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Aminocyclitols. XIII. Studies on the Synthesis of Streptamine

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Starting from *epi*-inositol, two new inosamines: *epi*-1 and *epi*-6, and two inosadiamines: *myo*-4, 6 and streptamine, have been prepared by a replacement of sulfonate group by an azide ion. The nuclear magnetic resonance spectroscopy has established the configurations of the products.

In connection with the previous studies of this series,[1] two new inosamines and two inosadiamines including streptamine[2] have been synthesized from *epi*-inositol through 1 : 2, 3 : 4-di-*O*-isopropylidene-*epi*-inositol (I)[3] in the present study.

***epi*-Inosamine-1 and -6.** 6-*O*-Acetyl-1-*O*-*p*-toluenesulfonyl-*epi*-inositol (III) was prepared from I by the method of Angyal *et al.*[4,5]

By an azide replacement reaction, II gave, after subsequent acetylation and hydrogenation, hexaacetyl-*epi*-inosamine-1 (IV) in 43% yield. A selective de-*O*-acetylation of IV yields *N*-acetyl-*epi*-inosamine-1 (V) in 89% yield.

The proton magnetic resonance spectra of IV and V shown in Table 1 are consistent with the configuration described above.

This reaction can be explained, if it is assumed that a displacement of the sulfonyloxy group occurs *via* an intermediary acetoxonium ion with a participation of the neighboring acetoxy group,[6] which is then attacked by a nucleophilic azide ion in a manner of trans-diaxial opening.[7] As there are two axial and two equatorial hydroxyl groups besides the acetoxonium ion, there must be two conformations superimposed. But it is clear that even if an attack of azide ion would take place at C-5 or C-6, only one isomer can be expected.

When I was treated with an excess amount of *p*-toluenesulfonyl chloride, di-*O*-*p*-toluenesulfonyl derivative (VI) was obtained, which is then converted to 1, 2-anhydro-*cis*-inositol by the method of Angyal *et al.*[4] Heating of this compound under pressure with ammonia in methanol, and the subsequent acetylation gave hexaacetyl-*epi*-inosamine-6 (VII) in a 49% yield. In this reaction, only one isomer is expected by a trans-opening of an oxirane ring. This was verified by the NMR spectrum of the product: the spectrum represents three sharp signals of a 2 : 3 : 1 relative intensity at 7.84, 8.00 and 8.09 τ, which correspond to two axial

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[1] T. Suami, F. W. Lichtenthaler and S. Ogawa, This Bulletin, **39**, 170 (1966); T. Suami and S. Ogawa, *ibid.*, **38**, 2026 (1965).

[2] M. G. Brink, F. A. Kuehl, Jr., and K. Folkers, *Science*, **102**, 506 (1945); H. E. Carter, R. K. Clark, Jr., S. R. Dickman, Y. H. Loo, J. S. Meek, P. S. Skell and W. A. Strong, *ibid.*, **103**, 53 (1946); R. L. Peck, R. P. Graber, A. Walti, E. W. Peel, C. E. Hoffhine, Jr., and K. Folkers, *J. Am. Chem. Soc.*, **68**, 29 (1946); R. L. Peck, C. E. Hoffhine, Jr., E. W. Peel, R. P. Graber, F. W. Holly, R. Mozingo and K. Folkers, *ibid.*, **68**, 776 (1946).

[3] S. J. Angyal and C. G. Macdonald, *J. Chem. Soc.*, **1952**, 686; S. J. Angyal and P. T. Gilham, *ibid.*, **1958**, 375.

[4] S. J. Angyal and P. T. Gilham, *ibid.*, **1957**, 3691.

[5] S. J. Angyal and L. Anderson, "Advances in Carbohydrate Chemistry.," Vol. 14, Academic Press, New York (1959), p. 135.

[6] E. S. Gould, "Mechanism and Structure in Organic Chemistry," Rinehart and Winston, New York (1956), p. 565.

[7] T. Suami, F. W. Lichtenthaler and S. Ogawa, This Bulletin, **38**, 754 (1965); **39**, 170 (1966).

