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100. Shichiro Akiya and Toshiaki Osawa : Nitrogen-containing Sugars. VI.*2 On the N,N-Phthaloyl Derivatives of D-Glucosamine. (2).

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In the preceding paper of this series,[1] synthesis of N,N-phthaloyl-1,3,4,6-tetra-O-acetyl-β-D-glucosamine (II) was reported and it was observed that the replacement reaction in C-1 position of (II) mainly resulted in the formation of a β-anomer and the formation of α-anomer was markedly obstructed. Among the several β-anomers reported in that paper, 1-bromo-N,N-phthaloyl-3,4,6-tri-O-acetyl-1-deoxy-β-D-glucosamine (III) is the first example of 1,2-*trans*-acetobromo-sugar obtained in glucose and glucosamine series. In this paper will be described the sequence of several replacement reactions at C-1 position of (III) as well as the properties of several new N,N-phthaloyl derivatives of D-glucosamine.

According to Micheel, 1,2-*trans*-acetobromo-sugars do not react with trimethylamine, in contrast to 1,2-*cis*-acetobromo-sugars which generally react with trimethylamine to give quaternary ammonium salt and this reaction is available for establishing the anomeric configuration of acetobromo-sugars. Reaction of (III) with trimethylamine in benzene at room temperature gave no particular product except for recovery of the starting compound (III) and even on heating the mixture at 100° in a sealed tube only (III) was recovered with some tarry product. On the other hand, reaction of N-tosyl-1-bromo-3,4,6-tri-O-acetyl-1-deoxy-α-D-glucosamine (VIII)[3] with trimethylamine at room temperature easily formed quaternary ammonium salt (IX).

Reaction of (III) with methanol in the presence of silver carbonate gave methyl N,N-phthaloyl-3,4,6-tri-O-acetyl-β-D-glucosaminide (IV) and did not give any ortho ester which was often obtained in the case of reaction of 1,2-*trans*-acetohalogen-sugars with methanol. As it is known[4] that the addition of quinoline as acid-acceptor in the methanolysis reaction of 1,2-*trans*-acetohalogen-sugars facilitates the formation of ortho ester, (III) was treated with methanol in the presence of quinoline, but no ortho ester and only (IV) was obtained. The formation of (IV) from (III) was found independent of the acid-acceptor and (IV) was obtained by the reaction of (III) with methanol. The fact that no ortho ester was obtained in the reaction of (III) with methanol might be attributed to the instability of ortho ester ion intermediate (XIV).

By shaking (III) in hydrous acetone in the presence of silver carbonate, N,N-phthaloyl-3,4,6-tri-O-acetyl-D-glucosamine (X), m.p. 166~167°, $[\alpha]_D^{21}$ +52.8°($CHCl_3$), was obtained. This compound was assumed to be the β-anomer from its rotational behavior and the fact that (X) yielded (II) on acetylation with pyridine-acetic anhydride mixture.

Schlubach discovered[5] the occurrence of a replacement of bromine by chlorine with simultaneous inversion for stable 1,2-acetobromo-sugars when it was treated with freshly prepared active silver chloride in an inert solvent for a short time, and this reaction is the most usual method for obtaining unstable 1,2-*trans*-acetochloro-sugars. Recently, Zémplen and co-workers[6] found that the reaction of penta-O-acetyl-β-D-glucose with anhydrous aluminium chloride in cold chloroform gave acetochloro-β-D-glucose. Korytnyk

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*2 Part V : This Bulletin, **7**, 277(1959).

1) Part IV. S. Akiya, T. Osawa : Yakugaku Zasshi, **77**, 726(1957).
2) F. Micheel, H. Micheel : Ber., **63**, 386(1930).
3) F. Micheel, H. Wulff : *Ibid.*, **89**, 1521(1956).
4) W. N. Haworth, E. L. Hirst, M. Stacey : J. Chem. Soc., **1931**, 2864.
5) H. H. Schlubach : Ber., **59**, 840(1926).
6) G. Zémplen, L. Mester : Acta Chim. Acad. Sci. Hung., **4**, 73(1954).

