BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 43 3577—3581 (1970)

Aminocyclitols. XXIV. Synthesis of Inosamines from Bromodeoxyinositols

Tetsuo SUAMI, Seiichiro OGAWA and Masaru UCHIDA

Department of Applied Chemistry, Faculty of Engineering, Keio University, Koganei-shi, Tokyo

(Received June 16, 1970)

Seven inosamines (*scyllo*, *chiro*-1, *myo*-2, *myo*-4, *allo*-5, *neo*-1 and *chiro*-3) have been prepared from four bromodeoxyinositols (*scyllo*, *chiro*-1, *allo*-5 and *neo*-1). When bromodeoxyinositols were treated with sodium azide in boiling aqueous 2-methoxyethanol or dimethylformamide, followed by acetylation, pentaacetyl azidodeoxyinositols were obtained in 60—80% yield. On catalytic hydrogenation using Adams' platinum oxide, the azido compounds yielded hexaacetyl inosamines in good yields. Proton magnetic resonance (PMR) spectra of acetyl azidodeoxyinositols have been studied.

In the course of synthetic studies on aminocyclitols derivatives,[1] it has been recognized that some derivatives showed remarkable biological activities against certain bacteria and Hela cells. Therefore, these findings led us to further investigations of a convenient synthesis of inosamines from a readily accessible material.

Wolfrom and his co-workers[2] have first succeeded

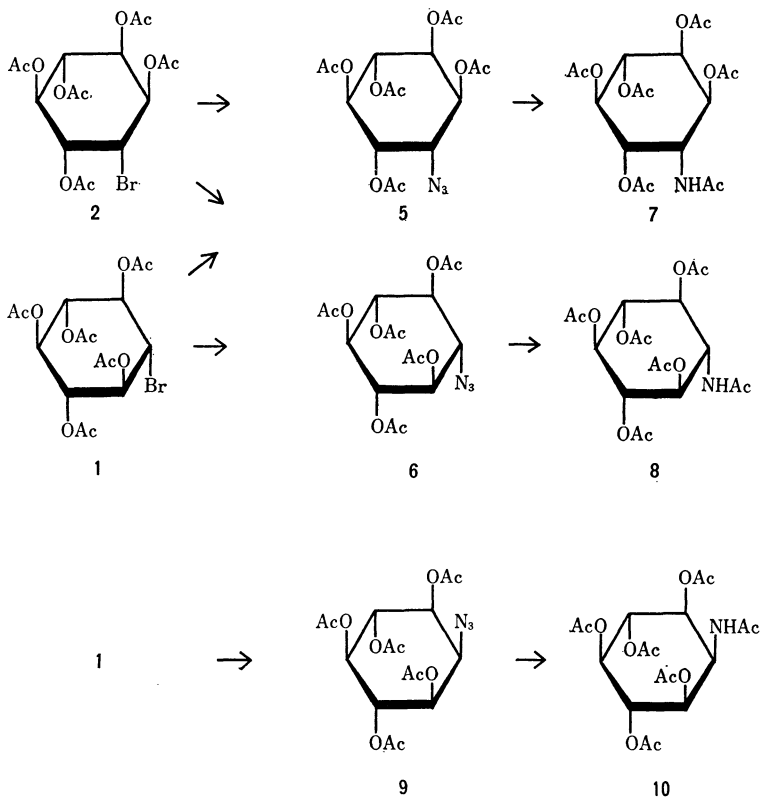


Fig. 1.

1) T. Suami, Y. Sato, Y. Fukai and Y. Sakota, *J. Heterocycl. Chem.*, **6**, 663 (1969); T. Suami and T. Machinami, This Bulletin, **43**, 2953 (1970).

2) M. L. Wolfrom, J. Radell, R. M. Husband and G. E. McCasland, *J. Amer. Chem. Soc.*, **79**, 160 (1957).

