Aminocyclitols. 32. Synthesis of Inosadiamine-1,4[1]

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Three new inosadiamines have been prepared by nitromethane cyclization of dialdehyde, followed by catalytic hydrogenation. Their structures were established to be *scyllo*-1,4, *myo*-1,4, and *epi*-inosadiamine-3,6 by PMR spectra.

Nitromethane cyclization of dialdehydes is a well known and well studied reaction in a field of carbohydrate chemistry.[2] The first successful application of this reaction to a carbohydrate was accomplished by Sowden and Fischer[3] in 1944 and later Grosheintz and Fischer[4,5] extended this reaction to intramolecular cyclization to prepare nitrodeoxyinositols. These reactions were extensively studied by several investigators.[6–10]

In connection with the preceding paper of this series,[11] we have attempted to prepare an inosadiamine-1,4 by means of the nitromethane cyclization of dialdehydes. In the present article, we wish to report the synthesis of three new inosadiamines: *scyllo*-1,4, *myo*-1,4, and *epi*-inosadiamine-3,6.

The starting material: 1,4-di-*O*-acetyl-2,3-*O*-cyclohexylidene-(1,4/2,3,5-5)-acetamide-1,2,3,4-cyclopentanetetrol (**1**) was prepared by the method of Ahluwalia *et al.*[12] Mild hydrolysis of **1** in 80% aqueous acetic acid afforded 1,4-di-*O*-acetyl-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (**2**).[13] The 1,4-di-*O*-benzoyl derivative (**3**) was prepared by the analogous reaction process.

Compound **2** was oxidized by periodate in an aqueous solution to give 3-acetamido-2,4-di-*O*-acetyl-2-deoxy-*xylo*-pentodialdose (**4**) as a syrup. Compound **4** was treated with nitromethane under the presence of sodium methoxide. The product was hydrogenated in the presence of Raney nickel under a hydrogen atomosphere and subsequently acetylated. The product was fractionated by means of recrystallization and column chromatography to give three new hexaacetyl inosadiamines (**7**), (**8**) and (**9**) in 3.5, 39, and 1.3% yields, respectively.

In the case of the reactions starting from the di-*O*-benzoyl derivative **3**, the analogous results were obtained.

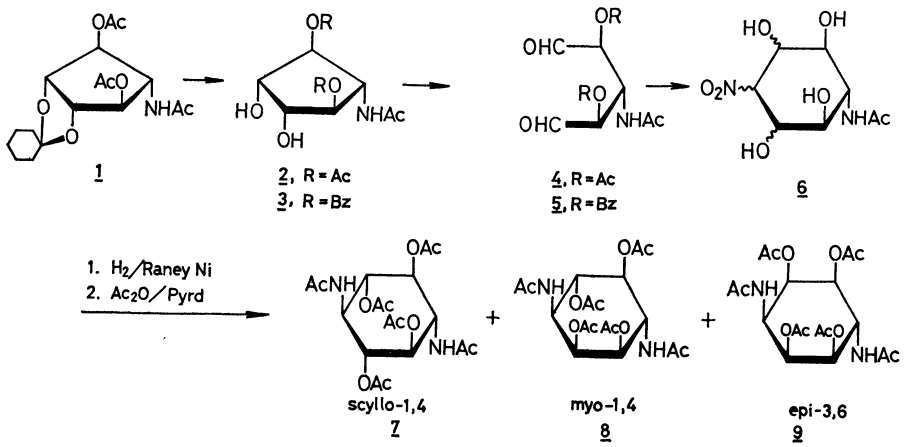
Table 1. Chemical shifts of the acetyl methyl protons in DMSO-d_6 (60 MHz) in τ-value

Compound		Acetoxy		Acetamido	
		ax.	eq.	ax.	eq.
7	*scyllo*-1,4		8.07(12H)		8.22(6H)
8	*myo*-1,4	7.82(3H)	8.05(3H)		8.20(3H)
			8.09(3H)		8.23(3H)
			8.10(3H)		
9	*epi*-3,6	7.88(6H)	8.13(6H)		8.17(3H)
					8.24(3H)

