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The Synthesis of 3-Amino-3-deoxy-D-allose and Related Substances[1]

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Starting from methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside, a facile synthesis of 3-amino-3-deoxy-D-allose was carried out; some new *O*-benzyl derivatives of 3-amino-3-deoxy-D-allopyranose are also described.

A variety of derivatives of 3-amino-3-deoxy-D-allose has been synthesized by various methods.[2-9] Recently, an alternative method of preparing this sugar has been reported.[10] In a practical sense, the synthesis demonstrated by Coxon and Hough[11] may be most convenient for getting this aminosugar. However, the known methods for the preparation of the derivative of this aminosugar with the pyranose-ring system[5-7] seem to be rather unpromising. This paper will be concerned with another route to 3-amino-3-deoxy-D-allose as well as with the *O*-benzyl derivative of 3-amino-3-deoxy-D-allopyranose. Recently, the *O*-benzyl derivative of aminosugars has frequently been synthesized as an useful synthetic intermediate.[11]

Methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside,[12] obtained by the one-step benzylation of readily-available methyl α-D-glucopyranoside, was treated with *p*-toluenesulfonyl chloride in pyridine to give the corresponding 3-*O*-*p*-toluenesulfonate (I), which, after debenzylation and acetylation, gave known methyl 2,4,6-tri-*O*-acetyl-3-*O*-*p*-toluenesulfonyl-α-D-glucopyranoside[13] (II), which was the starting material for the synthesis of 3-amino-3-deoxy-D-glucose (kanosamine).[14]

The nucleophilic displacement of the sulfonyloxy group of the sulfonate (I) by the azide ion encountered some difficulties. The nucleophilic substitution of the sulfonyloxy group of the benzylated sugar by the azide residue has been investigated by Stevens and his coworkers.[15] They have successfully utilized moist *N*,*N*-dimethylformamide (DMF) as a solvent. More recently, other high basic dipolar aprotic solvents, such as dimethylsulfoxide (DMSO)[16] and hexamethylphosphoric triamide (HMPA),[17] have been used and found to be excellent solvents for nucleophilic displacement reactions in the carbohydrate field. However, in the case of the replacement reaction of the sulfonate (I) with an azide ion, practically no reaction at all took place under those conditions. However, in DMSO or HMPA, the displacement did proceed under rather

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Table 1. S_N2 reaction of the sulfonates I and Ia with NaN_3

Materials (w:w:v)	Solv.	Temp. (°C)	Time (hr)	Results
I:NaN_3:solv.				
1:4:10	DMF[a)]	150	70	——
1:4:10	DMA	150	50	——
1:4:10	DMSO	100	50	−−
1:4:10	DMSO	130	20	−
1:1:10	DMSO	150	20	+−
1:2:10	DMSO	150	20	+
1:4:10	DMSO	150	20	++
1:4:10	HMPA	100	20	−
1:4:10	HMPA	130	20	+−
1:1:10	HMPA	150	20	+
1:4:10	HMPA	150	20	++
Ia:NaN_3:solv.				
1:4:10	HMPA	100	20	+−
1:1:10	HMPA	130	20	+
1:4:10	HMPA	130	20	++

a) containing water (3%)
—— no reaction
−− I or Ia≫product
− I or Ia>product
+− I or Ia≃product
+ I or Ia<product
++ I or Ia≪product

compulsive conditions to give methyl 3-azide-2,4,6-tri-*O*-benzyl-3-deoxy-α-D-allopyranoside (III) (Table 1). The reaction was monitored by thin-layer chromatography of the reaction mixture. HMPA gave slightly better results.

The azide (III) was treated with lithium aluminium hydride in dioxane[15] to give methyl 3-amino-2,4,6-tri-*O*-benzyl-3-deoxy-α-D-allopyranoside (IV), which was characterized as a crystalline 2,4-dinitrophenyl derivative (V). The corresponding *N*-acetyl and *N*-carbobenzoxy compound of IV could not be crystallized. The amine (IV) was converted into known methyl 2-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-allopyranoside (VI)[7] by catalytic hydrogenolysis, followed by acetylation. The treatment of V with a warm suspension of an anionic resin in moist acetone regenerated the amine (IV), which was then converted into Compound VI. Thus, as might be expected, the substitution of the sulfonyloxy group by the azide ion proceeded with an inversion of the configuration at the reaction center.