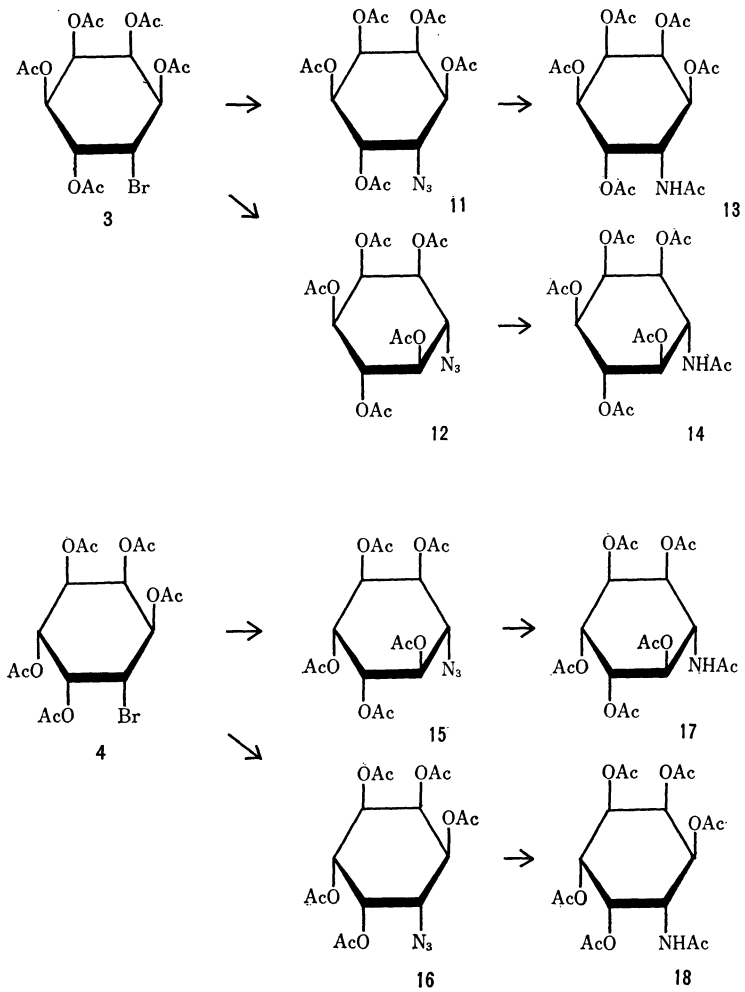


Fig. 2

in converting bromodeoxyinositols to aminodeoxyinositols (inosamines) by heating with ammonia in a sealed tube. By such treatment of crude pentaacetyl 1-bromo-1-deoxy-*scyllo*-inositol (**1**), though in a small yield, two inosamines could be isolated and the structures were proposed by the reaction sequence.

Later, we have reported that 2,4-dibromo-2,4-dideoxy-*chiro*-inosamine-3, on treatment with sodium azide, followed by hydrogenation, gave rise to two inosadiamines in a comparatively good yield.[3] Also, Nakajima and his co-workers[4] have described the synthesis of streptamine from dibromodideoxyinositol by the similar procedure.

The present article reports a facile synthesis of inosamines from readily available bromodeoxyinositols.

According to a modified method of McCasland,[5] two bromodeoxyinositols: **1** and pentaacetyl 1-bromo-1-deoxy-*chiro*-inositol (**2**) were prepared by drastic bromination of *myo*-inositol with acetyl bromide and acetic anhydride at 130—140°C. Analogously, pentaacetyl 5-bromo-5-deoxy-*allo*-inositol (**3**) and 1-bromo-1-deoxy-*neo*-inositol (**4**) were obtained from *epi*-inositol.[6,7]

When **1** was refluxed with an excess amount of sodium azide in 90% aqueous 2-methoxyethanol for 50 hr and subsequently acetylated, an unknown pentaacetyl azidodeoxyinositol (**5**) was obtained together with pentaacetyl 1-azido-1-deoxy-*scyllo*-inositol (**6**)[8] in 64 and 12% yield, respectively.