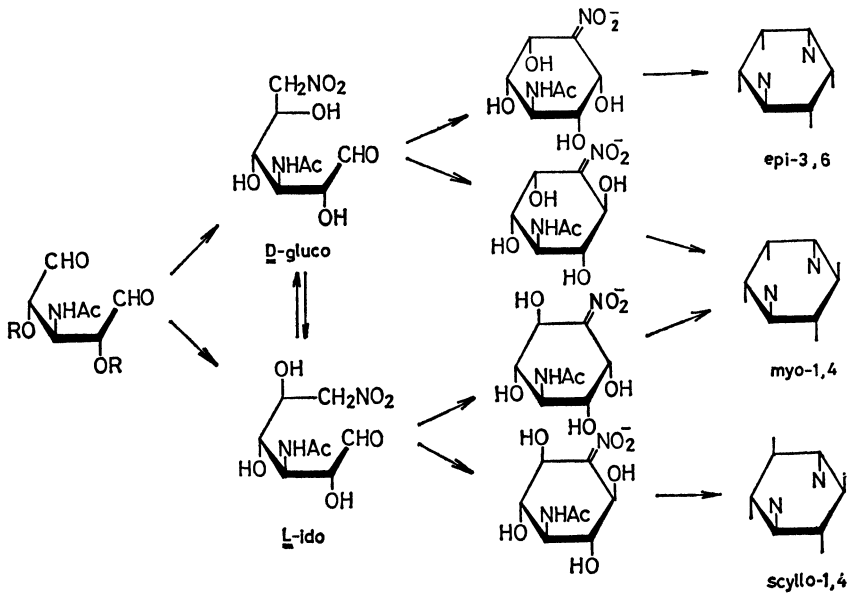
There are fourteen theoretically possible isomers in inosadiamine-1,4 and five ones are already described in the literatures.[14–17] The three inosadiamines obtained in the present experiment are not identical with any one of these known isomers. In the present reaction, three new chiral centers are introduced in the products and therefore, six isomers are conceivable. Among these six isomers, *muco*-3,6[16] and *chiro*-inosadiamine-1,4[15] are known isomers.

Compound **7** should be one of the remaining four unknown compounds. The PMR spectrum of **7** revealed a simple pattern of the signals due to the acetyl methyl protons and this was only compatible with hexaacetyl *scyllo*-inosadiamine-1,4.

The PMR spectrum of **8** revealed six sharp signals with a same intensity of three protons. The two signals at τ 8.20 and 8.23 are attributed to the two equatorial acetamido groups and the signal at τ 7.82 is due to an axial acetoxy group.[19] The other three signals are attributed to the equatorial acetoxy groups



Scheme 1.



Scheme 2.

and therefore, **8** was assigned as hexaacetyl *myo*-inosadiamine-1,4.

Compound **9** showed four sharp signals in its PMR spectrum. The signal at τ 7.88 is attributed to the two axial acetoxy groups and the two signals at τ 8.17 and 8.24 are due to the two equatorial acetamido groups. Hence, **9** was assigned to be hexaacetyl *epi*-inosadiamine-3,6.

Besides the above described three inosadiamines, another minor product was detectable on tlc, but the structural assignment of this product was unsuccessful owing to a poor yield.

The reaction mechanism of nitromethane cyclization has been well studied by Kovar and Baer[6] using 6-deoxy-3-*O*-methyl-6-nitro-D-glucose and -L-idose. The present experiments are coincident with their results.[6]

In the present reaction, the initial step of the reaction is an addition reaction between nitromethane and one of the two aldehyde groups in **4** to give two diastereomers: D-*gluco* and L-*ido* type intermediates. The second step of the reaction is intramolecular cyclization of the intermediates to give *myo*-1,4 and *epi*-3,6 type compounds from the D-*gluco*, and *myo*-1,4 and *scyllo*-1,4 type compounds from the L-*ido* *via* corresponding nitronate salts.

Exeprimental

All melting points were determined in capillary tubes and are uncorrected. Solutions were evaporated under diminished pressure below 40 °C. Acetylation was carried out with acetic anhydride in pyridine. PMR spectra were measured at 60 MHz on a Varian A-60D in dimethyl sulfoxide-d_6 (DMSO-d_6) with reference to tetramethylsilane as an internal standard and the peak positions are given in τ values.

*3-Acetamido-2,4-di-*O*-acetyl-3-deoxy*-xylo-*pentodialdose* (**4**). 1,4-Di-*O*-acetyl-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (**2**) was prepared by the method of Suami *et al.*[13] from 1,4-di-*O*-acetyl-2,3-*O*-cyclohexylidene-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol.[12] Compound **2** (6.0 g) was dissolved in cold water (60 ml) and sodium metaperiodate (5.13 g) was added to the solution under ice cooling with agitation. The solution was stirred overnight at room temperature and neutralized with sodium hydrogencarbonate. Methanol (60 ml) was added to the solution and the mixture was settled overnight in a refrigerator. The mixture was filtered and the filtrate was evaporated. The residue was extracted with a mixture of ethanol and ethyl acetate (1 : 1, v/v) and the extract was evaporated to give a crude product of **4** (6.7 g) as a pale yellow syrup. The product showed a positive Fehling test and a spot on tlc at R_f 0.3 in benzene–ethanol (5 : 1, v/v) solvent system.

*3-Acetamido-2,4-di-*O*-benzoyl-3-deoxy*-xylo-*pentodialdose* (**5**). 2,3-*O*-Cyclohexylidene-(1,4/2,3,5)-5-acetamide-1,2,3,4-cyclopentanetetrol[13] (1.37 g) was acylated with benzoyl chloride (1.8 ml) in pyridine (25 ml). After the mixture was agitated for 2 hr, the mixture was poured into ice cold water (600 ml) to give crystals. The crystals were collected by filtration to give 2.40 g (99%) of 1,4-di-*O*-benzoyl-2,3-*O*-cyclohexylidene-(1,4/2,3,5)-5-acetamide-1,2,3,4-cyclopentanetetrol, mp 187—188 °C.

