Aminocyclitols. XVIII. A Synthesis of *myo*-Inosadiamine-1,3 and Its Derivatives

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Actinamine has been synthesized as its hexaacetate from a readily available 2,4,5,6-tetra-*O*-acetyl-1,3-di-*O*-*p*-toluenesulfonyl-*myo*-inositol in a good over-all yield. Hydrazinolysis of this compound, followed by catalytic hydrogenation, afforded *myo*-inosadiamine-1,3 which was a key compound leading to di-*N*-acetyltetra-*O*-acetylactinamine. The configurations of the new compounds obtained were established by nuclear magnetic resonance data and by chemical means. A reaction mechanism is proposed.

Actinamine is a component of the antibiotic actinospectacin,[2] and its structure has been assigned to be *N*,*N*′-dimethyl-*myo*-inosadiamine-1,3.[3] The synthesis has been described by several authors.[4-7]

In the present Article, we wish to report a facile synthesis of *myo*-inosadiamine-1,3 from a readily available 2,4,5,6-tetra-*O*-acetyl-1,3-di-*O*-*p*-toluenesulfonyl-*myo*-inositol (**1**),[8a] which was converted into hexaacetylactinamine (**6**) by *N*-methylation and acetylation.

The displacement of two sulfonyloxy groups in **1** by sodium azide had been described in the previous paper of this series, where 1,4-diazido-1,4-dideoxy-*muco*-inositol was obtained as a sole product in 48% yield.[8b]

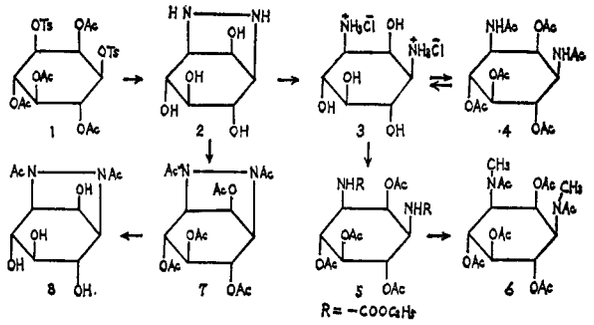
The successful replacement of a sulfonyloxy group in sugar derivatives by hydrazine had been reported by Wolfrom and his coworkers,[9] in cases where this replacement did not occur by an azide ion. Therefore, a diplacement of sulfonyloxy groups in **1** by hydrazine was attempted.

When **1** was heated in a mixture of anhydrous hydrazine and 2-methoxyethanol under reflux for 22 hr, an oily product was obtained by evaporating a reaction mixture. Reduction of the oily product in the presence of a catalyst, followed by acetylation, gave hexaacetyl-*myo*-inosadiamine-1,3 (**4**)[10] in a yield of 45% (Scheme I).

While an analogous reaction was carried out in anhydrous hydrazine without a diluent, **4** was obtained in 35% yield, along with the known hexaacetyl-*muco*-inosadiamine-1,4[5] as a minor product in 2.4% yield.

Several attempts were made to isolate an intermediary compound in the hydrazinolysis of **1**. When an intact hydrazinolysis product in the former reaction was treated with Amberlite IRA-400 to remove acidic

SCHEME I



substances, the crystalline product (**2**) of mp 188–189° dec was obtained in 39% yield.

Hydrogenation of **2** in the presence of a platinum catalyst in an acidic medium afforded *myo*-inosadiamine-1,3 dihydrochloride (**3**) in 92% yield.

3 was treated with ethyl chloroformate in an alkaline solution, followed by acetylation, to give 2,4,5,6-tetra-*O*-acetyl-*N*,*N*′-diethoxycarbonyl-*myo*-inosadiamine-1,3 (**5**) in 87% yield. Reduction of **5** with an excess amount of lithium aluminium hydride, followed by acetylation, gave **6** in 48% yield, which was identified with an authentic sample[11] by a mixture melting point determination, infrared and nuclear magnetic resonance (nmr) spectra. The over-all yield of hexaacetylactinamine from **1** was about 18%.

The structure of the intermediary compound **2** was elucidated on the basis of infrared, nmr spectra, and chemical evidences. Acetylation of **2** gave hexaacetyl derivative (**7**) of mp 186–187°, which showed no amide II band in the infrared spectrum,[12] suggesting a N,N-disubstituted amide structure.