3) T. Suami, S. Ogawa, Y. Nakashima and H. Sano, This Bulletin, **40**, 2958 (1967).

4) N. Kurihara, T. Kurokawa and M. Nakajima, *Agr. Biol. Chem.* (Tokyo), **31**, 1162 (1967).

5) G. E. McCasland and E. C. Horswill, *J. Amer. Chem. Soc.*, **75**, 4020 (1953).

6) G. E. McCasland and J. M. Reeves, *ibid.*, **77**, 1812 (1955).

7) T. Suami, A. Suzuki, M. Uchida and S. Yanagida, This Bulletin, **42**, 2672 (1969).

8) T. Suami, F. W. Lichtenthaler and S. Ogawa, *ibid.*, **39**, 170 (1966).

Also, on a similar treatment with sodium azide, **2** gave **5** and **6** in 67 and 6% yield, respectively.

The assignment of the structures of azidodeoxyinositols so obtained was carried out by a conversion to known inosamines, along with PMR spectra.

Hydrogenation of **5** using Adams' platinum oxide afforded hexaacetyl *chiro*-inosamine-1 (**7**)[2,9] in 76% yield. Then **5** could be assigned to be pentaacetyl 1-azido-1-deoxy-*chiro*-inositol. These result showed that the azidation reaction of **1** and **2** proceeded through a formation of a same acetoxonium ion intermediate and its preferential diaxial opening by an azide ion.

On the other hand, according to the preferred all equatorial conformation of **1**, it might be proposed that, if dipolar aprotic solvent was used as a reaction solvent, a direct S_N2 attack of azide ion would be possible. Analogous result had been observed in the case of the reaction of 1,3-di-*O*-acetyl-2-*O*-methanesulfonyl-1,2,3-cyclohexanetriol and sodium azide.[10]

Then the reaction of **1** and sodium azide was carried out in boiling aqueous dimethylformamide, instead of 2-methoxyethanol, and a successive acetylation of the reaction product yielded hitherto unknown pentaacetyl azidodeoxyinositol (**9**) in 61% yield. Hydrogenation of **9** gave hexaacetyl *myo*-inosamine-2 (**10**)[11] in 70% yield. Therefore, **9** could be assigned as pentaacetyl 2-azido-2-deoxy *myo*-inositol.

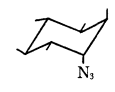
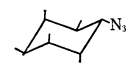
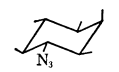
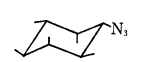
Compound **3**, by a similar treatment with sodium azide, gave pentaacetyl 5-azido-5-deoxy-*allo*-inositol (**11**) and pentaacetyl 4-azido-4-deoxy-*myo*-inositol (**12**) in 46 and 11% yield, respectively. On hydrogenation, **11** and **12** afforded corresponding hexaacetyl *allo*-inosamine-5 (**13**)[12] and hexaacetyl *myo*-inosamine-4 (**14**)[9,13] in 82 and 91% yield, respectively.

From **4**, pentaacetyl 3-azido-3-deoxy-*chiro*-inositol (**15**) and pentaacetyl 1-azido-1-deoxy-*neo*-inositol (**16**) were obtained by the analogous procedure in 68 and 10% yield, respectively. On hydrogenation, **15** and **16** gave corresponding hexaacetyl *chiro*-inosamine-3 (**17**)[9] and hexaacetyl *neo*-inosamine-1 (**18**)[12] in 78 and 68% yield, respectively.

Considering from the products obtained, the azidation reaction of **3** and **4** also proceeded through a formation of an acetoxonium ion intermediate.

