. Organic solutions were dried with anhydrous sodium sulphate and concentrated under diminished pressure at $<40°$. T.l.c. was performed on silica gel $GF_{254}$, and detection was effected by charring with $H_2SO_4$, and by use of $I_2$ vapour, aniline hydrogen phthalate, ammoniacal $AgNO_3$, or anisaldehyde in acetic acid containing 10% of $H_2SO_4$ (cyclohexylidene derivatives give carmine spots). Optical rotations were measured with a Bellingham and Stanley Ltd. polarimeter, i.r. spectra with a Perkin–Elmer 621 spectrophotometer, and p.m.r. spectra (90 MHz, internal $Me_4Si$) with a Perkin–Elmer R 32 spectrometer.

*Periodate oxidation of 5,6-*O*-cyclohexylidenetetra-*N*-(methoxycarbonyl)neamine*[2] (**3**). — Solutions of **3** (15 g, 23.7 mmol) in tetrahydrofuran (100 ml) and sodium metaperiodate (15.2 g) in water (100 ml) were mixed and stirred at 25° for 5 h in the dark. The solution was concentrated, the residue was extracted with hot chloroform ($3 \times 50$ ml), and the combined extracts were washed with water, dried, and concentrated. The residue (15 g) was recrystallized from water–ethanol to give pure 5,6-*O*-cyclohexylidene-2-deoxy-4-*O*-{(1*R*,2*R*)-1-[(1*R*)-1-formyl-2-(methoxycarbonylamino)-ethoxy]-2-formyl-2-(methoxycarbonylamino)ethyl}-1,3-di-*N*-(methoxycarbonyl)streptamine (**4**; 13.2 g, 88%), m.p. 127–133°, $[\alpha]_D^{20}$ −4° (*c* 0.57, *N*,*N*-dimethylformamide), $R_F$ 0.60 (8:1, ethyl acetate–ethanol) and 0.3 (ethyl acetate); $\nu_{max}^{Nujol}$ 3290 (broad NH, OH), 1710 (CHO), 1695 (NCOO), and 1530 $cm^{-1}$ (Amide II). P.m.r. data (methyl sulphoxide-$d_6$): $\delta$ 1.55 (bm, 12 H, H-2,2′ and cyclohexylidene protons), 3.52 (m, 12 H, 4 COOMe), 5.62 (m, 1 H, H-1′), 6.80–7.50 (4 H, NH), 8.30 and 9.12 (2 s, 1.5 H, CHO).

*Anal.* Calc. for $C_{26}H_{40}N_4O_{14} \cdot 0.5\,H_2O$: C, 48.66; H, 6.44; N, 8.73. Found: C, 48.75; H, 6.53; N, 8.60.

*5,6-O-Cyclohexylidene-2-deoxy-1,3-di-*N-*(methoxycarbonyl)streptamine* (**1d**). — (*a*) A solution of crude **4** (1.6 g, 2.52 mmol) in ethanol (25 ml) and triethylamine (2.5 ml) was stirred at 22° for 24 h, and then concentrated. The syrupy residue was dissolved in ethanol (25 ml) and treated overnight with a solution of $NaBH_4$ (0.2 g) in water (5 ml). The mixture was concentrated and methanol was twice evaporated from the residue before extraction with acetone (3 × 15 ml). The solid obtained by concentration of the extracts was eluted from silica gel with chloroform–ethyl acetate mixtures containing 1% of triethylamine to give **1d** (0.226 g, 25%), m.p. 108.5–111° (from ethyl acetate), $[\alpha]_D^{23}$ +14° (*c* 1, chloroform); $R_F$ 0.35 (ethyl acetate), 0.7 (8:1, ethyl acetate–ethanol), and 0.5 (12:1, ethyl acetate–ethanol); $\nu_{max}^{Nujol}$ 3390 (OH), 3260 (NH), 1690 (NCOO), and 1550 $cm^{-1}$ (Amide II). P.m.r. data (methyl sulphoxide-$d_6$): $\delta$ 1.48 (bm, 12 H, H-2,2′ and cyclohexylidene protons), 3.52 (s, 6 H, 2 COOMe), 5.14 (m, 1 H, O*H*), and 7.38 (b band, 2 H, 2 NH).