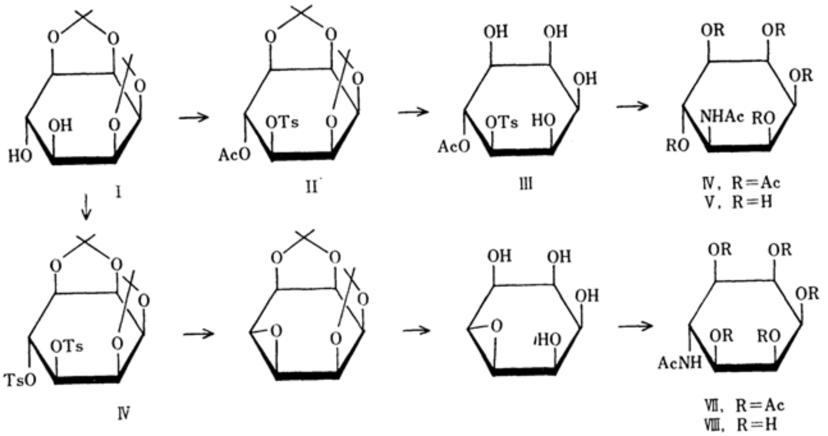


TABLE 1. CHEMICAL SHIFTS τ (IN ppm) OF INOSAMINES AND INOSADIAMINES

Compound	Solvent	OAc axial	OAc equatorial	NHAc equatorial	Amide proton
Hexaacetyl-*epi*-inosamine-1 (IV)	$CDCl_3$	7.86 (6)	7.95 (3) 8.00 (3) 8.03 (3)	8.09 (3)	3.89 (1)
	d_6-DMSO	7.90 (3) 7.88 (3)	8.05 (3) 8.08 (3) 8.13 (3)	8.22 (3)	2.13 (1)
N-Aceyl-*epi*-inosamine-1 (V)	D_2O			7.95 (3)	
Hexaacetyl-*epi*-inosamine-6 (VII)	$CDCl_3$	7.84 (6)	8.00 (9)	8.09 (3)	3.96 (1)
	d_6-DMSO	7.89 (6)	8.10 (9)	8.23 (3)	2.29 (1)
N-Acetyl-*epi*-inosamine-6 (VIII)	D_2O			7.95 (3)	
Hexaacetyl-*myo*-inosadiamine-4, 6 (XIV)	$CDCl_3$	7.81 (3)	7.94 (3) 8.00 (6)	8.10 (6)	3.47 (2)
	d_6-DMSO	7.86 (3)	8.09 (9)	8.25 (6)	2.38 (2)
Di-*N*-acetyl-*myo*-inosadiamine-4, 6 (XV)	D_2O			7.95 (6)	
Hexaacetyl-*scyllo*-inosadiamine-1, 3 (XVI)	d_6-DMSO		8.10 (12)	8.26 (6)	2.33 (2)

The number in parentheses represents a number of protons.

and three equatorial acetoxy groups and an acetamido group respectively.

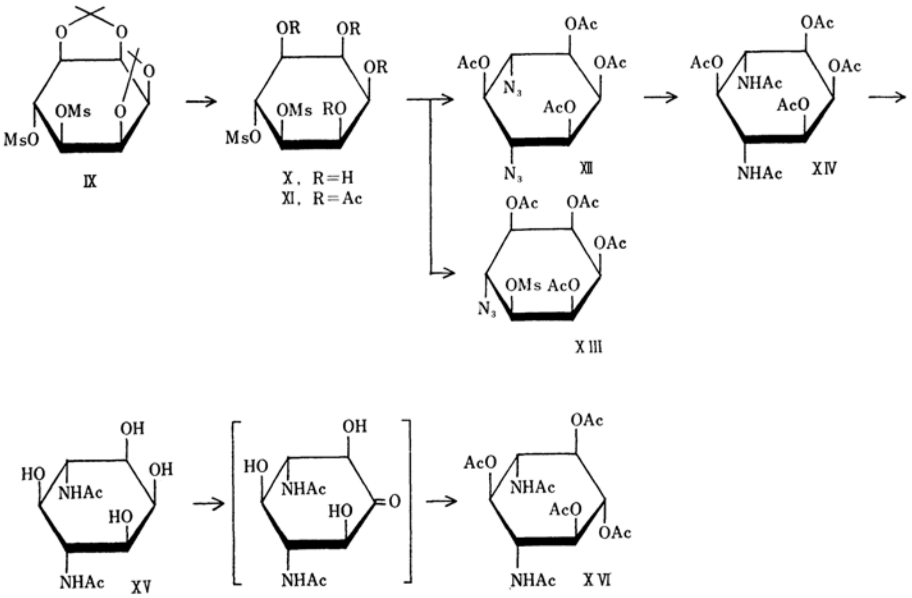
***myo*-Inosadiamine-4, 6 and Streptamine.** When I was treated with methanesulfonyl chloride in pyridine, di-*O*-methanesulfonyl derivative (IX) was obtained in a quantitative yield. Heating of IX in 50% aqueous acetic acid gave 5, 6-di-*O*-methanesulfonyl-*epi*-inositol (X) in 91% yield, which, on acetylation, yielded 1, 2, 3, 4-tetra-*O*-acetyl-5, 6-di-*O*-methanesulfonyl-*epi*-inositol (XI) in 89% yield.