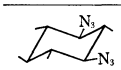
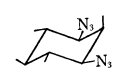
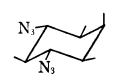
PMR data for the pentaacetyl azidodeoxyinositols are given in Table 1. The signals of the equatorial

Table 1. PMR data of pentaacetyl azidodeoxyinositol[a]

Compound		>CHN$_3$	−OAc axial	−OAc equatorial
	**5**	5.92 (m)[b]	7.83 (6)	7.90 (3) 7.96 (3) 8.00 (3) 8.03 (3)
	**6**	6.27[c]		7.92 (6) 8.02 (9)
	**9**	5.70 (t) J=3.0 Hz		7.91 (6) 8.01 (9)
	**11**[d]	5.87 (q) J=8.0 Hz 3.0 Hz	7.87 (3) 7.94 (6)	7.94 (3) 7.99 (3)
	**12**	6.06 (t) J=10.0 Hz	7.82 (3)	7.90 (3) 7.94 (3) 8.00 (3) 8.02 (3)
	**15**	6.12 (t) J=10.5 Hz	7.84 (6)	7.90 (3) 7.95 (3) 8.02 (3)
	**16**	6.18 (q) J=11.0 Hz 3.0 Hz	7.87 (6)	7.96 (3) 8.04 (6)

—=—OAc

Table 2. PMR data of tetraacetyl diazidodideoxyinositol[a]

Compound		>CHN$_3$	-OAc axial	-OAc equatorial
	**19**	6.36 (t)[b] J=9.5 Hz		7.80 (3) 7.90 (6) 7.99 (3)
	**20**	6.23 (q) J=9.0 Hz 3.0 Hz	7.81 (3)	7.93 (6) 7.98 (3)
	**21**[e]	6.16 (t) J=10.5 Hz	7.80 (3)	7.80 (3) 7.94 (6)

a) Chemical shifts are expressed in τ-values. Values in parenthesis show number of protons. First order coupling constants are expressed.

b) Abbreviations: m, multiplet; t, triplet; q, quartet.

c) Measurement is difficult, because of the poor solubility of **6** in $CDCl_3$.

d) It might be considered that, owing to the distortion of chair conformation, signals of the axial acetoxy groups are somewhat up-shifted and have the same chemical shifts as that of equatorial one does.

e) The PMR spectrum of hexaacetyl *myo*-inosadiamine-4,6, which was obtained by hydrogenation of **21**, showed four peaks at τ 8 region: τ 7.81 (3), 7.94 (3), 8.00 (6) and 8.10 (6). Therefore it is apparent that, in the PMR spectrum of **21**, the signal of equatorial acetoxy group on C-5 and that of axial one on C-2 overlap, because of the down-shift of the former.

9) M. Nakajima, N. Kurihara and A. Hasegawa, *Chem. Ber.*, **95**, 141 (1962).

10) T. Suami, F. W. Lichtenthaler and S. Ogawa, This Bulletin, **38**, 754 (1965).

11) H. E. Carter, R. K. Clark, Jr., B. Lytle and G. E. McCasland, *J. Biol. Chem.* (Tokyo), **175**, 683 (1948).

12) M. Nakajima, A. Hasegawa and N. Kurihara, *Chem. Ber.*, **95**, 2708 (1962).

13) H. Straube-Rieke, H. A. Lardy and L. Anderson, *J. Amer. Chem. Soc.*, **75**, 649 (1953).

acetoxy methyl groups adjacent to azido groups, which are either in an equatorial or an axial conformation, appeared at a region of τ 7.90—7.95 and whose chemical shifts are substantially in a down field (0.05—0.07 ppm in all cases studied) from those of equatorial ones which are adjacent to acetoxy or acetamide groups (τ 7.93—8.03[14]). This phenomenon is readily explained by a strong local magnetic field exerted by an azido group. In the case of tetraacetyl diazidodideoxyinositols listed in Table 2, the similar effect of azido groups on the chemical shifts of vicinal acetoxy groups is recognized. The signal of acetoxy methyl protons on C-5 in tetraacetyl 1,3-diazido-1,3-dideoxy-*scyllo*-inositol (**19**)[15] appears at τ 7.99, but those on C-4 and C-6 are down-shifted by 0.09 ppm (τ 7.90) and a signal of that on C-2 which are surrounded by two azido groups is considerably downshifted (τ 7.80). Similar results are also obtained in tetraacetyl 1,3-diazido-1,3-dideoxy-*myo*-inositol (**20**)[15] and tetraacetyl 4,6-diazido-4,6-dideoxy-*myo*-inositol (**21**).[16]