Found: C, 67.92; H, 6.13; N, 2.77%. Calcd for $C_{27}H_{29}NO_7$: C, 67.63; H, 6.10; N, 2.92%.

The above described product (2.5 g) was heated in 80% aqueous acetic acid (70 ml) under reflux for 3 hr and the solution was evaporated to give a crystalline residue. The residue was recrystallized from a mixture of ethanol and ethyl acetate (1 : 5, v/v) to give 1.61 g (72%) of 1,4-di-*O*-benzoyl-(1,4/2,3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (**3**), mp 177—178 °C.

Found: C, 62.95; H, 5.41; N, 3.35%. Calcd for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; N, 3.51%.

Compound **3** (7.64 g) was dissolved in ethanol (200 ml) and a solution of sodium metaperiodate (7.01 g) in cold water (300 ml) was added to the solution under ice cooling with agitation. After stirred overnight at room temperature, the mixture was neutralized with sodium hydrogencarbonate. The mixture was filtered and the filtrate was evaporated to give 7.14 g (94%) of **5** as a crude syrup. The product showed a positive Fehling test and a spot on tlc at R_f 0.7 in benzene–ethanol (5 : 1, v/v) system.

Nitromethane Cyclization of **4**. To a mixture of **4** (6.7 g), nitromethane (2.4 ml) and methanol (30 ml), 2.2 M methanolic sodium methoxide (20 ml)was added under ice cooling

with agitation. After settled overnight in a refrigerator, the reaction mixture was adjusted to pH 6 with glacial acetic acid and evaporated to give a brown residue (11.9 g).

Hexaacetyl scyllo-*Inosadiamine-1,4 (7).* The crude nitromethane cyclization product (11.9 g) was hydrogenated in water (25 ml) under the presence of Raney nickel T-4 catalyst[18] in 3.4 kg/cm^2 hydrogen atomosphere for 12 hr. After the catalyst was removed by filtration, the solution was evaporated to give a dark residue (11.5 g). The residue was acetylated overnight at room temperature to give a dark product. The product was recrystallized two times from ethanol to give 120 mg of **7**, mp above 290 °C. The mother liquor was evaporated and the residue was recrystallized from ethanol to give another crop of **7** (207 mg). Total yield was 327 mg (3.5% from **4**).

Found: C, 49.95; H, 6.03; N, 6.52%. Calcd for $C_{18}H_{26}N_2O_{10}$: C, 50.23; H, 6.09; N, 6.51%.

Hexaacetyl myo-*Inosadiamine-1,4 (8).* The ethanolic mother liquor of **7** was evaporated and the residue was recrystallized from a mixture of benzene and ethanol (5 : 1, v/v) to give 2.50 g of **8**. The mother liquor was evaporated and the residue was fractionated on a silica gel column (Wakogel C-300, 80 g, 30×400 mm) with benzene–ethanol (5 : 1, v/v) as an eluating solvent. The fractions which showed a single spot on tlc at R_f 0.28 in the same solvent system were collected and evaporated to give another crop of **8** (1.14 g). The product was recrystallized from ethanol to give 3.63 g (39% from **4**) of **8**, mp 258—259 °C.

Found: C, 50.39; H, 6.11; N, 6.47%. Calcd for $C_{18}H_{26}N_2O_{10}$: C, 50.23; H, 6.09; N, 6.51%.

Hexaacetyl epi-*Inosadiamine-3,6 (9).* Another product was obtained from the column chromatography by collecting the fractions which showed a single spot at R_f 0.26 on tlc in the same solvent. The product was recrystallized from a mixture of benzene and ethanol (5 : 1, v/v) to give 121 mg (1.3% from **4**) of **9**, mp 228—230 °C.

Found: C, 50.07; H, 6.05; N, 6.51%. Calcd for $C_{18}H_{26}N_2O_{10}$: C, 50.23; H, 6.09; N, 6.51%.

The mother liquor was evaporated and the residue was recrystallized repeatedly from a mixture of acetone, benzene and ethyl acetate (1 : 10 : 1, v/v) to give 5 mg of hexaacetyl inosadiamine, mp 278—280 °C. The product showed practically a single spot at R_f 0.20 on tlc in a benzene–ethanol (5 : 1, v/v) solvent system and gave a correct analysis for hexaacetyl inosadiamine (Found: C, 50.37, H, 6.26; N, 6.71%).

Nitromethane Cyclization of 5. To a mixture of **5** (8.5 g), nitromethane (10 ml) and methanol (200 ml), 2.2 M methanolic sodium methoxide (30 ml) was added under ice cooling with agitation. The reaction mixture was worked up as described in the case of **4** to give compounds **7**, **8** and **9** in 4.1, 32 and 1.6% yields, respectively.

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