X was heated with sodium azide in aqueous 2-methoxyethanol for 40 hr and subsequently acetylated to give 1, 2, 3, 5-tetra-*O*-acetyl-4, 6-diazido-4, 6-dideoxy-*myo*-inositol (XII) in 54% yield and 1, 2, 3, 4-tetra-*O*-acetyl-6-azido-6-deoxy-5-*O*-methanesulfonyl-*epi*-inositol (XIII) in 7.6% yield. When the same reaction was carried out with XI instead of X, XII and XIII are obtained in 31% and 13% yield respectively.

A catalytic hydrogenation of XII with a platinum catalyst yielded hexaacetyl-*myo*-inosadiamine-4, 6 (XIV) in 91% yield.

A selective de-*O*-acetylation of XIV in methanolic ammonia afforded di-*N*-acetyl-*myo*-inosadiamine-4, 6 (XV) in 94% yield. As there is one axial hydroxyl group on C-2 in XV, a selective oxidation can be carried out successfully. This was achieved by a catalytic oxidation in a presence of platinum catalyst under a stream of oxygen. The crude ketone obtained, was, without further purification, reduced by sodium amalgam in a weakly acidic solution and subsequently acetylated to give hexaacetyl-streptamine (XVI) in 13% yield.

The NMR spectrum of XI reveals two sharp signals at 6.85 and 6.89 τ with an equal intensity, which correspond to two methanesulfonyloxy groups in an equatorial conformation, and four sharp signals of equal intensities at 7.81, 7.84, 7.91 and 8.00 τ, in which the former two are attributed to two axial acetoxy groups and the latter two correspond to two equatorial ones.



The NMR spectrum of XII exhibits a sharp signal at 7.94 τ corresponding to two equatorial acetoxy groups on C-1 and C-3. An acetoxy group on C-5 is overlapped with an axial one on C-2, giving a peak at 7.80 τ. The conformation of acetoxy group on C-5 is clear from the signal of ring proton: the proton on C-5 is coupled with the protons on C-4 and C-6 and appears at 5.04 τ as a triplet with the coupling constant of 10.5 cps,[8] showing all the protons on C-4, C-5 and C-6 are in axial positions, and hence the acetoxy group on C-5 and two azido groups possess an equatorial orientation. Generally, an equatorial acetoxy group shows a signal at 7.94—8.02 τ,[9] but in the present case the signal is shifted to a slightly lower field overlapping with a signal of an axial acetoxy group, and this might be attributed to the presence of two neighboring azido groups. When the azido groups was reduced to amino groups, this effect disappeared, and the acetoxy signal shifted to the normal region for an equatorial acetoxy group.

The NMR spectrum of XIV reveals four sharp peaks with a 1 : 1 : 2 : 2 relative intensity at 7.81, 7.94, 8.00 and 8.10 τ, which correspond to an axial (on C-2), an equatorial (on C-5) and two equatorial acetoxy groups (on C-1 and C-3), and two equatorial acetamido groups (on C-4 and C-6).

From a mechanistic standpoint, an initial step of the displacement of methanesulfonyloxy group (on C-6) of X occurred with a participation of hydroxyl group (on C-1) to give an intermediate oxirane ring. This cyclic intermediate was attacked by an azide ion in a manner of trans-diaxial opening. Then another methanesulfonyloxy group (on C-5) was replaced by an azide ion in a direct S_N2 reaction to give XII. Formation of 6-azido-6-deoxy-5-*O*-methanesulfonyl-*epi*-inositol, a minor product, can be explained by a trans-diequatorial opening of the intermediate by an azide ion. The elimination of another methanesulfonyloxy group on C-5 did not take place in this case and the reaction stopped at this stage. This is not surprising, because the methanesulfonyloxy group in this compound is an equatorial position in its favored conformation, and consequently the rate of the replacement is rather slow compared with that of the main reaction in which the methanesulfonyloxy group is in an axial position.[10]

When the same reaction was carried out with XI, the same products were obtained, but the ratio in the yield between XII and XIII was quite different from that of the former reaction. A cyclic acetoxonium ion might be proposed as an intermediate in this reaction, instead of an oxirane ring in the former case. The difference in steric environment in an intermediate might be responsible for the different manner of its ring opening.

