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# Aminocyclitols. XXV. Synthetic Studies on Streptamine and Its Analogs

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In connection with the previous papers of this series,[1] streptamine[2] and its analogs were synthesized from *myo*-inosadiamine-1,3 dihydrochloride (**1**),[3] which was prepared by hydrazinolysis of 2,4,5,6-tetra-*O*-acetyl-1,3-di-*O*-*p*-toluenesulfonyl-*myo*-inositol,[4] followed by a catalytic hydrogenation.

Since an axial hydroxyl group on C-2 was expected to be the least reactive toward an acetylation among four hydroxyl groups in **1**, a selective acetylation seemed to be possible. That is, when **1** was acetylated with acetic anhydride in anhydrous pyridine at 5—10°C for 7 days, di-*N*,*N'*-acetyl-4,5,6-tri-*O*-acetyl-*myo*-inosadiamine-1,3 (**2**) was obtained in 59% yield. Its proton magnetic resonance (PMR) spectrum in dimethyl sulfoxide-$d_6$ (DMSO-$d_6$) reveals the acetyl methyl protons as two sharp signals at $\tau$ 8 region:[5] $\tau$ 8.20 (6) and 8.11 (9), which were attributed to two equatorial acetamido and three equatorial acetoxy groups, respectively. Therefore the absence of a signal at a region of an axial acetoxy group ($\tau$ 7.80—7.91)[5] supported the proposed structure of **2**.[6] Then **2** was treated with methanesulfonyl chloride at 0—5°C for 2 days and

1) T. Suami, S. Ogawa, and M. Uchida, This Bulletin, **43**, 3577 (1970).

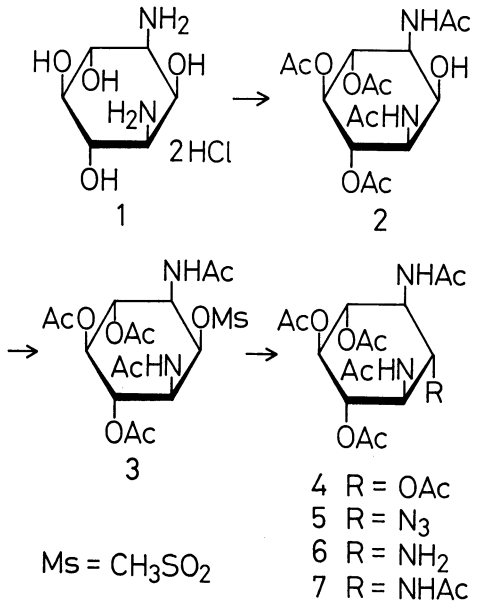
2) M. L. Wolfrom, S. M. Olin, and W. J. Polglase, *J. Amer. Chem. Soc.*, **72**, 1724 (1950); K. Heyns and H. Paulsen, *Chem. Ber.*, **89**, 1152 (1956); T. Suami and S. Ogawa, This Bulletin, **38**, 2026 (1965); S. Ogawa, T. Abe, H. Sano, K. Kotera, and T. Suami, *ibid.*, **40**, 2405 (1967); N. Kurihara, T. Kurokawa, and M. Nakajima, *Agr. Biol. Chem.*, **31**, 1166 (1967); F. W. Lichtenthaler, H, Leinert, and T. Suami, *Chem. Ber.*, **100**, 2383 (1967).

3) T. Suami and S. Ogawa, This Bulletin, **40**, 1295 (1967).

4) T. Suami, F. W. Lichtenthaler, and S. Ogawa, *ibid.*, **40**, 1488 (1967).

5) F. W. Lichtenthaler and P. Emig, *Carbohyd. Res.*, **7**, 121 (1968).

6) The PMR spectrum of hexaacetyl *myo*-inosadiamine-1,3[3] in DMSO-$d_6$ shows four peaks: $\tau$ 8.21 (6), 8.06 (3), 8.03 (6) and 7.82 (3).




subsequently settled at room temperature for 2 days to give di-*N,N'*-acetyl-4,5,6-tri-*O*-acetyl-2-*O*-methanesulfonyl-*myo*-inosadiamine-1,3 (**3**) in 56% yield.

When **3** was treated with anhydrous sodium acetate in boiling 2-methoxyethanol, a Walden inversion occurred at C-2 to afford streptamine in 56% yield as its hexaacetyl derivative (**4**), which was identified with an authentic sample.[7] This result confirmed as well the assignment of structure of **2**.

While, on treatment with sodium azide in boiling 2-methoxyethanol, **3** gave di-*N,N'*-acetyl-4,5,6-tri-*O*-acetyl-2-azido-2-deoxy-*scyllo*-inosadiamine-1,3 (**5**) in 57% yield. A catalytic hydrogenation of **5** afforded di-*N,N'*-acetyl-4,5,6-tri-*O*-acetyl-2-amino-2-deoxy-*scyllo*-inosadiamine-1,3 (**6**)[8] in 88% yield, which, on acetylation, gave known hexaacetyl *scyllo*-inosatriamine-1,2,3 (**7**)[8,9] in 53% yield.

## Experimental

The melting points were determined on a Mitamura Riken micro hot stage and are uncorrected. The PMR spectra were determined with a Varian A-60D spectrometer at the frequency of 60 MHz in DMSO-$d_6$ with tetramethylsilane as an internal standard. The infrared spectra were recorded in potassium bromide pellets.