The observed lack of reactivity of the sulfonyloxy group in the nucleophilic substitution reaction might be explained, at least, by the idea that the formation of the transition state, which requires the backside approach of the azide anion to C-3, would be interfered with by the 1,3-diaxial interactions by the axial methoxy group at the anomeric center.[18]

We have applied these conditions to another sulfonate, 3-*O*-*p*-toluenesulfonyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[19] (Ia), which has been mentioned as having little susceptibility to nucleophilic substitution reactions.[20] The replacement reaction of this sulfonate with sodium azide was recently carried out in moist DMF, in which heating was continued for 15 days a 115°C.[4] When this was treated with sodium azide in hot HMPA, however, the replacement reaction proceeded well above 125°C and was completed after 24 hr. This result showed that the sulfonate was slightly more susceptible to the replacement with the azide anion under those reaction conditions than was the sulfonate I.

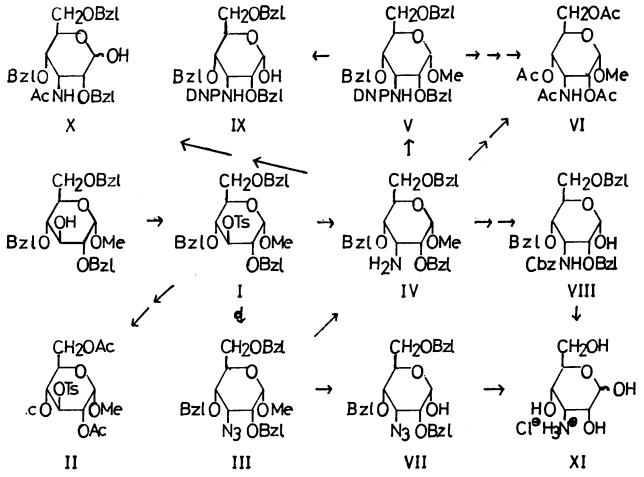

Chart 1.

The difference between the susceptibilities of these sulfonates might be interpreted on the basis of the recent conformational findings[21] that the most stable conformer of methyl α-D-glucopyranoside and its related substances in various solvents is one whose methyl group is oriented to have a *gauche* relationship with the ring oxygen and the C-2 carbon. Therefore, it is conceivable that the access of the azide anion to the reaction center from the opposite side of the leaving sulfonyloxy group would allow the aglycon to rotate to have an unfavorable eclipse relationship to the ring oxygen (Chart 2). On the other hand, the sulfonate (Ia) would not encounter such barriers.

By the way, the nucleophilic replacement of the sulfonyloxy group of syrupy methyl 3-*O*-methanesul-

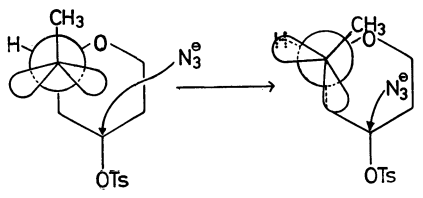

Chart 2.

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fonyl-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside by the azide ion was of no practical use.

The amination of the sulfonate (I) was also carried out by ammonolysis in methanol at 150°C for 30 hr; this gave the amine (IV).

The azide compound (III) was hydrolyzed to furnish a fine crystalline reducible compound (VII), which was then smoothly hydrogenolyzed over palladium-black in the presence of hydrochloric acid to gave the hydrochloride of 3-amino-3-deoxy-D-allose. This aminosugar was also obtained *via* the *N*-carbobenzoxy derivative (VIII).

Two other C-1 free compounds, the *N*-acetyl derivative (X) and the *N*-2,4-dinitrophenyl derivative (IX), were also synthesized. All the crystalline hydrolyzed products (VII, VIII, and IX) were assigned the α-configuration on the basis of their mutarotative behavior.[22] It should be noted that the concentration of the strong acid in the mixed acid used in these hydrolyses was lower than that used in the hydrolyses of the *O*-benzyl sugar with the gluco configuration[11] (Table 2).

