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101. **Shichiro Akiya and Toshiaki Osawa** : Nitrogen-containing Sugars. VII.[*2] On the N,N-Succinyl Derivatives of D-Glucosamine.

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In the preceding papers of this series, the studies on several replacement reactions at C-1 of N,N-phthaloyl derivatives of D-glucosamine were described[*2], 1) and it was concluded that there should be some steric hindrance for the formation of α-anomers in these derivatives. In this connection, it seemed of interest to examine the properties of N,N-succinyl derivatives of D-glucosamine which have the structure of the same type with N,N-phthaloyl derivatives without the benzene ring.

This paper describes several replacement reactions at C-1 of N,N-succinyl derivatives of D-glucosamine. N,N-Succinyl-1,3,4,6-tetra-O-acetyl-β-D-glucosamine (II), m.p. 130~131°, $[\alpha]_{\mathrm{D}}^{29}$ $+21.9°$(CHCl$_3$), was prepared by condensation of 1,3,4,6-tetra-O-acetyl-β-D-glucosamine2) (I) with succinic anhydride. Treatment of (II) with boiling 5% methanolic hydrogen chloride to a constant rotation of the reaction solution and subsequent acetylation with pyridine-acetic anhydride mixture gave a crystalline compound (IV), m.p. 104~105°, $[\alpha]_{\mathrm{D}}^{29}$ $-2.6°$(CHCl$_3$). This compound was identified with authentic methyl N,N-succinyl-3,4,6-tri-O-acetyl-β-D-glucosaminide which was synthesized by the following reaction. Thus, (IV) was obtained by treatment of methyl N-ethoxycarbonyl-β-D-glucosaminide (V) with barium hydroxide to eliminate ethoxycarbonyl group and followed by condensation with succinic anhydride in pyridine in the presence of acetic anhydride as the dehydration and acetylation agent. Bromination of (II) with hydrogen bromide in acetic acid-acetic anhydride mixture (2:1) gave a syrupy product (III). Although (III) was not obtained in crystalline form, its structure was assumed to be N,N-succinyl-1-bromo-3,4,6-tri-O-acetyl-1-deoxy-D-glucosamine by its conversion to (IV) by reaction with methanol and silver carbonate.

On the other hand, chlorination of (II) with hydrogen chloride in acetic anhydride yielded a crystalline compound (VI), m.p. 132~134°, $[\alpha]_{\mathrm{D}}^{27}$ $+21.3°$(CHCl$_3$). The same compound was also obtained by treatment of (II) with anhydrous aluminium chloride in cold chloroform or with titanium tetrachloride in boiling chloroform. Reaction of (VI) with methanol in the presence of silver carbonate as an acid-acceptor gave (IV). From above facts and its rotational behavior, (VI) was assumed to be N,N-succinyl-1-chloro-3,4,6-tri-O-acetyl-1-deoxy-β-D-glucosamine.

In these reactions described above, α-anomers were not isolated. Then, methyl N,N-succinyl-3,4,6-tri-O-acetyl-α-D-glucosaminide (VIII), m.p. 212~215°, $[\alpha]_{\mathrm{D}}^{26}$ $+166.7°$(CHCl$_3$), was prepared by catalytic hydrogenation of methyl N-benzyloxycarbonyl-3,4,6-tri-O-acetyl-α-D-glucosaminide (VII)3) in the presence of palladium-carbon and subsequent condensation with succinic anhydride. Further, N,N-succinyl-1,3,4,6-tetra-O-acetyl-α-D-glucosamine (X), m.p. 138~140°, $[\alpha]_{\mathrm{D}}^{24}$ $+97.8°$(CHCl$_3$), was obtained by condensation of succinic anhydride and 1,3,4,6-tetra-O-acetyl-α-D-glucosamine4) (IX).

Acetolysis of (II) and (VIII) in acetic anhydride-acetic acid mixture (7:3) containing sulfuric acid in a concentration of 0.5*M* until constant rotation of the reaction mixture gave

