Aminocyclitols. 34. Synthesis of Inosadiamine-1,4 Derivatives

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Three new inosadiamine-1,4 derivatives have been prepared by nitromethane cyclization of a dialdehyde obtained by periodate oxidation of 1,4-di-*O*-methyl-(1,2,3,4,5/0)-5-acetamido-1,2,3,4-cyclopentanetetrol. The cyclization product was catalytically hydrogenated and subsequently acetylated to give three inosadiamine derivatives. Their structures were established by PMR spectra as *myo*-2,5, *epi*-1,4, and *cis*-inosadiamine-1,4 derivatives.

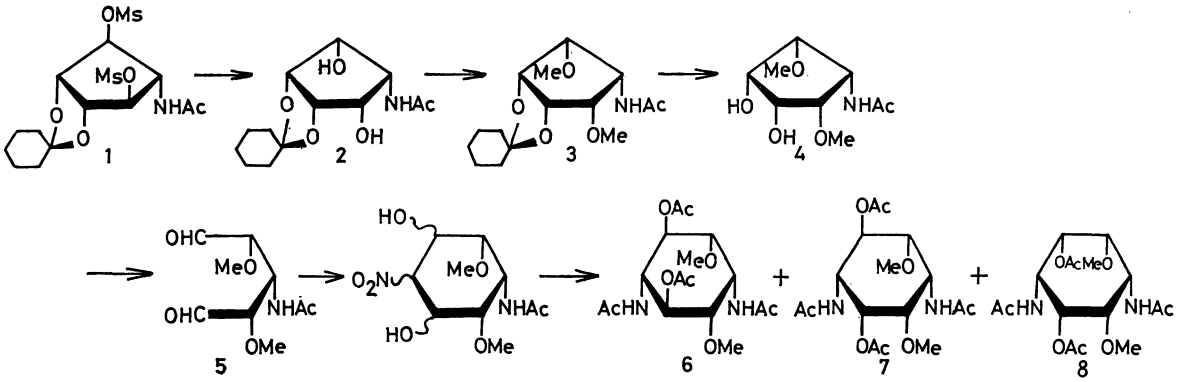
In connection with the results given in the preceding paper,[1] we have prepared three inosadiamine-1,4-derivatives: 1,3-di-*O*-methyl-*myo*-inosadiamine-2,5 (**6**), 3,5-di-*O*-methyl-*epi*-inosadiamine-1,4 (**7**) and 3,5-di-*O*-methyl-*cis*-inosadiamine-1,4 derivatives (**8**), by the nitromethane cyclization of dialdehyde (**5**).

When the starting material 2,3-*O*-cyclohexylidene-1,4-di-*O*-mesyl-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol[2] (**1**) was subjected to displacement of the sulfonyloxy groups by heating in water in the presence of sodium acetate, 2,3-*O*-cyclohexylidene-(1,2,3,4,5/0)-5-acetamido-1,2,3,4-cyclopentanetetrol (**2**) was obtained in 72% yield. *O*-Methylation of **2** afforded the 1,4-di-*O*-methyl derivative (**3**), which was further converted to 1,4-di-*O*-methyl-(1,2,3,4,5/0)-5-acetamido-1,2,3,4-cyclopentanetetrol (**4**) by hydrolysis. Oxidation of **4** by sodium metaperiodate yielded the dialdehyde (**5**) as a syrup. Cyclization of **5** with nitromethane in the presence of sodium methoxide gave deoxynitroinosamine derivatives, which were catalytically hydrogenated and subsequently acetylated. The product was purified by column chromatography to give the three products **6**, **7**, and **8**.

Results and Discussion

Since three new chiral centers are introduced in the products, it is possible for six diastereomers to occur in the reaction: *allo*-2,5, *cis*-1,4, *epi*-1,4, *epi*-3,6, *myo*-2,5 and *neo*-inosadiamine-2,5 derivative.

The PMR spectrum of **6** revealed three signals due to the four acetyl groups. Unequivocal distinction between the signal of an acetoxyl and that of an acetamido group was established by means of deuterioacetylation technique.[3] The two signals at δ 1.85 and 2.00 are attributable to the two acetamido groups and the signal at δ 2.04 is ascribed to the two equatorial acetoxyl groups.[4] The results are summarized in Table 1. The two methoxyl groups revealed their signal at δ 3.38 as a singlet. This indicates that these



Scheme 1.

TABLE 1. CHEMICAL SHIFTS OF METHYL PROTONS IN DMSO-d_6

Compound	Acetamido		Acetoxyl		Methoxyl
	equatorial	axial	equatorial	axial	
6: *myo*-2,5	1.85 (3H)[a]	2.00 (3H)	2.04 (6H)		3.38 (6H)
12	1.84 (3H)	2.00 (3H)			3.34 (6H)
7: *epi*-1,4	1.87 (3H)	2.02 (3H)	2.05 (3H)	2.23 (3H)	3.38 (3H), 3.39 (3H)
13	1.87 (3H)	2.03 (3H)			3.40 (3H), 3.42 (3H)
8: *cis*-1,4	1.85 (3H)	2.02 (3H)	2.09 (6H)		3.51 (6H)
14	1.85 (3H)	2.02 (3H)			3.51 (6H)

a) Peak positions are given in δ values, the number of protons being given in parentheses.