Experimental

The melting points reported were determined on a Mitamura Riken micro hot stage. The infrared spectra were determined by potassium bromide disks. The NMR spectra of the samples were determined at a frequency of 60 Mcps in deuteriochloroform, deuterium

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[8] S. Brownstein and R. Miller, *J. Org. Chem.*, **24**, 1886 (1959).

[9] F. W. Lichtenthaler, *Chem. Ber.*, **96**, 2047 (1963); T. Suami and S. Ogawa, This Bulletin, **37**, 195 (1964).

[10] E. L. Eliel and R. S. Ro, *J. Am. Chem. Soc.*, **79**, 5995 (1957).

oxide or deuteriodimethylsulfoxide with tetramethylsilane, sodium trimethylsilylpropanesulfonate or tetramethylsilane respectively as an internal standard. The peak positions are given in τ-values.

6-*O*-Acetyl-1-*O*-*p*-toluenesulfonyl-*epi*-inositol (III). This compound was prepared by the method of Angyal *et al.*4,5) from 6-*O*-acetyl-1, 2 : 3, 4-di-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-*epi*-inositol (II).3)

Hexaacetyl-*epi*-inosamine-1 (IV). A 1.11 g portion of III was heated with sodium azide (1.0 g) in 2-methoxyethanol (25 m*l*) for 20 hr under reflux. The reaction mixture was evaporated *in vacuo*, and the residue was acetylated with acetic anhydride in pyridine giving an oily product, which showed a characteristic infrared absorption of azido group at 2100 cm^{-1}. The product was hydrogenated in ethanol (20 m*l*) over Adams platinum catalyst (50 mg) under 50 psig of hydrogen pressure for 24 hr at room temperature. The reduction product was acetylated again as described above. The product crystallized by triturating in a mixture of ethanol and ether, giving 0.55 g (43%) of crystals melting at 201—202°C. Recrystallization from ethanol gave needles melting at 204—206°C.

Found: C, 50.25; H, 5.78; N, 3.20%. Calcd for $C_{18}H_{25}NO_{11}$: C, 50.11; H, 5.84; N, 3.23%.

***N*-Acetyl-*epi*-inosamine-1 (V).** A selective de-*O*-acetylation of IV (255 mg) in methanol (15 m*l*) previously saturated with ammonia gave 117 mg (89.4%) of crystals melting at 242—244°C. Recrystallization from aqueous ethanol gave an analytical sample melting at 244—244.5°C.

Found: C, 43.23; H, 6.88; N, 6.15%. Calcd for $C_5H_{15}NO_6$: C, 43.43; H, 6.84; N, 6.33%.

Hexaacetyl-*epi*-inosamine-6 (VII). A 515 mg portion of 1, 2-anhydro-3, 4 : 5, 6-di-*O*-isopropylidene-*cis*-inositol which had been prepared by the method of Angyal *et al.*4) was heated in 50% aqueous acetic acid on a steam bath for 30 min. The solution was evaporated under reduced pressure to dryness giving a crude 1, 2-anhydro-*cis*-inositol. The product was heated with 30 m*l* of methanol saturated with dry ammonia in an autoclave at 100—120°C for 10 hr. The mixture was evaporated and the residue was acetylated with acetic anhydride in pyridine to give crystals (437 mg, 48.5%) melting at 189—191°C. Recrystallization from ethanol gave colorless crystals which showed the same melting point.

Found: C, 50.49; H, 5.63; N, 3.29%. Calcd for $C_{18}H_{25}NO_{11}$: C, 50.11; H, 5.84; N, 3.23%.

***N*-Acetyl-*epi*-inosamine-6 (VIII).** VII (277 mg) was de-*O*-acetylated in methanol saturated with ammonia as described above to give 119 mg (82.6%) of a crude product melting at 200—201°C. Recrystallization from aqueous ethanol gave analytically pure sample melting at 202—203°C.

Found: C, 43.62; H, 6.88; N, 6.19%. Calcd for $C_8H_{15}NO_6$: C, 43.43; H, 6.84; N, 6.33%.