*Di*-N,N'-*acetyl-4,5,6-tri*-O-*acetyl*-myo-*inosadiamine-1,3 (2)*. Throughly dried *myo*-inosadiamine-1,3 dihydrochloride (**1**)[3] (0.40 g) was dissolved in hot anhydrous pyridine (18 m*l*) and cooled to 0—5°C by ice and water. To the solution was added acetic anhydride (1.1 m*l*, 5.5 molar equivalents) dropwise during 10 min under stirring. After keeping at 5—10°C for 7 days, the reaction mixture was filtered to remove an insoluble material and the filtrate was evaporated to dryness. The crystalline residue was recrystallized from ethanol to afford colorless needles (0.32 g, 59%) of **2**, mp 307—308.5°C. IR: 3460 (OH), 1750 (ester), 1670, 1615, and 1553 $cm^{-1}$ (amide).

Found: C, 49.63; H, 6.29; N, 7.03%. Calcd for $C_{16}H_{24}N_2O_9$: C, 49.48; H, 6.23; N, 7.21%.

*Di*-N,N'-*acetyl-4,5,6-tri*-O-*acetyl-2*-O-*methanesulfonyl*-myo-*inosadiamine-1,3 (3)*. Throughly dried **2** (120 mg) was dissolved in boiling anhydrous pyridine (6 m*l*) and cooled to 0—5°C by ice and water. Methanesulfonyl chloride (0.1 m*l*) was added dropwise under stirring and the reaction mixture was stored below 10°C for 4 days. An insoluble material was filtered off and the filtrate was evaporated to yield a crystalline residue which was triturated with ethanol, and the crystals were collected by filtration. The crude crystals of **3** weighed 81 mg (56%), mp 229—231°C. Further recrystallization from ethanol gave an analytical sample (52 mg), mp 231—231.5°C. IR: 1750 (ester), 1645, 1560 (amide), and 1180 $cm^{-1}$ ($OSO_2CH_3$).

Found: C, 44.56; H, 5.84; N, 5.92; S, 6.51%. Calcd for $C_{17}H_{26}N_2O_{11}S$: C, 43.77; H, 5.62; N, 6.00; S, 6.87%.

*Hexaacetyl Streptamine (4)*. A mixture of **3** (150 mg), anhydrous sodium acetate (150 mg) and 2-methoxyethanol (20 m*l*) was refluxed for 22 hr. The reaction mixture was evaporated to dryness and the resulting residue was treated with a mixture of acetic anhydride (15 m*l*) and pyridine (15 m*l*) at room temperature overnight. After filtering off an insoluble material, the mixture was evaporated to dryness and the residue was triturated with ethanol to give colorless crystals (78 mg, 56%) of **4**, mp 300°C (showing a transition at 237—238°C). This compound was identified with an authentic sample of **4** derived from antibiotic streptomycin[6] by comparing with IR spectra and the melting behaviors.

*Di*-N,N'-*acetyl-4,5,6-tri*-O-*acetyl-2-azido-2-deoxy*-scyllo-*inosadiamine-1,3 (5)*. A mixture of **3** (200 mg), sodium azide (91 mg) and 2-methoxyethanol (10 m*l*) was refluxed for 20 hr. The reaction mixture was then worked up similarly as described under the preparation of **4**. The crude crystals of **5** so obtained was recrystallized from ethanol to give colorless needles (100 mg, 57%), mp 263—264°C (decomp.). Recrystallization from ethanol afforded an analytical sample, whose melting point did not change. IR: 2150 ($N_3$), 1750 (ester), 1655 and 1670 $cm^{-1}$ (amide).

Found: C, 46.75; H, 5.63; N, 16.60%. Calcd for $C_{16}H_{23}N_5O_8$: C, 46.49; H, 5.61; N, 16.94%.

*Di*-N,N'-*acetyl-3,4,5-tri*-O-*acetyl-2-amino-2-deoxy*-scyllo-*inosadiamine-1,3 (6)*. A solution of **5** (94 mg) in 90% aqueous dimethylformamide (10 m*l*) was hydrogenated in the presence of Raney nickel T-4[10] in a Parr shaker type apparatus under the initial hydrogen pressure of 4.5 $kg/cm^2$. After 14 hr, the catalyst was filtered off and the filtrate was evaporated to give a white powder (78 mg, 88%) of **6**. Recrystallization from ethanol gave colorless needles which showed a transition at 191—193°C. IR: 3400 ($NH_2$), 1750 (ester), 1640 and 1560 $cm^{-1}$ (amide).

Found: N, 10.85%. Calcd for $C_{16}H_{25}N_3O_8$: N, 10.67%.

*Hexaacetyl* scyllo-*Inosatriamine-1,2,3 (7)*. A 40 mg portion of **6** was treated with acetic anhydride (1 m*l*) and pyridine (1 m*l*) at room temperature overnight. The crude product was recrystallized from ethanol and ether to give colorless needles (23 mg, 53%) of **7**, mp 298—303°C (decomp.) This compound was identified with an authentic sample by comparing with the IR spectra.[8]

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7) R. L. Peck, R. P. Graber, A. Walti, E. W. Peel, C. E. Hoffhine, Jr., and K. Folker *J. Amer. Chem. Soc.*, **68**, 29 (1946).

8) F. W. Lichtenthaler, P. Voss, and N. Majer, *Angew. Chem.* **81**, 221 (1969).

9) The authors thank Professor F. W. Lichtenthaler for identifying **7** with an authentic sample.[8]

10) S. Nishimura, This Bulletin, **32**, 61 (1959).

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