Table 2. Hydrolyses of *O*-benzyl sugars

Product	H_2SO_4 in aq. Acetic Acid (N)	Temp. (°C)	Time (hr)	Yield (%)
VII	0.26	100	2.5	54
VIII	0.14	90	8.0	28
IX	0.28	90	11.0	48
X	0.14	100	2.0	27

Experimental

General Procedures. The solvent systems used for the column chromatography over silica gel (Kanto Chemical Co.) or the tlc (Silica Gel G; Merck) were as follows: A, benzene–2-butanone; B, benzene–acetone. The melting points were determined by means of a Yanagimoto micro-melting point apparatus; uncorrected values are given. The specific rotation was measured in a 1-dm tube by means of an Atago Polux apparatus. The IR spectra were determined by means of a JASCO IRA-1 infrared spectrophotometer. The PMR spectra were measured with a Varian S-60T apparatus in $CDCl_3$, with TMS as the internal standard. The elemental analyses were made by means of a Perkin-Elmer Model 240 Elemental Analyser apparatus.

Methyl 2,4,6-Tri-O-benzyl-3-O-p-toluenesulfonyl-α-D-glucopyranoside (I). A solution of methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside[12] (13 g) and *p*-toluenesulfonyl chloride (15 g) in pyridine (26 ml) was kept standing for 4 days at 28°C. The mixture was then diluted with benzene, and the solution was thoroughly washed by aqueous sodium carbonate and then by water. The yellow syrup thus obtained (18 g) was crystallized with cyclohexane to give crude crystals (14 g, 81%), which were then recrystallized from diisopropyl ether to give colorless crystals (10 g, 58%), mp 96—97°C, $[\alpha]_D^{25}$ +34° (*c* 1.9, $CHCl_3$), ν_{max}^{KBr} (cm^{-1}): 1365 and 1171 (sulfonyl). δ (ppm): 2.29 (3H, singlet; $C\underline{H}_3C_6H_4SO_2$–), 3.31 (3H, singlet; $C\underline{H}_3O$–), 7.27 and 7.32 (15H, quasi singlets; $C_6\underline{H}_5CH_2O$–).

Found: C, 67.54; H, 6.29%. Calcd for $C_{35}H_{38}O_8S$: C, 67.94; H, 6.19%.

Methyl 2,4,6-Tri-O-acetyl-3-O-p-toluenesulfonyl-α-D-glucopyranoside[13] *(II).* I (0.20 g) was hydrogenolyzed over palladium-on-carbon (5%, 30 mg) in methanol (7 ml) at room temperature under atmospheric pressure. The glass thus obtained was then heated with acetic anhydride (6 ml) and sodium acetate (0.1 g) at 95°C for 3 hr. A crude acetate (0.16 g) was recrystallized from diisopropyl ether to afford colorless crystals (0.10 g, 65%); mp 95—96°C, $[\alpha]_D^{25}$ +91° (*c* 1.7, $CHCl_3$). The mp admixed with an authentic sample showed no depression. The IR spectrum (KBr) of II could be superimposed upon that of the authentic sample.

Methyl 2,4,6-Tri-O-benzyl-3-(2,4-dinitroanilino)-3-deoxy-α-D-allopyranoside (V). Via the Replacement Reaction in DMSO: A suspension of I (1.0 g) and sodium azide (4.0 g) in DMSO (10 ml) was vigorously stirred on an oil bath (150°C) under reflux for 15 hr. Another portion (1.0 g) of the azide was then added to the mixture, which was further stirred for 5 hr at the same temperature. The mixture was then diluted with benzene, and the insoluble matters were filtered off. The filtrates were concentrated and then evaporated under reduced pressure (3 mmHg) at 70°C to give a dark brown residue, which was chromatographed over the silica gel, developed with the A solvent system (40: 1). After the elution of some by-products as well as the unchanged starting material, the main product appeared; it gave a homogeneous syrup (0.54 g, 68%) of methyl 3-azido-2,4,6-tri-*O*-benzyl-3-deoxy-α-D-allopyranoside (III); ν_{max}^{film} 2155 cm^{-1}. The oily azide (III) (0.58 g) was immediately refluxed with lithium aluminum hydride (0.08 g) in dioxane (10 ml) for 2 hr.[15] After the decomposition of the excess hydride with water the mixture was extracted with benzene to afford a ninhydrin-positive syrup (0.50 g, 91%) of methyl 3-amino-3-deoxy-2,4,6-tri-*O*-benzyl-α-D-allopyranoside (IV). The traces of the by-products were removed by means of column chromatography over silica gel using B solvent system (1: 1). A mixture of the amine (IV) (0.28 g), 2,4-dinitrofluorobenzene (0.10 ml), and triethylamine (0.10 ml) in DMF (2 ml) was kept standing at room temperature overnight. The red solution was then evaporated at 55°C under reduced pressure to give a dark red residue, which was subsequently chromatographed over silica gel, elution being done with the A solvent system (20: 1). The yellow glass thus obtained was crystallized with diisopropyl ether to give yellow crystals (0.23 g, 60%; mp 120—122°C). Two recrystallizations from the same solvent gave an analytical sample; mp 122—123°C, $[\alpha]_D^{25}$ +124° (*c* 0.9, $CHCl_3$), ν_{max}^{KBr} (cm^{-1}): 1620, 1590, 1528, 1500, and 1333 (NHDNP), 1070 (ether).