Paper Chromatography. The samples were hydrolyzed in 6 N hydrochloric acid at 100°C for 1.5 hr and evaporated *in vacuo*. The crude hydrochlorides were developed in an ethyl acetate - pyridine - acetic acid - water (5 : 5 : 1 : 3) system at room temperature in an ascending paper chromatography with Toyo Roshi No. 5. The spots were detected with ninhydrin: R_f of *epi*-inosamine-1, -2,11) -6 and D-glucosamine, 0.12, 0.11, 0.11 and 0.26.

1, 2 : 3, 4-Di-*O*-isopropylidene-5, 6-di-*O*-methanesulfonyl-*epi*-inositol (IX). Methanesulfonyl chloride (2.8 m*l*) was added to a solution of 1, 2 : 3, 4-di-*O*-isopropylidene-*epi*-inositol (I) (1.64 g) in anhydrous pyridine (20 m*l*) at 5°C. After settled at room temperature overnight, the solution was poured into ice and water. Then the solution was evaporated under reduced pressure to give a crystalline residue, which was collected and washed with cold water. The crude product (2.54 g, 97.0%) melted at 146—148°C. Recrystallization from ethanol gave colorless plates melting at 147.5—148.5°C.

Found: C, 40.53; H, 5.87; S, 14.93%. Calcd for $C_{14}H_{24}O_{10}S_2$: C, 40.39; H, 5.81; S, 15.40%.

5, 6-Di-*O*-methanesulfonyl-*epi*-inositol (X). A mixture of IX (1.91 g) and 50% aqueous acetic acid (20 m*l*) was heated on a steam bath for 2 hr. The solution was evaporated under reduced pressure to give an oily residue, which was crystallized by adding ethanol. The crude product (1.51 g, 90.5%) melted at 158—162°C after sintering at 122—130°C. Recrystallization from 2-methoxyethanol gave an analytical sample melting at 163—164°C after sintering at 120°C.

Found: C, 29.32; H, 4.95; S, 18.97%. Calcd for $C_8H_{16}O_{10}S_2$: C, 28.57; H, 4.79; S, 19.07%.

1, 2, 3, 4-Tetra-*O*-acetyl-5, 6-di-*O*-methanesulfonyl-*epi*-inositol (XI). X (1.20 g) was acetylated with acetic anhydride (10 m*l*) in pyridine (10 m*l*) at room temperature overnight. An excess acetylating reagent was removed by evaporation and the residue was triturated with ethanol to give crystals (1.71 g, 88.6%) melting at 165—168°C.

Recrystallization from ethanol gave an analytically pure sample melting at 166.5—168.5°C.

Found: C, 38.27; H, 4.61; S, 12.80%. Calcd for $C_{16}H_{24}O_{14}S_2$: C, 38.10; H, 4.80; S, 12.72%.

1, 2, 3, 5-Tetra-*O*-acetyl-4, 6-diazido-4, 6-dideoxy-*myo*-inositol (XII). (a) A mixture of X (12.0 g), sodium azide (12.0 g) and 90% aqueous 2-methoxyethanol (350 m*l*) was heated under reflux for 40 hr. The mixture was evaporated to give a brown residue. The residue was acetylated with acetic anhydride and pyridine. After an excess acetylating reagent was removed, the residue gave crystals by adding ethanol. The crystals were collected by filtration and recrystallized from ethanol to give 5.1 g (53.8%) of plates melting at 147—149°C.

Found: C, 42.46; H, 4.68; N, 20.91%. Calcd for $C_{14}H_{18}N_6O_8$: C, 42.21; H, 4.55; N, 21.10%.

After XII had been removed, the filtrate gave another crystalline product by standing in a refrigerator for a long period. The product was twice recrystallized from ethanol giving 0.81 g (7.6%) of 1, 2, 3, 4-tetra-*O*-acetyl-6-azido-6-deoxy-5-*O*-methanesulfonyl-*epi*-insitol (XIII) melting at 160—161°C. NMR (in $CDCl_3$): 1 equatorial OMs, 6.85τ (3H); 2 axial OAc, 7.82τ (6H); 2 equatorial OAc, 7.90τ(3H) and 8.00τ (3H).

Found: C, 39.72; H, 4.75; N, 9.67; S, 6.98%. Calcd for $C_{15}H_{21}N_3O_{11}$: C, 39.91; H, 4.69; N, 9.31; S, 7.10%.

(b) A mixture of XI (6.4 g), sodium azide (6.3 g) and 90% aqueous 2-methoxyethanol was heated under reflux for 40 hr. The reaction mixture was treated

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11) E. L. May and E. Mosettig, *J. Org. Chem.*, **14**, **14**, 1137 (1949).