While, the signals of protons on carbon atoms bearing azido groups appeared at τ 6.06—6.36 (axial) and τ 5.70—5.90 (equatorial). Therefore, it may be possible to distinguish axial protons from equatorial ones by the differences of about 0.40 ppm. But the considerable down-shift effects on chemical shift of the axial proton are observed in the case of **11** by the possibility of serious distortion of the chair conformation or a long range deshielding effect of 1,3-diaxial acetoxy groups.

Experimental

The melting points were determined on a Mitamura Riken micro hot stage and are uncorrected. The PMR spectra were determined with a Japan Electron Optics Laboratory JNM-C-60 spectrometer or a Varian Associates A-60D spectrometer at the frequency of 60 MHz in deuteriochloroform with tetramethylsilane as an internal standard. Evaporations were accomplished under reduced pressure at 40—50°C with a Tokyo Rikakikai rotary evaporator.

Pentaacetyl 1-Bromo-1-deoxy-*scyllo*-inositol (1) and Pentaacetyl 1-Bromo-1-deoxy-*chiro*-inositol (2). These compounds were prepared from *myo*-inositol following a modified method of McCasland.[5]

Throughly dried *myo*-inositol (2.5 g) was treated with acetyl bromide (2.2 m*l*) and acetic anhydride (7.8 m*l*) in a sealed tube at 130—140°C for 8 hr. Then the reaction mixture was poured into ethanol (10 m*l*) and resulting precipitates were collected by filtration. Ten sealed tubes gave 37.5 g of crude **1**, mp 220—235°C. Two recrystallizations from ethylacetate and acetone afforded pure crystals of **1** (36.5 g), mp 238—240°C (lit,[5] mp 241—241.5°C). The yield was 29%. Then the mother liquor of **1** yielded crude **2** (39.0 g), mp 96—103°C, after allowing to stand at room temperature for several weeks. Three recrystallizations from ethanol gave practically pure **2** (31.4 g, 24.8%), mp 114—116°C (lit,[5] mp 124—125°C). (Found: C, 42.30; H, 4.79; Br, 17.79%).

Pentaacetyl 5-Bromo-5-deoxy-*allo*-inositol (3) and 1-Bromo-1-deoxy-*neo*-inositol (4). These compounds were prepared from *epi*-inositol following a modified method of McCasland.[6,7]

Pentaacetyl 1-Azido-1-deoxy-*chiro*-inositol (5) and Pentaacetyl 1-Azido-1-deoxy-*scyllo*-inositol (6). a) A mixture of **2** (2.0 g), sodium azide (1.5 g) and 90% aqueous 2-methoxyethanol (80 m*l*) was refluxed for 50 hr. Then the reaction mixture was evaporated to dryness and the residue was treated with a mixture of pyridine (20 m*l*) and acetic anhydride (20 m*l*) at room temperature overnight. An insoluble material was filtered off and the filtrate was evaporated to give a solid residue. The crude compound was recrystallized from ethanol to afford needles (110 mg, 6.3%), mp 206—207°C, which was identified with an authentic sample of **6** (lit,[8] mp 205—205.5°C) by mixed melting point and comparing with IR spectra. The second and third crops obtained from the mother liquor of **6** were combined and recrystallized from ethanol to give crystals (1.5 g, 66.8%) of **5**, mp 111—113°C. Analytical sample was obtained by recrystallization from methanol, mp 115.5—117°C.