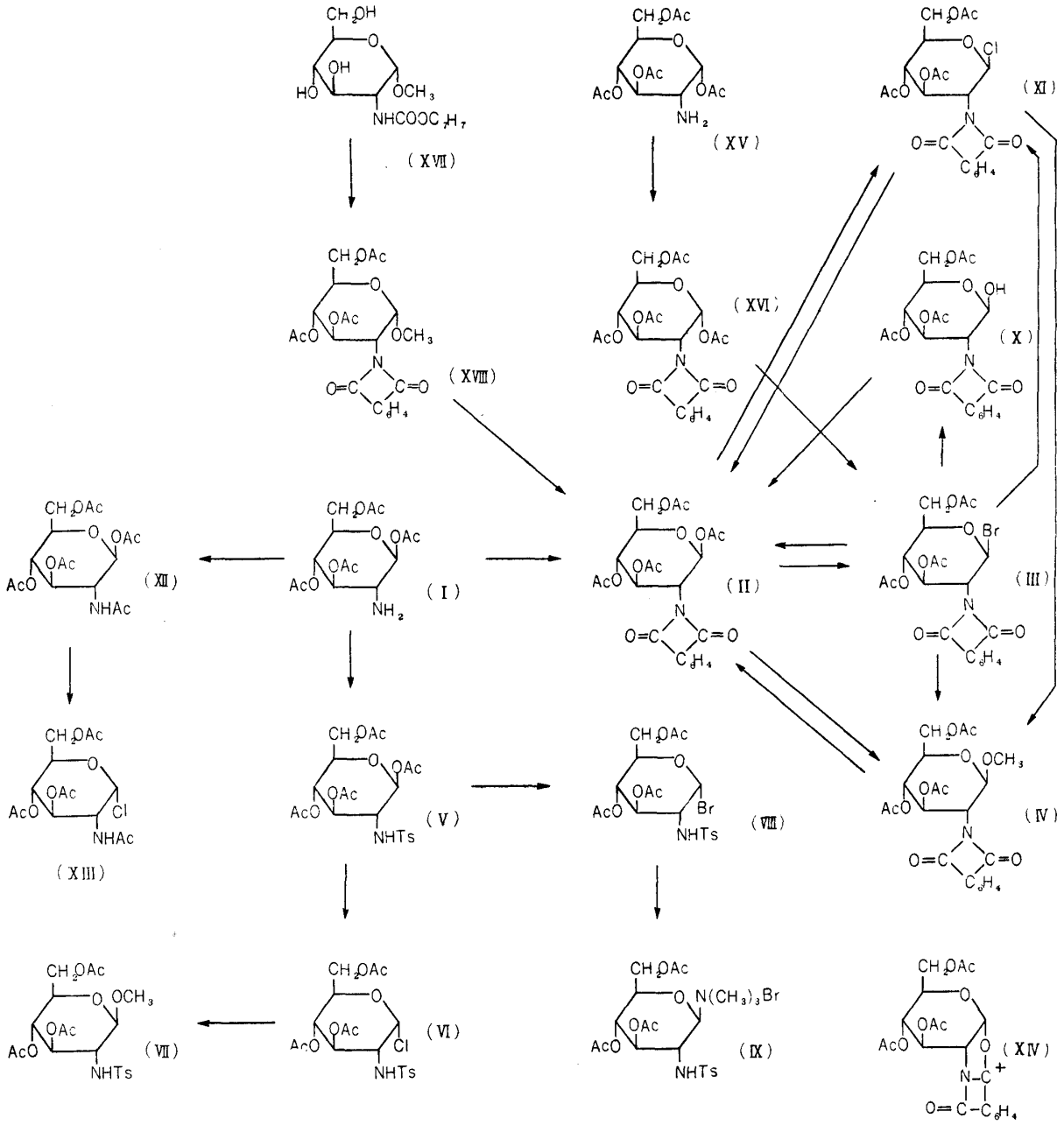

Chart 1.

and Mills recommended[7] that this reaction was one of the useful methods in the preparation of 1,2-*trans*-acetochloro-sugars from 1,2-*trans*-acetylated sugars.