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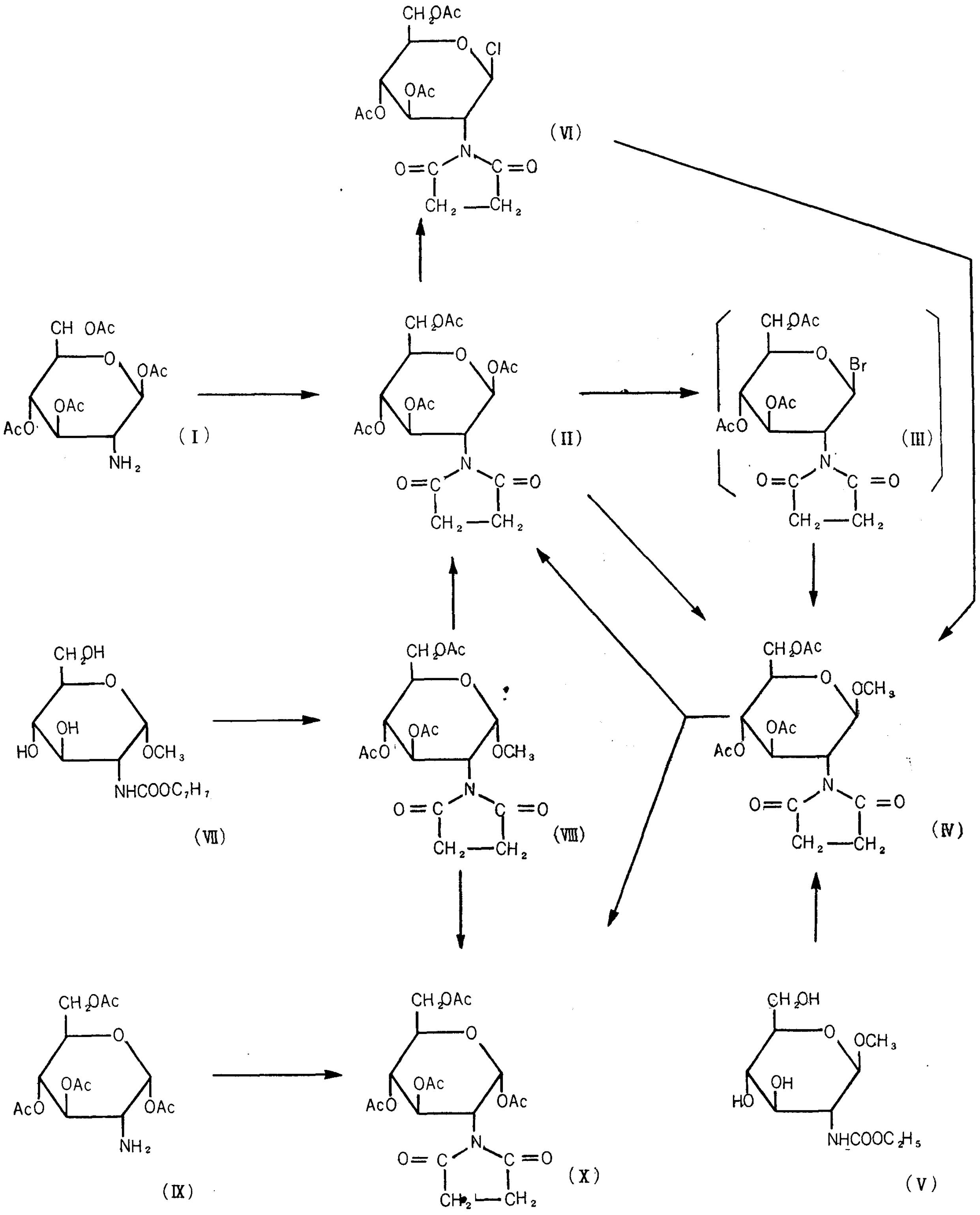

Chart 1.

the same equilibrium mixture from either of these compounds. Chromatographic separation of this acetolysate on silica gel column using benzene-chloroform (2:1) separated it into (II) (50%) and (X) (6%).

These experiments described above indicated that the replacement reactions at C-1 of N,N-succinyl derivatives of D-glucosamine gave mainly β-anomers and there is still some steric hindrance for the formation of α-anomers, as in the case of N,N-phthaloyl derivatives. However, as was seen in the acetolysis experiment which yielded small amount of α-anomer in the case of N-succinyl derivatives, it was presumed that the effect of the steric hindrance in the former derivatives was somewhat less than that in the latter derivatives.

Experimental

N,N-Succinyl-1,3,4,6-tetra-O-acetyl-β-D-glucosamine (II)—A solution of 3 g. of 1,3,4,6-tetra-O-acetyl-β-D-glucosamine (I) and 1 g. of succinic anhydride dissolved in 20 cc. of pyridine was heated for 30 min. at 90°. Then, 20 cc. of Ac_2O was added and heated at 90° for additional 1 hr. The reaction mixture was poured into water and extracted with $CHCl_3$. The $CHCl_3$ solution was washed successively with water, 5% HCl, and water, dried over $CaCl_2$, and evaporated *in vacuo*. The residue was recrystallized from EtOH to white needles, m.p. 130~131°, $[\alpha]^{29}_{D}$ +21.9°(c=1.55, $CHCl_3$). Yield, 2.3 g. *Anal.* Calcd. for $C_{18}H_{23}O_{11}N$: C, 50.35; H, 5.40; N, 3.26. Found : C, 50.13; H, 5.20; N, 3.23.