Found: C, 46.18; H, 5.25; N, 10.33%. Calcd for $C_{16}H_{21}N_3O_{10}$: C, 46.26; H, 5.10; N, 10.12%.

b) A mixture of **1** (1.2 g), sodium azide (1.8 g) and 90% aqueous 2-methoxyethanol (30 m*l*) was refluxed for 64 hr. An insoluble material was filtered off and the filtrate was evaporated to dryness. The residue was dried by codistillation with toluene and then treated with a mixture of acetic anhydride (10 m*l*) and pyridine (10 m*l*) at 80°C for 2 hr. A filtered reaction mixture was poured into ice and water. An oily precipitate solidified gradually to give a white solid, which was collected by filtration. The crude product was fractionally crystallized from ethanol to yield **6** (0.12 g, 12%), mp 200—205°C. On evaporation, followed by trituration with methanol, the mother liquor afforded **5** (0.68 g, 64%), mp 110—113°C.

When **1** was treated with sodium azide similarly as described in (a), **5** was obtained only in 17% yield and **1** was recovered in 50% yield.

Hexaacetyl *chiro*-Inosamine-1 (7). A solution of **5** (270 mg) in ethanol (40 m*l*) was hydrogenated in the presence of Adams' platinum oxide (20 mg) in a Parr shaker type apparatus for 20 hr (at the initial hydrogen pressure of 3.4 kg/cm^2). The catalyst was filtered off and the filtrate was evaporated to dryness. The residue was treated with a mixture of acetic anhydride (5 m*l*) and pyridine (5 m*l*) at room temperature overnight. The reaction mixture was evaporated to give a solid residue, which was crystallized from ethyl acetate yielding 210 mg (76.2%) of **7**, mp 157—159°C (lit,[9] mp 156—157°C). **7** was identified with an authentic sample[9] by mixed melting point and IR spectra. (Found: C, 50.42; H, 6.17; N, 3.00%).

Hexaacetyl *scyllo*-Inosamine (8). A 67 mg portion of **6** was hydrogenated in a mixture of ethanol (30 m*l*) and dimethylformamide (10 m*l*) in the presence of

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

15) S. Ogawa, T. Abe, H. Sano, K. Kotera and T. Suami, This Bulletin, **40**, 2405 (1967).

16) T. Suami and S. Ogawa, *ibid.*, **38**, 2026 (1965).

Adams' platinum oxide (15 mg) for 20 hr. Filtering off the catalyst, the filtrate was evaporated to dryness and the residue was acetylated to give crude **8**, which was recrystallized from ethanol to afford needles (45 mg, 80.0%), mp 272—283°C with decomposition (lit,[2,11] mp 275—280°C). The product was identified with an authentic sample by mixed melting point and IR spectra.

Pentaacetyl 2-Azido-2-deoxy-*myo*-inositol (9). A mixture of **1** (2.0 g), sodium azide (1.5 g) and 90% aqueous dimethylformamide (80 m*l*) was refluxed for 25 hr. The reaction mixture was treated similarly as described in the preparation of **5** and **6**. The crude product was acetylated to give crude **9** (1.1 g), mp 200—210°C. Recrystallization from ethanol afforded needles (0.85 g, 61%), mp 207.5—209°C.

Found: C, 46.10; H, 5.26; N, 9.93%. Calcd for $C_{16}H_{21}N_3O_{10}$: C, 46.26; H, 5.10; N, 10.12%.

Hexaacetyl *myo*-Inosamine-2 (10). A solution of **9** (1.0 g) in 2-methoxyethanol (80 m*l*) was hydrogenated in the presence of Adams' platinum oxide (50 mg) for 20 hr. The hydrogenated product was acetylated to give crude **10** (0.81 g), mp 240—245°C. Recrystallization from ethanol afforded needles (0.76 g, 70%), mp 248—250°C (lit.[11] mp 242°C). (Found: C, 50.08; H, 6.06; N, 3.17%).