The elementary analysis of **2** showed that one molecule of hydrazine replaced the two sulfonyloxy groups in the same molecule of **1**. Hence a bridged bicyclic structure of 6,7-diazabicyclo[3.2.1]octane system might be a most probable one for the structure of **2**. An analogous bicyclic compound was described by Freudenberg, *et al.*,[13] in the reaction of methyl 2-chloro-2-deoxy-D-glucoside with hydrazine.

Catalytic hydrogenation of **7** did not cleave the N–N bond and **7** was recovered quantitatively. The same inertness of the N–N bond in 2,3-dicarbomethoxy-2,3-diazabicyclo[2.2.1]heptyl derivative has been observed

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(8) (a) S. J. Angyal, P. T. Gilham, and G. J. Melrose, *J. Chem. Soc.*, 5252 (1965); (b) T. Suami, F. W. Lichtenthaler, and S. Ogawa, *Bull. Chem. Soc. Jap.*, **40**, 1488 (1967).

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(10) The authors wish to express an appreciation to Dr. F. W. Lichtenthaler (Institut für Organische Chemie, T. H. Darmstadt, Germany) for an authentic sample.

(11) The authors thank Dr. P. F. Wiley (Upjohn Co., Kalamazoo, Mich.) for supplying an authentic sample of hexaacetylactinamine.

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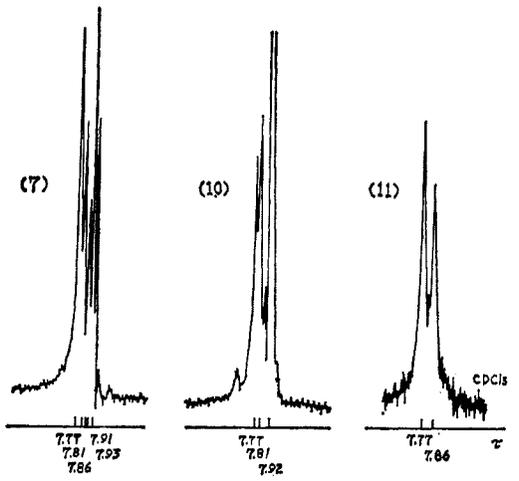


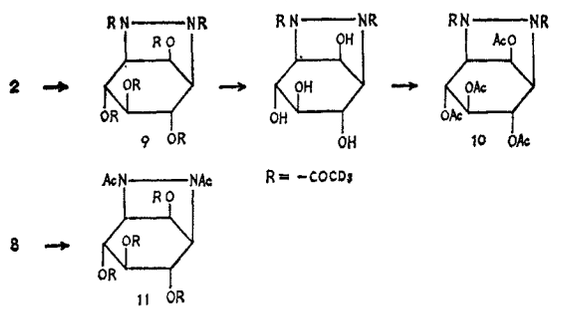
Figure 1.—Nmr spectrum of **7**, **10**, and **11** in $CDCl_3$.

by Allred, *et al.*,[14] and in acyl hydrazine derivatives by Gillis, *et al.*[15]

Nmr spectroscopy has proved to be an extremely useful tool for the conformational studies of sugars[16] and cyclitols.[17] This was true in the present study on the configuration of the bridged bicyclic compound. The nmr spectrum of **7** in $CDCl_3$ revealed five sharp signals at τ 7.77, 7.82, 7.86, 7.91, and 7.93, which were attributed to the four acetoxy and two acetamido groups (Figure 1). To distinguish the signals arising from the two acetamido groups among the five signals, the following method seemed to be feasible. Very recently, in the nmr spectra of acetylated amino sugars, each of the acetyl groups was definitely assigned by a synthesis of their derivatives which had been deuterated in the individual acetyl group.[18]

In the present study, the two hexaacetyl derivatives of **2** (**10** and **11**) which were specifically deuterated in the two *N*-acetyl methyl groups and the four *O*-acetyl methyl groups, respectively, were synthesized, and a direct comparison of the nmr spectra of deuterated and nondeuterated compounds was attempted (Scheme II).