Treatment of (III) with freshly prepared silver chloride in ether-benzene mixture (2:1) gave N,N-phthaloyl-1-chloro-3,4,6-tri-O-acetyl-1-deoxy-D-glucosamine (XI), m.p. 149°, $[\alpha]_D^{19}$ +61.7° ($CHCl_3$), which was also obtained by treatment of (II) with aluminium chloride in cold chloroform. Reaction of (XI) with methanol in the presence of silver carbonate gave (IV), and (XI) was transformed to (II) by reaction with silver acetate in boiling benzene. From above series of experiments and the rotational behavior of the product, (XI) was concluded to be N,N-phthaloyl-1-chloro-3,4,6-tri-O-acetyl-1-deoxy-β-D-glucosamine.

In both cases, treatment of (II) with hydrogen chloride in acetic anhydride or titanium tetrachloride in boiling chloroform gave the same product (XI). However, these

7) W. Korytnyk, J. A. Mills: J. Chem. Soc., **1959**, 636.

two chlorination reagents gave acetochloro-α-D-glucosamine[8] (XIII) and N-tosyl-1-chloro-3,4,6-tri-O-acetyl-1-deoxy-α-D-glucosamine (VI), m.p. 138°, $[\alpha]_D^{20}$ +106.8°($CHCl_3$), from penta-O-acetyl-β-D-glucosamine (XII) and N-tosyl-1,3,4,6-tetra-O-acetyl-β-D-glucosamine (V), respectively. The structure of (VI) was confirmed by its conversion to methyl N-tosyl-3,4,6-tri-O-acetyl-β-D-glucosaminide (VII) by treatment with methanol and silver carbonate.

As far as the foregoing series of experiments were concerned, no α-anomer of N,N-phthaloyl derivatives of D-glucosamine was obtained by any replacement reactions of β-anomers.

N,N-Phthaloyl-1,3,4,6-tetra-O-acetyl-α-D-glucosamine (XVI), m.p. 124~126°, $[\alpha]_D^{25}$ +116.1°($CHCl_3$), was obtained by condensation of 1,3,4,6-tetra-O-acetyl-α-D-glucosamine (XV) with phthalic anhydride, and methyl N,N-phthaloyl-3,4,6-tri-O-acetyl-α-D-glucosaminide (XVIII), m.p. 159~161°, $[\alpha]_D^{25}$ +180.3°($CHCl_3$), was prepared by hydrogenation of methyl N-benzyloxycarbonyl-3,4,6-tri-O-acetyl-α-D-glucosaminide (XVII) in the presence of palladium-carbon followed by condensation with phthalic anhydride.

Treatment of (XVI) with hydrogen bromide in acetic anhydride afforded (III). Acetolysis of (IV) or (XVIII) in a mixture of acetic anhydride-acetic acid (7:3) containing sulfuric acid in a concentration of 0.5*M* until constant rotation of the reaction mixture gave the same reaction product (II).

From the results observed in all of the above-described experiments, it should be concluded that the replacement reaction at C-1 position of N,N-phthaloyl derivatives of D-glucosamine furnishes mainly β-anomers and these glucosamine derivatives clearly have some steric hinderance for the formation of α-anomers.

Experimental

Attempted Reaction of N,N-Phthaloyl-1-bromo-3,4,6-tri-O-acetyl-1-deoxy-β-D-glucosamine (III) with Trimethylamine—a) A solution of 0.5 g. of (III) dissolved in 5 cc. of benzene containing 0.5 g. of trimethylamine was kept standing overnight at room temperature. When the solvent was evaporated, the starting material (III) was recovered quantitatively.

b) A mixture of 0.5 g. of (III) dissolved in 5 cc. of benzene containing 0.5 g. of trimethylamine was heated for 3.5 hr. in a sealed tube at 100°. After cool, the solvent was removed *in vacuo*. The water-insoluble residue was composed of the starting material and its decomposition products. No water-soluble quaternary ammonium salt was obtained.