Found: C, 64.64; H, 5.66; N, 6.63%. Calcd for $C_{34}H_{35}N_3O_9$: C, 64.85; H, 5.60; N, 6.67%.

Via the Replacement Reaction in HMPA: A suspension of I (1.0 g) and sodium azide (4.0 g) in HMPA (10 ml) was stirred at 145°C for 15 hr. Another portion (1.0 g) of the azide was then added to the mixture, after which it was further stirred at 155°C for 5 hr. The mixture was treated in the manner described in Method A to give an oil (0.58 g, 73%) of III, which was then treated with lithium aluminum hydride (0.13 g) in dioxane (13 ml) to give the amine (IV) (0.49 g, 89%).

The amine (IV) (73 mg) was treated with 2,4-dinitrofluorobenzene (50 mg) and triethylamine (33 mg) in DMF (0.7 ml) to give yellow crystals (55 mg, 55%). The mp of this compound was not depressed by admixture with V.

Via Ammonolysis: I (0.30 g) and a solution of ammonia (12 g, saturated at 0°C) in methanol (30 g) was charged in an autoclave, and then the mixture was heated at 155°C

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for 30 hr with stirring. The resulting mixture was concentrated, diluted with methanol, and then passed through a column of Amberite IRA-400 (OH type, stored in methanol). The ninhydrin-positive fractions gave an oil (0.15 g, 67%) of IV. The amine (IV) (0.13 g) was treated with 2,4-dinitrofluorobenzene (0.05 ml) and triethylamine (0.05 ml) in DMF. The yellow crystals thus obtained (0.12 g, 68%) were recrystallized from diisopropyl ether to give a pure sample. The mp of this compound was not depressed by admixture with V.

*Methyl 2-Acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-*D*-allopyranoside*[7] *(VI).* *From V*: A mixture of V (130 mg) and Dowex 1×2 (OH type, 4 ml) in acetone (40 ml) was stirred at 55°C for 50 hr under reflux, with the occasional addition of water (up to 5 ml). The subsequent evaporation of the solvent afforded a syrup which was diluted with methanol (3 ml) and then treated with acetic anhydride (3 ml). The crude syrup was chromatographed over silica gel and developed with the A solvent system (5: 1) to give a homogeneous syrup which was subsequently hydrogenolyzed in methanol in the presence of palladium-on-carbon (5%, 50 mg) under atmospheric pressure. The hydrogenolyzed product was heated with acetic anhydride (1 ml) in the presence of sodium acetate (0.1 g) to give a crude acetate (mp130—131°C). Recrystallization from diisopropyl ether gave a pure sample (37 mg, 50%); mp 134—135°C $[\alpha]_D^{25}$ +90° (*c* 2.3, $CHCl_3$). The mp of this compound admixed with the authentic specimen showed no depression. The IR and PMR spectra of the two compounds were superimposable.

Via the Catalytic Hydrogenolysis of IV: A sample (100 mg) of oily IV was hydrogenolyzed over palladium-on-carbon (5%, 20 mg) in methanol (6 ml) containing 0.02 ml of concd hydrochloric acid at room temperature under atmospheric pressure. A colorless glass (52 mg) thus obtained was subsequently heated with acetic anhydride (4 ml) in the presence of sodium acetate (0.4 g). A crude acetate (74 mg, 95%) thus obtained was crystallized with diisopropyl ether. The mp of this compound was not depressed by admixture with VI.