SCHEME II



The nmr spectrum of **10** revealed three signals at τ 7.77, 7.81, and 7.92 (Figure 1). A disappearance of the signal at τ 7.86 and a marked decrease of the intensity of the signal at τ 7.77 suggested that the signals of

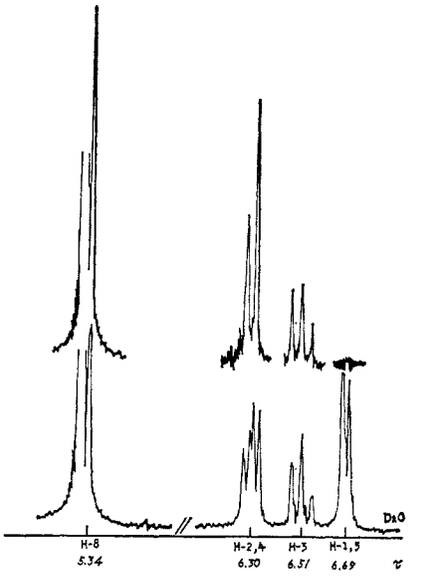


Figure 2.—Nmr spectrum of **2** in D_2O.

the acetamido groups were located at τ 7.77 and 7.86. This was further confirmed by the nmr spectrum of **11** which revealed two sharp signals at τ 7.77 and 7.86 (Figure 1). This spectrum could be reasonably explained on the basis of a hindered internal rotation of acetamido groups and the spectrum was a result of a superposition of the signals arising from the rotational conformers caused by the hindrance of the internal rotation. The analogous observations have been described on the restricted rotation around a CO–N bond by several authors.[19-23]

The pattern of the signals in the lower field was ascribed to the six ring protons of the cyclohexane ring, which appeared at τ 4.48 (2 H), 4.90 (H), 5.10 (H), and 5.22, 5.37 and 5.48 (2 H). In a bicyclo[3.2.1]octane system, it has been described that the dihedral angle between *syn*-H-8 and a bridgehead proton H-1 (or H-5) is close to 90° (J = 0 cps), and that between *anti*-H-8 and H-1 (or H-5) is approximately 40° (J = 5 cps).[24-26]

Since the catalytic hydrogenation of **2** gave *myo*-inosadiamine-1,3 in an almost quantitative yield, the hydroxyl group on C-8 must be in an *anti* orientation to the three-membered bridge. Hence the sharp singlet with an intensity of one proton at τ 5.10 should be attributed to the *syn*-H-8 proton.[27]

The nmr spectrum of **2** in D_2O gave more informations on the assignment of the configuration (Figure 2). The expected singlet arising from the *syn*-H-8[24-27] appeared at τ 5.34. The doublet centered at τ 6.69 was ascribed to the H-1 and H-5 protons. The observed coupling constant (J = 2.5 cps) was consistant with the

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(26) M. E. Munk, C. S. Sodano, R. L. McLean, and T. H. Haskell, *ibid.*, **89**, 4158 (1967).
(27) The H-8 proton of *p*-nitrobenzoate ester of *N*-acetylactinobolamine methyl ketal appears as a triplet (J = 5.0 cps) at τ 5.10, which has been assigned to an *anti* proton.[26] This might be held in a pyrazolidine ring besides pyrrolidine and cyclopentane ring in a bicyclo[3.2.1]octane system.

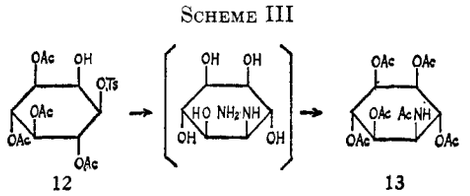
value described by Jefford, *et al.*,[25,28] for the coupling constant between the bridgehead proton (H-5) and the *endo* proton (H-4) in 1-methyl-2,3-benzobicyclo[3.2.1]-octan-4-ol. The triplet at τ 6.51 was assigned to H-3 and the coupling constant (J = 4.2 cps) was close to the value observed in the nmr spectra of bicyclo[3.2.1]-octan-3-ols.[29] The quartet centered at τ 6.30 (J = 4.2 and 2.5 cps) was ascribed to the H-2 and H-4 protons.

A spin-decoupling technique is a valuable aid in an analysis of a complex spectrum, and was used in the present study to confirm the above mentioned assignment of the signals. When H-1 and H-5 (τ 6.69) protons were irradiated, the quartet at τ 6.30 collapsed to a doublet with a coupling constant of 4.2 cps. This irradiation also removed a small splitting from H-8 giving a more sharp signal at τ 5.34, but did not affect the triplet of H-3. Hence the above described assignment of the signals was reasonably accepted.