Methyl N,N-Succinyl-3,4,6-tri-O-acetyl-β-D-glucosaminide (IV)—a) Under a completely anhydrous condition, 1 g. of (II) was refluxed with 20 cc. of 5% HCl/MeOH for 4 hr. After cool, the reaction mixture was neutralized with $PbCO_3$, filtered, and the filtrate was concentrated *in vacuo* to a syrup. This syrup was dissolved in 20 cc. of pyridine-Ac_2O mixture (1:1) and kept overnight at room temperature. The acetylation mixture was poured into water and extracted with $CHCl_3$. The $CHCl_3$ solution was washed successively with water, 5% HCl, and water, dried over $CaCl_2$, and evaporated *in vacuo* to a syrup which was crystallized by EtOH-petr. ether. Recrystallization from 30% MeOH gave white needles, m.p. 104~105°, $[\alpha]^{29}_{D}$ −2.6°(c=1.17, $CHCl_3$). Yield, 0.6 g. *Anal.* Calcd. for $C_{17}H_{23}O_{10}N$: C, 50.87; H, 5.78; N, 3.49. Found : C, 51.38; H, 6.01; N, 3.53.

b) A solution of 1 g. of (II) was dissolved in 15 cc. of Ac_2O-AcOH mixture (1:2) saturated with HBr at 0° was kept standing for 3 hr. at room temperature. The reaction mixture was diluted with $CHCl_3$ and poured into ice-water. The $CHCl_3$ solution was washed three times with water, dried over $CaCl_2$ and evaporated *in vacuo* to a syrup. This syrup was shaken with a suspension of 1 g. of Ag_2CO_3 in 30 cc. of MeOH for 3 hr. After filtering off the Ag salt, the filtrate was evaporated *in vacuo*. The residue was recrystallized from 30% MeOH to white needles, m.p. 104~105°, $[\alpha]^{25}_{D}$ −2.6° (c=1.50, $CHCl_3$). Yield, 0.4 g. In admixture with the sample obtained by (a), no depression of m.p. was observed.

c) A solution of 0.6 g. of methyl N-ethoxycarbonyl-β-D-glucosaminide (V) and 0.8 g. of $Ba(OH)_2$ dissolved in 25 cc. of water was refluxed for 40 min. The precipitated $BaCO_3$ was filtered off and the filtrate was concentrated *in vacuo* to a syrup. A solution of this syrup and 0.22 g. of succinic anhydride dissolved in 10 cc. of pyridine was heated for 30 min. at 90°. Then, 10 cc. of Ac_2O was added and heated for additional 1 hr. at 90°. The reaction mixture was poured into water and extracted with $CHCl_3$. The $CHCl_3$ solution was washed successively with water, 5% HCl, and water, dried over $CaCl_2$, and evaporated *in vacuo*. The residue was recrystallized from 30% MeOH to white needles, m.p. 104~105°, $[\alpha]^{25}_{D}$ −2.6°(c=1.32, $CHCl_3$). Yield, 0.4 g. In admixture with the sample obtained by (a), no depression of m.p. was observed.

d) 0.2 g. of N,N-succinyl-1-chloro-3,4,6-tri-O-acetyl-1-deoxy-β-D-glucosamine was shaken with the suspension of 0.3 g. of Ag_2CO_3 in 10 cc. of MeOH. After filtration, the filtrate was evaporated *in vacuo*. The residue was recrystallized from 30% MeOH to white needles, m.p. 104~105°, $[\alpha]^{25}_{D}$ −2.6°(c=0.85, $CHCl_3$). Yield, 0.1 g. In admixture with the sample obtained by (a), no depression of m.p. was observed.

N,N-Succinyl-1-chloro-3,4,6-tri-O-acetyl-1-deoxy-β-D-glucosamine (VI)—a) A solution of 1 g. of (II) and 0.35 cc. of $TiCl_4$ dissolved in 10 cc. of anhyd. $CHCl_3$ was refluxed for 6 hr. When cooled, the reaction mixture was diluted with $CHCl_3$, poured into ice water, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed succesively with ice-water, cold $NaHCO_3$ solution, and ice-water, dried over $CaCl_2$, and evaporated *in vacuo* to a syrup which was crystallized from toluene-petr. ether. Recrystallization from toluene gave white needles, m.p. 132~134°, $[\alpha]^{27}_{D}$ +21.3°(c=0.47, $CHCl_3$). Yield, 0.5 g. *Anal.* Calcd. for $C_{16}H_{20}O_9NCl$: C, 47.37; H, 4.97; N, 3.45. Found : C, 47.84; H, 4.94; N, 3.44.