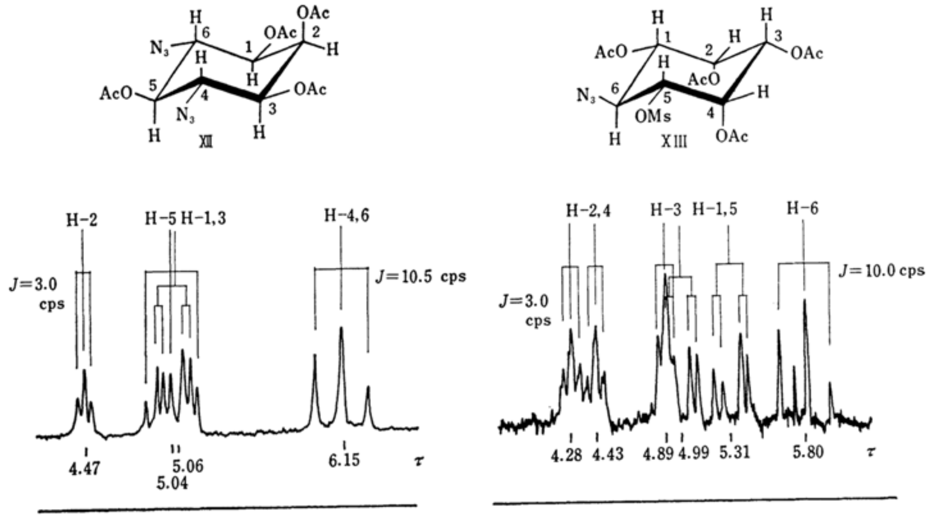

Fig. 1. Partial NMR spectra at 60 Mcps of XII and XIII in $CDCl_3$.

analogously as described above in (a) to give 1.6 g (31.4%) of XII and 0.73 g (12.7%) of XIII.

(c) A mixture of 5, 6-di-*O*-*p*-toluenesulfonyl-*epi*-inositol (5.0 g),[4] sodium azide (4.0 g) and 90% aqueous 2-methoxyethanol (125 m*l*) was treated analogously as described in (a) to give 1.8 g (47%) of XII.

Hexaacetyl-*myo*-inosadiamine-4, 6 (XIV). A 612 mg portion of XII was hydrogenated in ethanol (60 m*l*) with Adams platinum oxide (60 mg) in 50 psig of hydrogen pressure for 3 hr. The catalyst was removed by filtration and the filtrate was evaporated to give an oily residue. The residue was acetylated by acetic anhydride and pyridine to give colorless crystals (602 mg, 91%), mp 290—292°C after coloring at 280°C. A sample was recrystallized from ethanol, showing the same melting point.

Found: C, 50.34; H, 6.16; N, 6.72%. Calcd for $C_{18}H_{26}N_2O_{10}$: C, 50.23; H, 6.09; N, 6.51%.

Di-*N*-acetyl-*myo*-inosadiamine-4, 6 (XV). XIV (257 mg) was selectively de-*O*-acetylated in methanol saturated with ammonia as described above, giving 150 mg (94%) of the crude product. Recrystallization from aqueous ethanol gave needles melting at 320—322°C (decomp.) after sintering and coloring at 305°C.

Found: C, 45.94; H, 7.05; N, 10.58%. Calcd for $C_{10}H_{18}N_2O_6$: C, 45.79; H, 6.92; N, 10.68%.

Hexaacetyl-streptamine (XVI). A solution of XV (373 mg) in 20 m*l* of water was oxidized in the presence of platinum black in a stream of oxygen at 40°C for 22 hr with a mechanical shaking. After the catalyst was removed, the filtrate was evaporated under reduced pressure to 25 m*l* volume of the residual solution. A 6.0 g portion of sodium amalgam (3%) was added portionwise to this solution at 30—40°C and the pH of mixture was maintained at 5.5—6.5 by adding glacial acetic acid. After an evolution of gas had ceased, the solution was decanted and the mercury was washed with water. The combined aqueous solution was evaporated to dryness and the residue was treated with a mixture of acetic anhydride (10 m*l*) and pyridine (10 m*l*) overnight at room temperature.

A small amount of XV was recovered as an insoluble material in the acetylation mixture. Then an excess acetylating reagent was evaporated under reduced pressure. The crystalline residue was triturated in ethanol giving 76.9 mg (12.5%) needles, transition point, 241—247°C.

The product was identified with an authentic sample which had been prepared from dihydrostreptomycin by the method of Peck *et al.*[2]

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