The cyclohexane ring in 6,7-diazabicyclo[3.2.1]-octane-2,3,4,8-tetrol can theoretically exist in a chair conformation as well as in a boat conformation. Considering the fact that in the nmr spectrum of **2**, none of a large coupling constant (J = *ca.* 10 cps) suggesting a quasi-diaxial relationship between adjacent protons[30-32] was observed, the cyclohexane ring must exist in a chair form. Thus the configuration and structure of **2** was established to be *axial,axial,axial,-anti(equatorial)*-6,7-diazabicyclo[3.2.1]octane-2,3,4,8-tetrol,[33] and the proposed structure was compatible with the chemical and spectral properties.

The reaction mechanism was developed from the structure of **2**. It seemed reliable to assume that a displacement of one of the two sulfonyloxy groups took place with a participation of the vicinal *trans* acetoxy group in **1** to form an intermediary acetoxonium ion, which was then attacked by hydrazine. This occurred in a manner of *trans*-diaxial opening of the cyclic acetoxonium ion, since hydrazinolysis of 3,4,5,6-tetra-*O*-acetyl-1-*O*-*p*-toluenesulfonyl-*myo*-inositol (**12**),[34] followed by hydrogenation and acetylation, yielded hexaacetyl-*muco*-inosamine-1 (**13**)[35] as a sole product in a yield of 66% (Scheme III).

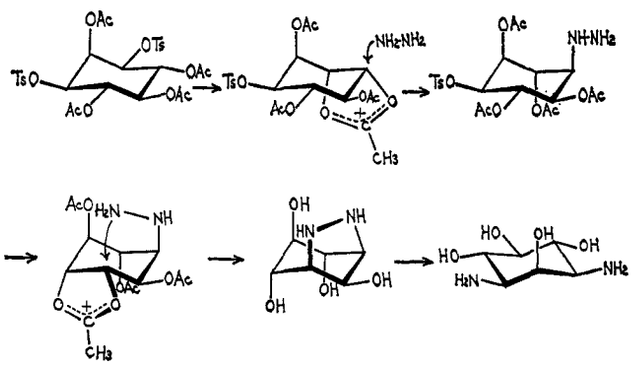
SCHEME III



12 **13**

Then the replacement of another sulfonyloxy group in **1** gave another acetoxonium ion, which was attacked by the hydrazino group, but not by another hydrazine molecule, to give the bridged bicyclic compound, as shown in Scheme IV. At this instance, if hydrazine was used without any diluent, a few acetoxonium ions were attacked by hydrazine in a manner of *trans*-diaxial opening to give a minor product which was corresponding to *muco*-inosadiamine-1,4 derivative.[8] The formation of a bridged bicyclic compound made it possible to obtain *cis*-1,3-diamino derivative selectively.

SCHEME IV



Experimental Section

The melting points were determined on a Mitamura Ricken micro hot stage. The melting points marked with asterisks were measured in a liquid bath and are corrected. The infrared spectra were determined by means of pressed potassium bromide disks. The nmr spectra of the samples were determined at a frequency of 60 and 100 Mc with Japan Electron Optics JNM-C-60 or Varian HA-100 spectrometer in deuteriochloroform, deuterium oxide, or d_6-dimethyl sulfoxide, with tetramethylsilane, sodium trimethylsilylpropanesulfonate, or tetramethylsilane, respectively, used as an internal reference.

Hexaacetyl-*myo*-inosadiamine-1,3 (4). **A.**—A mixture of 2,4,5,6-tetra-*O*-acetyl-1,3-di-*O*-*p*-toluenesulfonyl-*myo*-inositol (**1**) (12.0 g),[7] anhydrous hydrazine (48 ml), and 2-methoxyethanol (240 ml) was heated under reflux for 22 hr. The mixture was evaporated under reduced pressure to give a dark oily residue.[36] The residue was hydrogenated in 50 ml of water with Raney nickel catalyst under an initial hydrogen pressure of 3.4 kg/cm^2 for 22 hr at 50° with a Parr shaker-type hydrogenation apparatus. After the catalyst was removed by filtration, the filtrate was evaporated under reduced pressure to yield an oily residue. The residue was acetylated with acetic anhydride (30 ml) in pyridine (30 ml) overnight at room temperature. Then the mixture was evaporated under reduced pressure to give a crystalline product. Recrystallization from ethanol afforded **4**, yield 3.73 g (45.1%). Recrystallization from ethanol afforded an analytically pure **4** as colorless plates: yield 3.43 g (41.5%); mp *283.5–285° (lit.[3,4] mp 269, 270–271°). A mixture melting point determination with an authentic sample[10] did not show any depression and ir spectrum of **4** was superimposable with that of an authentic sample.[10]

B.—A mixture of **1** (5.0 g) and anhydrous hydrazine (50 ml) was heated under reflux for 48 hr in a nitrogen stream. Then the mixture was treated analogously as described in A. Fractional recrystallization from ethanol yielded 1.03 g (35.2%) of **4**, mp *284–286°. Recrystallization from ethanol afforded pure **4** as colorless plates, mp *285.5–286.5°.