b) A mixture of 1.0 g. of (II) and 0.7 g. of anhyd. $AlCl_3$ in 10 cc. of dehyd. $CHCl_3$ was shaken for 40 min. The reaction mixture was poured into ice-water, the $CHCl_3$ solution was dried over $CaCl_2$, and evaporated *in vacuo*. The residue was recrystallized from toluene to white needles, m.p. 132~134°, $[\alpha]^{25}_{D}$ +21.4°(c=1.03, $CHCl_3$). Yield, 0.6 g. In admixture with the sample obtained by (a), no depression of m.p. was observed.

c) A solution of 1.0 g. of (II) dissolved in 15 cc. of Ac_2O saturated with HCl at 0^c was kept standing for 18 hr. at room temperature. The reaction mixture was diluted with $CHCl_3$, poured into ice-water, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed successively with water, cold $NaHCO_3$ solution, and water, dried over $CaCl_2$, and evaporated *in vacuo*. The residue was recrystallized from AcOEt-petr. ether to white needles, m.p. 132~134°, $[\alpha]_D^{25}$ +21.3°(c=2.07, $CHCl_3$). Yield, 0.53 g. In admixture with the sample obtained by (a), no depression of m.p. was observed.

Methyl N,N-Succinyl-3,4,6-tri-O-acetyl-α-D-glucosaminide (X)—2.5 g. of methyl N-benzyloxycarbonyl-α-D-glucosaminide (IX) was catalytically hydrogenated in 30 cc. of MeOH in the presence of 1.5 g. of 20% Pd-C. After 1 mole of H_2 had been absorbed, the reaction mixture was filtered and the filtrate was evaporated *in vacuo*. A solution of the residue and 0.7 g. of succinic anhydride dissolved in 20 cc. of pyridine was heated for 30 min. at 90°. Then, 20 cc. of Ac_2O was added and heated for additional 1 hr. at 90°. The reaction mixture was poured into water and extracted with $CHCl_3$. The $CHCl_3$ solution was washed successively with water, 5% HCl, and water, dried over $CaCl_2$, and evaporated *in vacuo*. The residue was recrystallized from EtOH to white needles, m.p. 212~215°, $[\alpha]_D^{26}$ +166.7°(c=0.78, $CHCl_3$). Yield, 0.7 g. *Anal.* Calcd. for $C_{17}H_{23}O_{10}N$: C, 50.87; H, 5.78; N, 3.49. Found : C, 51.83; H, 6.15; N, 3.51.

N,N-Succinyl-1,3,4,6-tetra-O-acetyl-α-D-glucosamine (VIII)—A solution of 0.8 g. of 1,3,4,6-tetra-O-acetyl-α-D-glucosamine (VII) and 0.3 g. of succinic anhydride dissolved in 10 cc. of pyridine was heated for 30 min. at 90°. Then, 10 cc. of Ac_2O was added and the heating was continued further for 1 hr. at 90°. The reaction mixture was poured into water and extracted with $CHCl_3$. The $CHCl_3$ solution was washed successively with water, 5% HCl, and water, dried over $CaCl_2$, and evaporated *in vacuo*. The residue was recrystallized from 30% MeOH to white needles, m.p. 138~140°, $[\alpha]_D^{24}$ +97.8° (c=0.91, $CHCl_3$). Yield, 0.4 g. *Anal.* Calcd. for $C_{18}H_{23}O_{11}N$: C, 50.35; H, 5.40; N, 3.26. Found : C, 49.93; H, 5.34; N, 3.09.

Acetolysis of (IV) or (X)—A solution of 1.25 g. of (IV) or (X) dissolved in 50 cc. of Ac_2O-AcOH mixture (7:3) containing 1.4 cc. of conc. H_2SO_4 was kept standing at room temperature. After 24 hr., the same reaction mixture having the same final rotation was obtained from both (IV) and (X). The reaction mixture was poured into water containing 10 g. of AcONa and extracted with $CHCl_3$. The $CHCl_3$ solution was washed successively with water, cold $NaHCO_3$ solution, and water, dried over $CaCl_2$, and evaporated *in vacuo*. The residue was dissolved in benzene-$CHCl_3$ mixture (2:1), put on the top of a column (26.5×1.5 cm.) of silica gel and eluted with the same solvent. From the first eluate, white needles of m.p. 130~131° (0.60 g.) were obtained which, on admixture with the authentic sample of (II), gave no depression of m.p. Next eluate gave white needles of m.p. 138~140° (0.07 g.) which was identical with (VIII) by mixed m.p. determination.

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Summary

Several replacement reactions at C-1 position of N,N-succinyl derivatives of D-glucosamine are described. From the results of these reactions, it was concluded that the replacement reactions at C-1 of N,N-succinyl derivatives of D-glucosamine gave mainly β-anomers and there is still some steric hinderance for the formation of α-anomers, as in the case of N-phthaloyl derivatives.

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