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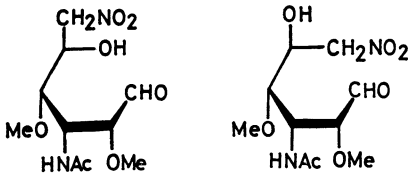
methoxyl groups are located in an equivalent state. Hence, *myo*-2,5 and *cis*-1,4 configurations are conceivable. The signal of the two ring protons on the carbons which bear the acetoxyl groups appeared at δ 5.35 (J=10 Hz) as a triplet, indicating that *trans* configurations exsist between the acetoxyl and the methoxyl groups, and between the acetoxyl and the newly introduced acetamido groups. Furthermore, the two ring protons on the carbons which bear the methoxyl groups revealed their signal at δ 3.62 as double doublet (J=10 and 3 Hz), suggesting a *cis*-configuration between the methoxyl and another acetamido group. Thus, the configuration of *myo*-inosadiamine-2,5 was established for **6**.

The PMR spectrum of **7** revealed four signal at δ 1.87, 2.02, 2.05, and 2.23 for the four acetyl groups. The first two peaks are attributed to an equatorial and an axial acetamido group, respectively, the last two peaks to an equatorial and an axial acetoxyl group, respectively. The two methoxyl groups showed their signals at δ 3.38 and 3.39, indicating a nonequivalent conformation of the surroundings. Thus, **7** was assigned to be *epi*-inosadiamine-1,4 derivative.

The PMR spectrum of **8** revealed two signals at δ 1.85 and 2.02 for the two acetamido groups, and a signal at δ 2.09 for the two acetoxyl groups. The signal of the two methoxyl groups appeared at δ 3.51. These data indicate a symmetrical structure of **8**, *cis*-inosadiamine-1,4 being proposed for the configuration.



D-*allo* L-*talo*

Scheme 2.

The analogous reaction mechanism[1,5] is proposed for the present nitromethane cyclization. That is the initial step of the reaction is an addition between nitromethane and one of the two aldehyde groups of **5**, giving two diastereomers: D-*allo* and L-*talo* type intermediates. The second step of the reaction is an intramolecular cyclization of the intermediates to give *cis*-1,4 and *epi*-1,4 from the D-*allo*, and *epi*-1,4 and *myo*-2,5 from the L-*talo* intermediate.

Experimental

All the melting points were determined in capillary tubes, and are uncorrected. Solutions were evaporated under reduced pressure. De-*O*-acetylation was carried out in methanolic ammonia at ambient temperature. PMR spectra were measured at 60 MHz on a Varian A-60D spectrometer in dimethyl-d_6 sulfoxide with tetramethylsilane as an internal standard. The peak positions are given in δ values.

2,3-O-Cyclohexylidene-(1,2,3,4,5/0)-5-acetamido-1,2,3,4-cyclopentanetetrol (2). 2,3-*O*-Cyclohexylidene-1,4-di-*O*-mesyl-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol[2] (**1**, 20.0 g) and sodium acetate (97.0 g) were heated in boiling water (300 ml) under reflux for 16 h. After cooling to ambient temperature, the solution was repeatedly extracted with chloroform. The resulting solution was dried over anhydrous sodium sulfate and evaporated. The residue was recrystallized from ethyl acetate to give 9.20 g (72%) of **2**, mp 170—171 °C.

Found: C, 57.80; H, 7.81; N, 5.11%. Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16%.

1,4-Di-O-methyl-(1,2,3,4,5/0)-5-acetamido-1,2,3,4-cyclopentanetetrol (4). A mixture of **2** (10.8 g), methyl iodide (11.0 ml) and silver oxide (22.0 g) in *N,N*-dimethylformamide (100 ml) was stirred for 10 h in the dark, and an insoluble matter was removed by filtration. The filtrate was evaporated to give 2,3-*O*-cyclohexylidene-1,4-di-*O*-methyl-(1,2,3,4,5/0)-5-acetamido-1,2,3,4-cyclopentanetetrol (**3**) as a syrup (13.4 g). PMR ($CDCl_3$) δ 1.99 (s, 3, NAc), 3.40 (s, 6, $2OCH_3$).

Compound **3** (13.4 g) was heated under reflux for 2 h in 0.1 M hydrochloric acid (105 ml), and the solution was evaporated to give a crystalline residue (10.1 g). Recrystallization from benzene afforded 6.28 g (72% from **2**) of **4**, mp 123—125 °C.

Found: C, 49.03; H, 7.60; N, 6.17%. Calcd for $C_9H_{17}NO_5$: C, 49.30; H, 7.82; N, 6.39%.