After the mother liquor was evaporated, the residue was recrystallized from ethanol–ether to give 71 mg (2.1%) of hexaacetyl-*muco*-inosadiamine-1,4 (**14**),[8] mp 252.5–253.5°, which was identified with an authentic sample by a mixture melting point determination and comparison of ir spectra (lit.[8] mp 248–250°).

C.—A mixture of 1,3-di-*O*-*p*-toluenesulfonyl-*myo*-inositol (1.5 g)[8] and anhydrous hydrazine (30 ml) was heated under reflux for 48 hr in a nitrogen stream. Then the mixture was treated analogously as described in A. Fractional recrystallization from

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(33) Nomenclature: *axial* and *equatorial* designate those in a cyclohexane derivative. An analogous nomenclature has been used in bicyclo[3.2.1]-octane-2,8-diol by N. A. LeBel and L. A. Spurlock, *J. Org. Chem.*, **29**, 1337 (1964).

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(35) T. Suami and S. Ogawa, *Bull. Chem. Soc. Jap.*, **37**, 1238 (1964); T. Suami, F. W. Lichtenthaler, and S. Ogawa, *ibid.*, **39**, 170 (1966).

(36) All hydrazine should be removed before heating with Raney nickel as the heating of hydrazine with metals can lead to violent explosions.

ethanol yielded 0.15 g (10.6%) of **14**, mp 252.5–253.5°, and 0.36 g (25.4%) of **4**, mp *285.5–286.5°.

6,7-Diazabicyclo[3.2.1]octane-2,3,4,8-tetrol (2).—A mixture of **1** (5.0 g), anhydrous hydrazine (20 ml), and 2-methoxyethanol (100 ml) was heated for 22 hr as described above. After excess reagent was removed by evaporation, an intact hydrazinolysis product was dissolved in 40 ml of cold water. To the solution was added Amberlite IRA-400 and the mixture was settled overnight at room temperature. After the resin was removed by filtration, the filtrate was evaporated to dryness *in vacuo*. The residue was washed with 20 ml of hot ethanol and dissolved in a small amount of water. To the solution was added ethanol and the solution was kept in a refrigerator to give 545 mg (38.6%) of **2**, mp *188–189° dec.

Anal. Calcd for $C_6H_{12}N_2O_4$ (176.2): C, 40.93; H, 6.87; N, 15.90. Found: C, 40.93; H, 6.88; N, 15.70.

***myo*-Inosadiamine-1,3 Dihydrochloride (3). A.**—A mixture of **2** (182 mg) and 4.13 ml of 1 *N* hydrochloric acid in 15 ml of water was hydrogenated with platinum oxide (28 mg) under 3.4 kg/cm² of hydrogen pressure for 22 hr. After the catalyst was removed by filtration, the filtrate was evaporated *in vacuo*. The residue was crystallized in ethanol–water to give 246 mg (91.5%) of **3**, mp 219–237° dec.

B.—A 479-mg portion of **4** was heated in 25 ml of 6 *N* hydrochloric acid under reflux for 2 hr. The solution was evaporated under reduced pressure, and the residue was crystallized from ethanol–water to give 286 mg (98.7%) of **3**. Recrystallization from ethanol–water yielded an analytically pure sample of **3**, mp 221–241.5° dec.

Anal. Calcd for $C_6H_{16}N_2O_4Cl_2$ (251.1): C, 28.70; H, 6.42; N, 11.15; Cl, 28.24. Found: C, 28.89; H, 6.85; N, 10.84; Cl, 28.36.

Hexaacetyl-6,7-diazabicyclo[3.2.1]octane-2,3,4,8-tetrol (7).—A 144-mg portion of **2** was acetylated with acetic anhydride (3.5 ml) and pyridine (6.0 ml) at room temperature overnight. After the mixture was evaporated *in vacuo*, the residue was crystallized in ethanol to give 211 mg (59.4%) of colorless needles, mp 184–185.5°. Recrystallization from ethanol yielded an analytically pure sample of **7**, mp 186.5–187.5°.