Via the N*-Acetylation and Reduction of IV*: A sample (200 mg) of oily IV was treated with acetic anhydride (1 ml) in methanol (4 ml) for 2 hr at 25°C to give a ninhydrin-negative syrup, which was dissolved in liquid ammonia (30 ml) and then treated with small pieces of sodium at −80°C until a blue color remained. The reduced mixture was acetylated by heating with acetic anhydride (8 ml) and sodium acetate (0.2 g). The crude acetate was chromatographed over silica gel with the A solvent system (1: 1) to give a pure acetate (94 mg; 60%). The mp admixed with VI showed no depression.

*3-Azido-2,4,6-tri-*O*-benzyl-3-deoxy-α-*D*-allopyranose (VII).* A mixture of oily III (0.23 g), acetic acid (4 ml), and dilute sulfuric acid (2N; 0.6 ml) was heated on a boiling-water bath for 2.5 hr. The mixture was then extracted with benzene to give a brown syrup (0.19 g), which was subsequently chromatographed over silica gel irrigated with the A solvent system (20: 1). After the recovery of a small quantity of the unreacted starting material, the main product was eluted. A homogenous colorless syrup was crystallized with *n*-hexane to give long needles (0.12 g; 54%), which were then recrystallized from the same solvent to afford an analytical sample; mp 108—109°C, $[\alpha]_D^{25}$ +26° (*c* 1.0, $CHCl_3$), $[\alpha]_D^{25}$ +30° (*c* 1.1, pyridine)→+25° (90 hr), $[\alpha]_D^{25}$ +29° (*c* 1.1, pyridine-phenol (8: 1, v/v])→+14° (20 hr). ν_{max}^{KBr} (cm^{-1}): 3410 (OH), 2123 (N_3), 1093 (ether), 820, 754, 733, and 692 (phenyl).

Found: C, 68.07; H, 5.97; N, 8.61%. Calcd for $C_{27}H_{29}N_3O_5$: C, 68.19; H, 6.15; N, 8.84%.

*2,4,6-Tri-*O*-benzyl-3-carbobenzoxyamino-3-deoxy-α-*D*-allopyranose (VIII).* To a mixture of III (0.21 g) in pyridine (4 ml), a solution (1.5 g) of carbobenzoxy chloride in toluene (30%) was added in three portions under cooling; after having been stirred for 18 hr at 25°C, the mixture was treated with a little water and extracted with benzene to gave an orange syrup which was subsequently chromatographed over silica gel irrigated with the A solvent system (20: 1). Homogeneous ninhydrin-negative oil (0.20 g, 74%) was immediately hydrolyzed by heating in a mixed acid prepared from acetic acid (6 ml) and dil. sulfuric acid (1N, 1 ml) at 90°C for 8 hr. The tlc of the hydrolyzate showed the presence of at least six products. A crude mixture which was chromatographed over silica gel was developed with the A solvent system (10: 1). After the elution of the unchanged material as well as other by-products, the aniline phthalate-positive main product (R_f 0.32; the A solvent system [5: 1]) was eluted to give a syrup which was subsequently crystallized with diisopropyl ether to afford a colorless solid (0.07 g, 28%). Recrystallization from the same solvent gave a pure sample; mp 152—153°C, $[\alpha]_D^{25}$ +34° (*c* 0.6, $CHCl_3$), $[\alpha]_D^{25}$ +61° (*c* 1.1, pyridine)→+51° (70 hr), $[\alpha]_D^{25}$ +61° (*c* 0.6, pyridine-phenol [8: 1])→+40° (180 min). ν_{max}^{KBr} (cm^{-1}): 3410 (OH), 3326, 1727, 1517 (NH–Cbz), 1052 (ether), 736, 733, and 690 (phenyl).

Found: C, 72.31; H, 7.24; N, 2.48%. Calcd for $C_{35}H_{37}NO_7$: C, 72.02; H, 6.39; N, 2.40%.

*2,4,6-Tri-*O*-benzyl-3-deoxy-3-(2,4-dinitroanilino)-α-*D*-allopyranose (IX).* A mixture of VI (0.30 g), acetic acid (6 ml), and dil sulfuric acid (2N, 1 ml) was heated at 90°C for 11 hr. The mixture was then treated in the manner described for VII to give an yellow syrup which was subsequently, chromatographed on silica gel with the irrigation of the A solvent system (5: 1). After the elution of the unchanged starting material, the hydrolyzed product (IX) (0.14 g, 48%) was obtained; recrystallization from diisopropyl ether furnished a pure sample, mp 164—165°, $[\alpha]_D^{25}$ +89° (*c* 1.1, $CHCl_3$), $[\alpha]_D^{25}$ +103° (*c* 0.4, pyridine–phenol [8: 1], 45 min)→+96° (7 hr), ν_{max}^{KBr} (cm^{-1}): 3290, 1621, 1592, 1505, 1334 (NH–DNP), 1075 (ether).