3-Acetamido-2,4-di-O-methyl-3-deoxy-ribo-*pentodialdose (5).* Compound **4** (1.50 g) was added with mechanical agitation under ice cooling to a solution of sodium metaperiodate (1.61 g) in cold water (20 ml). The solution was left to settle overnight at ambient temperature. After being neutralized with sodium hydrogen carbonate, the solution was filtered. The filtrate was evaporated to give **5** as a crude residue. The product was used for a successive reaction without purification.

Nitromethane Cyclization of 5. To a solution of **5** (1.48 g) and nitromethane (0.74 ml) in methanol (6.0 ml), 1.4 M methanolic sodium methoxide (10 ml) was added under ice cooling with agitation. After being left to settle in a refrigerator overnight, the solution was evaporated. The residue was hydrogenated in 20% aqueous acetic acid (12 ml) in the presence of Raney nickel T-4[6] at 3.4 kg/cm^2 of hydrogen atmosphere with a Parr apparatus for 16 h. After the catalyst was removed by filtration, the filtrate was evaporated. The residue was acetylated with acetic anhydride in pyridine in the usual manner. The product was dissolved in 10 ml of benzene–ethanol (4: 1, v/v), and the solution was stored in a refrigerator for a few days to give 244 mg of tetra-*N,O*-acetyl-3,5-di-*O*-methyl-*cis*-inosadiamine-1,4 (**8**) as crystals.

The mother liquor was evaporated, and the residue was fractionated on a silica gel column (28×380 mm) in benzene–ethanol (5: 1, v/v). Each aliquot was monitored on TLC with the same solvent. The fractions (R_f 0.37 on TLC) were combined and evaporated to give 309 mg (12% from **4**) of tetra-*N,O*-acetyl-1,3-di-*O*-methyl-*myo*-inosadiamine-2,5 (**6**). A part of the product was recrystallized from ethanol to give an analytical sample, mp 203—205 °C.

Found: C, 51.50; H, 6.93; N. 7.35%. Calcd for $C_{16}H_{26}N_2O_8$: C, 51.33; H, 7.00; N, 7.48%.

The fractions (R_f 0.30 on TLC) gave 417 mg (16% from **4**) of tetra-*N,O*-acetyl-3,5-di-*O*-methyl-*epi*-inosadiamine-1,4 (**7**) as a syrup.

Found: C, 51.14; H, 6.88; N, 7.34%. Calcd for $C_{16}H_{26}N_2O_8$: C, 51.33; H, 7.00; N, 7.48%.

The fractions (R_f 0.22 on TLC) gave another crop (202 mg) of **8**. The total yield (446 mg) was 17% from **4**. A part of the product was recrystallized from benzene–ethanol (4: 1, v/v) to give an analytical sample, mp 290—292 °C.

Found: C, 51.06; H, 6.91; N, 7.33%. Calcd for $C_{16}H_{26}N_2O_8$: C, 51.33; H, 7.00; N, 7.48%.

2,5-Di-N-acetyl-1,3-di-O-methyl-myo-*inosadiamine-2,5 (9).*

Compound **6** (180 mg) was de-*O*-acetylated, and the product was recrystallized from ethanol to give 76 mg (54%) of **9**, mp 240—242 °C.

Found: C, 49.76; H, 7.57; N, 9.48%. Calcd for $C_{12}H_{22}N_2O_6$: C, 49.65; H, 7.64; N, 9.65%.

A 50 mg portion of **9** was acylated with acetic anhydride-d_6 (0.2 ml) in pyridine (1 ml), and the product was recrystallized from ethyl acetate to give 35 mg (53%) of 4,6-di-*O*-acetyl-d_3 derivative (**12**), mp 203—205 °C.

1,4-Di-N-*acetyl-3,5-di*-O-*methyl*-epi-*inosadiamine-1,4 (10)*. Compound **7** (340 mg) was de-*O*-acetylated, and the product was recrystallized from ethyl acetate–ethanol (10: 1, v/v) to give 210 mg (80%) of **10**, mp 207—208°C.

Found: C, 49.45; H, 7.42; N, 9.76%. Calcd for $C_{12}H_{22}N_2O_6$: C, 49.65; H, 7.64; N, 9.65%.

An 80 mg portion of **10** was acylated with acetic anhydride-d_6 in pyridine, and the product was purified on a silica gel column in benzene–ethanol (5: 1, v/v) to give 83 mg (79%) of 2,6-di-*O*-acetyl-d_3 derivative (**13**) as a syrup.

1,4-Di-N-*acetyl-3,5-di*-O-*methyl*-cis-*inosadiamine-1,4 (11)*. Compound **8** (400 mg) was de-*O*-acetylated, and the product was recrystallized from methanol to give 188 mg (61%) of **11**, mp above 295 °C.

Found: C, 49.40; H, 7.54; N, 9.48%. Calcd for $C_{12}H_{22}N_2O_6$: C, 49.65; H, 7.64; N, 9.65%.

A 50 mg portion of **11** was acylated with acetic anhydride-d_6 in pyridine, and the product was recrystallized from ethanol to give 32 mg (49%) of 2,6-di-*O*-acetyl-d_6 derivative (**14**), mp 290—292 °C.

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