Pentaacetyl 5-Azido-5-deoxy-*allo*-inositol (11) and Pentaacetyl 4-Azido-4-deoxy-*myo*-inositol (12). A mixture of **3** (2.0 g), sodium azide (1.5 g) and 90% aqueous 2-methoxyethanol (60 m*l*) was refluxed for 20 hr. The reaction mixture was treated similarly as described in the preparation of **5** and **6**. The crude crystalline product was fractionally crystallized from ethanol to afford **11** (0.64 g, 46%), mp 129—130°C, and **12** (0.16 g, 11%), mp 147—150°C. Recrystallization of **11** from ethanol or methanol did not raise its melting point. Analytically pure **12** was obtained by recrystallization from methanol, mp 149—151°C.

11: Found: C, 46.40; H, 5.33; N, 9.80%.

12: Found: C, 46.30; H, 5.30; N, 10.03%.

Calcd for $C_{16}H_{21}N_3O_{10}$: C, 46.26; H, 5.10; N, 10.12%.

Hexaacetyl *allo*-Inosamine-5 (13). A 0.42 g portion of **11** was hydrogenated in the presence of Adams' platinum oxide (20 mg) in ethanol (50 m*l*) for 20 hr. The hydrogenated product was treated with acetic anhydride and pyridine at room temperature overnight. The crude product was crystallized from ethanol and ether to yield crude **13**, mp 180—196°C. Recrystallization from ethanol gave pure crystals (0.36 g, 82%), mp 195—196°C (lit,[12] mp 195°C). (Found: C, 50.50; H, 5.94; N, 3.47%).

Hexaacetyl *myo*-Inosamine-4 (14). A 0.10 g portion of **12** was hydrogenated in ethanol (50 m*l*) in the presence of Adams' platinum oxide (20 mg) for 12 hr. The hydrogenated product was treated with acetic anhydride and pyridine at room temperature overnight. The crude product was crystallized from ethanol to give **14** (95 mg, 91%), mp 228—236°C. Recrystallization from ethanol gave pure sample, mp 234—236°C (lit,[9] mp 236°C). The compound was identified with an authentic sample[9] by mixed melting point and IR spectra.

Pentaacetyl 3-Azido-3-deoxy-*chiro*-inositol (15) and Pentaacetyl 1-Azido-1-deoxy-*neo*-inositol (16). A mixture of **4** (1.0 g), sodium azide (1.0 g) and 90% aqueous 2-methoxyethanol (50 m*l*) was refluxed for 40 hr. The reaction mixture was treated similarly as described in the preparation of **5** and **6**. The crude crystals were fractionally crystallized from ethanol to afford **15** (1.2 g, 68%), mp 153—156°C, and **16** (0.17 g, 10%), mp 185—187°C.

15: Found: C, 46.66; H, 5.39; N, 10.37%.

16: Found: C, 46.85; H, 5.48; N, 10.11%.

Calcd for $C_{16}H_{21}N_3O_{10}$: C, 46.26; H, 5.10; N, 10.12%.

Hexaacetyl *chiro*-Inosamine-3 (17). A 0.55 g portion of **15** was hydrogenated in ethanol (50 m*l*) in the presence of Adams' platinum oxide (20 mg) for 5 hr. The hydrogenated product was acetylated to give crude **17**, which was crystallized from ethanol and ether to afford crystals (0.39 g, 78%), mp 184—187°C. Recrystallization from the same solvent gave a pure sample, mp 186—188°C (lit,[9] mp 189—191°C). (Found: C, 50.35; H, 5.70; N, 3.40%).

Hexaacetyl *neo*-Inosamine-1 (18). A 0.10 g portion of **16** was hydrogenated in ethanol (50 m*l*) in the presence of Adams' platinum oxide (20 mg) for 5 hr. The hydrogenated product was acetylated and crystallized from ethanol to give **18** (70 mg, 68%), mp 237—240°C (lit,[12] mp 240°C). (Found: C, 49.83; H, 5.87; N, 3.21%).

The authors wish to thank Professor Sumio Umezawa for his helpful advices and Mr. Saburo Nakada for his elementary analyses. This research has been financially supported by a grant of the Japanese Ministry of Education.