Anal. Calcd for $C_{18}H_{24}N_2O_{10}$ (428.4): C, 50.46; H, 5.65; N, 6.54. Found: C, 50.91; H, 5.92; N, 6.36.

A 100-mg portion of **7** was hydrogenated in 10 ml of ethanol in the presence of platinum oxide. After the reduction product was acetylated in acetic anhydride and pyridine, **7** was recovered quantitatively.

Hexatrideuterioacetyl-6,7-diazabicyclo[3.2.1]octane-2,3,4,8-tetrol (9).—A 224-mg portion of **2** was acetylated with 0.85 ml of d_3-acetyl chloride in 7 ml of pyridine under ice cooling. The solution was settled overnight at room temperature and then poured into ice cold water. After the solution was evaporated under reduced pressure, the residue was dissolved in a small amount of water and extracted by six 5-ml portions of chloroform. The chloroform extracts were evaporated and the residue was crystallized from ethanol to give 165 mg (29.1%) of the product, mp 180–182.5°.

2,3,4,8-Tetra-*O*-acetyl-6,7-*N*,*N*′-trideuterioacetamido-6,7-diazabicyclo[3.2.1]octane-2,3,4,8-tetrol (10).—A 114-mg portion of **9** was dissolved in 16 ml of methanol previously saturated with dry ammonia and settled overnight at room temperature. The solution was evaporated under reduced pressure and the residue was acetylated with acetic anhydride in pyridine to give 89 mg of crystalline product in 80.2% yield, mp 185.5–186.5°.

6,7-Di-*N*,*N*′-acetyl-2,3,4,8-tetra-*O*-trideuterioacetyl-6,7-diazabicyclo[3.2.1]octane-2,3,4,8-tetrol (11).—A 100-mg portion of **8** was O-acetylated with 0.23 ml of d_3-acetyl chloride in 4 ml of pyridine by an application of the procedure described for the preparation of **9**. Crystallization of the product in ethanol–ether gave 29 mg (17.0%) of **11**, mp 184.5–185.5°.

Di-*N*,*N*′-acetyl-6,7-diazabicyclo[3.2.1]octane-2,3,4,8-tetrol (8).—A 448-mg portion of **7** was dissolved in 50 ml of methanol previously saturated with ammonia. The solution was settled at room temperature overnight and evaporated to dryness under reduced pressure. The residue was washed with ten 4-ml portions of ethyl acetate and crystallized in methanol–ether to give 138 mg (51.3%) of the crude product, mp 209.5–211.5°. Recrystallization from methanol–ether afforded colorless needles, mp 222–223°.

Anal. Calcd for $C_{10}H_{16}N_2O_6$ (260.2): C, 46.15; H, 6.20; N, 10.77. Found: C, 46.39; H, 6.33; N, 11.13.

Hexaacetyl-*muco*-inosamine-1 (13).—1,4,5,6-Tetra-*O*-acetyl-3-*O*-*p*-toluenesulfonyl-*myo*-inositol (**12**)[34] (1.70 g) was heated in 20 ml of anhydrous hydrazine under reflux for 50 hr in a nitrogen stream. The solution was evaporated under reduced pressure and the residual oil was hydrogenated in 12 ml of water with Raney nickel catalyst for 21 hr under 3.4 kg/cm² of an initial hydrogen pressure. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was acetylated with acetic anhydride (8 ml) and pyridine (8 ml). An excess acetylating reagent was removed by evaporation and the residue was crystallized in ethanol to give 377 mg (43.9%) of **13**, mp 203–205°, which was identified with an authentic sample[35] by a mixture melting point determination and a comparison of ir spectra (lit.[35] mp 205–205.5°). When the same hydrazinolysis was carried out in 2-methoxyethanol, **13** was obtained in 37.7% yield.

2,4,5,6-Tetra-*O*-acetyl-*N*,*N*′-diethoxycarbonyl-*myo*-inosadiamine-1,3 (5).—**3** was converted into **5** by the procedure described in a previous paper[6] in 86.8% yield.

Hexaacetylactinamine (6).—Reduction of **5** by lithium aluminium hydride gave **6** in the procedure described in the previous paper[6] in 47.6% yield.

Registry No.—**2**, 16703-84-7; **3**, 16656-63-6; **7**, 16703-87-0; **8**, 16656-64-7; **9**, 16703-85-8; **10**, 16703-86-9; **11**, 16656-65-8.

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