Found: C, 64.06; H, 5.43; N, 6.91%. Calcd for $C_{33}H_{33}N_3O_9$: C, 64.38; H, 5.40; N, 6.83%.

*3-Acetamido-3-deoxy-2,4,6-tri-*O*-benzyl-*D*-allopyranose (X).* The acetylation of the amine (IV) (0.21 g) with acetic anhydride (1 ml) in dry methanol (4 ml) at 25°C for 1 hr gave quantitatively a ninhydrin-negative syrupy *N*-acetate, to which was added acetic acid (6 ml) containing dil sulfuric acid (1N, 1 ml). After having been heated over a boiling-water bath for 2 hr, the reaction mixture was treated in the same manner as in the case of VII to give a crude syrup, which was then chromatographed over silica gel, with irrigation with the A solvent (5: 1). After the recovery of the unchanged *N*-acetate of IV (0.10 g), the product appeared to be a homogeneous hard syrup (0.06 g, 27%), $[\alpha]_D^{25}$ +19.3° (*c* 2.9, $CHCl_3$), ν_{max}^{film} (cm^{-1}): 1650, 1530 (NH–Ac), δ(ppm): 1.99 (3H, singlet; $C\underline{H}_3COO$).

Found: C, 69.96; H, 6.71; N, 2.83%. Calcd for $C_{29}H_{33}NO_6$: C, 70.86; H, 6.71; N, 2.85%.

*3-Amino-3-deoxy-*D*-allose Hydrochloride*[10] *(XI).* *From VII*: VII (60 mg) was hydrogenolyzed over palladium black (20 mg) in methanol (8 ml) containing a calculated amount of hydrochloric acid under the pressure (10 lb/in²) of hydrogen. The colorless glass thus obtained was taken up with a small volume of ethanol and then precipitated by the addition of excess diisopropyl ether to give an amorphous hygroscopic mass; (23 mg; 85%); mp 157—160° (decomp.), $[\alpha]_D^{25}$ +25° (*c* 0.7, water). R_{f3AG}[23] = 1.08±0.01 (*n*-butanol: pyridine:

23) 3AG=3-amino-3-deoxy-D-glucose hydrochloride.

water: acetic acid=6: 4: 3: 1), Toyo filter paper No. 50; developed at 20°C for 50 hr in the descending manner and sprayed with ninhydrin in pyridine (0.3%) and aniline hydrogen phthalate in aqueous *n*-butanol (2.5%). The authentic sample[10] had the same value of R_{f3AG}.

From VIII: A small sample was hydrogenolyzed in the manner just described. The paper chromatogram of the hydrogenolyzed solution showed the existence of a single product, detectable by spraying with ninhydrin as well as aniline hydrogenphthalate, which had the same R_{f3AG} value as authentic 3-amino-3-deoxy-D-allose hydrochloride.[10]

3-Acetamido-3-deoxy-1,2 : 5,6-di-O-isopropylidene-α-D-allofuranose[3] *(XII)*. A mixture of 3-*O*-*p*-toluenesulfonyl-1,2: 5,6-di-*O*-isopropylidene-α-D-glucofuranose (Ia)[19] (1.0 g) and sodium azide (4.0 g) in HMPA (10 ml) was vigorously stirred at 130°C for 24 hr. The crude mixture was then chromatographed over silica gel using the A solvent system (20: 1) gave a pure oil (0.49 g, 71%), which was subsequently reduced by the treatment with lithium aluminum hydride (0.1 g) in hot dioxane (10 ml). The amine (0.38 g, 85%) thus obtained was acetylated with acetic anhydride (0.15 ml) in methanol (4 ml) at 25°C for 2 hr to furnish Compound XII (0.38 g, 86%); mp 132—134°C, $[\alpha]_D^{25}$ +67° (*c* 1.3, $CHCl_3$). The mp admixed with the authentic sample showed no depression. The IR and PMR spectra of XI were identical with those of an authentic specimen.