(*b*) A solution of **4** (2 g, 3.1 mmol) in methanol (30 ml) was treated with NaOMe (0.2 g) at 22° for 24 h. After work-up as in (*a*), the residue was extracted with chloroform. The filtered extracts gave a glassy product which was purified as in (*a*) to give **1d** (0.38 g, 34%), m.p. 109–111°.

(*c*) A solution of **1e** (2 g, 5 mmol) in dry methanol (40 ml) was treated with NaOMe (50 mg) at 22° for 12 h. The mixture was neutralized with $CO_2$, and concentrated to dryness, and the residue was extracted with chloroform. The extracts were filtered and concentrated, and the residue (1.75 g) was recrystallized from ethanol to give **1d** (1.66 g, 93%), m.p. 109–111°.

*Anal.* Calc. for $C_{16}H_{26}N_2O_7$: C, 53.62; H, 7.31; N, 7.81. Found: C, 53.52; H, 7.20; N, 7.53.

*4-O-Acetyl-5,6-O-cyclohexylidene-2-deoxy-1,3-di-*N-*(methoxycarbonyl)streptamine* (**1e**). — A mixture of **4** (16 g, 25.2 mmol), ethanol (250 ml), and triethylamine (25 ml) was stirred at 22° for 24 h, and then concentrated. A solution of the syrupy residue in water (150 ml) was treated with a solution of $NaBH_4$ (2 g) in water (20 ml) for 12 h. The mixture was concentrated, the solid residue was extracted with chloroform (3 × 30 ml), and the filtered extracts were washed with water, dried, and concentrated. The residue was treated conventionally with pyridine (50 ml) and acetic anhydride (5 ml) for 24 h. The crude syrupy product was eluted from silica gel with ethyl acetate to give **1e** (4.84 g, 48%), m.p. 164–166° (from ethanol), $[\alpha]_D^{23}$ −5° (*c* 1.2, chloroform); $R_F$ 0.5 (ethyl acetate) and 0.3 (1:1, chloroform–ethyl acetate); $\nu_{max}^{CHCl_3}$ 3420 and 3320 (NH), 1715 (broad OAc, NCOO), 1510 (Amide II), and 1230 $cm^{-1}$ (acetate). P.m.r. data ($CDCl_3$): $\delta$ 1.10–1.80 (bm, 12 H, H-2,2′ and cyclohexylidene protons), 2.10 (s, 3 H, OAc), 2.30–3.00 (bm, 2 H, H-1,3), 3.63 and 3.66 (2 s, 6 H, 2 NCOOMe), and 4.85–6.40 (bm, 3 H, H-4 and 2 NH).

*Anal.* Calc. for $C_{18}H_{28}N_2O_8$: C, 53.99; H, 7.05; N, 6.99. Found: C, 54.01; H, 6.97; N, 6.52.

*5,6-O-Cyclohexylidene-2-deoxystreptamine* (**1f**). — A solution of **1e** (0.2 g, 0.05 mmol) in methanol (4 ml) was stirred with a solution of $Ba(OH)_2 \cdot 8H_2O$ (0.6 g) in water (3 ml) at 80° for 24 h, and then neutralized with $CO_2$ and centrifuged. The

supernatant solution was concentrated to dryness, the residue was extracted with methanol, and the filtered extracts were concentrated to a syrup which was eluted from Amberlite CG50 ($NH_4^+$) resin with 0.1–0.2M aqueous methanolic ammonia (1:1). Evaporation of the eluates gave a syrup which was dissolved in water (0.5 ml) and neutralized with 0.25M sulphuric acid. The sulphate of **1f** (83 mg, 48%), which was precipitated with *p*-dioxane, had m.p. 212° (dec.), $[\alpha]_D^{20}$ −9° (*c* 0.57, water); $R_F$ 0.4 (100:30:3, chloroform–methanol–conc. ammonia) and 0.65 (8:1 methanol–conc. ammonia).

*Anal.* Calc. for $C_{12}H_{22}N_2O_3 \cdot H_2SO_4$: C, 42.34; H, 7.10; N, 8.23. Found: C, 42.45; H, 7.20; N, 8.17.

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