Reaction of N-Tosyl-1-bromo-3,4,6-tri-O-acetyl-1-deoxy-α-D-glucosamine (VIII) with Trimethylamine—A solution of 0.2 g. of (VIII) dissolved in 5 cc. of benzene containing 0.2 g. of trimethylamine was kept standing overnight at room temperature. After evaporation of the solvent, the residue was reprecipitated from EtOH-Et_2O. $[\alpha]_D^{19}$ +34.1°(c=3.37, H_2O). *Anal.* Calcd. for $C_{22}H_{34}O_9N_2Br$: C, 45.43; H, 5.73; N, 4.82. Found : C, 44.88; H, 5.10; N, 4.53.

Reaction of (III) with MeOH in the Absence of Acid-acceptor—A solution of 0.2 g. of (III) dissolved in 5 cc. of MeOH was refluxed for 1 min. and left to stand overnight at room temperature. After evaporation of MeOH *in vacuo*, the residue was acetylated with pyridine-Ac_2O at room temperature. After 24 hr., the reaction mixture was poured into water, extracted with $CHCl_3$, and the $CHCl_3$ solution was washed successively with water, 5% HCl, and water, and after drying over $CaCl_2$, the solution was concentrated *in vacuo*. The residue was recrystallized from MeOH to white plates, m.p. 156~157°, $[\alpha]_D^{19}$ +45.5°*3(c=3.5, $CHCl_3$). In admixture with authentic methyl N,N-phthaloyl-3,4,6-tri-O-acetyl-β-D-glucosaminide, no depression of m.p. was observed.

Reaction of (III) with MeOH in the Presence of Quinoline as Acid-acceptor—A solution of 1.9 g. of (III) dissolved in 30 cc. of MeOH containing 3 cc. of quinoline was kept standing for 5 hr. at 40° and overnight at room temperature. The reaction mixture was diluted with $CHCl_3$ and washed successively with water, 5% HCl, cold $NaHCO_3$ solution, and water. The $CHCl_3$ solution was dried over Na_2SO_4 and evaporated *in vacuo*. On trituration with Et_2O, the residue crystallized and was recrystallized from AcOEt-petr. ether to white needles, m.p. 156~157°, $[\alpha]_D^{17}$ +45.5°(c=3.23, $CHCl_3$). Yield, 1.2 g. In admixture with authentic methyl N,N-phthaloyl-3,4,6-tri-O-acetyl-β-D-glucosaminide, no depression of m.p. was observed.

*3 Optical rotational value described in Part IV was found to be incorrect and is revised to the constant given here.

8) D. H. Leaback, P. G. Walker : J. Chem. Soc., **1957**, 4754.

Reaction of (III) with AcOAg—Under complete anhydrous conditions, 0.5 g. of (III) dissolved in 20 cc. of benzene was stirred with dry AcOAg for 3 hr. at boiling temperature of benzene. After filtering through charcoal, the solution was concentrated *in vacuo*. The residue was recrystallized from EtOH to white needles, m.p. 92~95°, $[\alpha]_D^{20}$ +59.2°*[3] (c=1.7, $CHCl_3$). Yield, 0.4 g. In admixture with authentic N,N-phthaloyl-1,3,4,6-tetra-O-acetyl-β-D-glucosamine (II), no depression of m.p. was observed.

N,N-Phthaloyl-3,4,6-tri-O-acetyl-β-D-glucosamine (X)—To the solution of 0.5 g. of (III) in 10 cc. of Me_2CO, 0.5 cc. of water and 0.5 g. of Ag_2CO_3 were added and the mixture was shaken vigorously for 4 hr. After filtering through charcoal, the solution was concentrated *in vacuo*. The residue was recrystallized from AcOEt to white needles, m.p. 166~167°, $[\alpha]_D^{21}$ +52.8° (c=1.25, $CHCl_3$). Yield, 0.3 g. *Anal.* Calcd. for $C_{20}H_{21}O_{10}N$: C, 55.17; H, 4.86; N, 3.09. Found: C, 54.69; H, 4.23; N, 3.41.

Acetylation of (X)—A solution of 0.40 g. of (X) dissolved in a mixture of 5 cc. of pyridine and 5 cc. of Ac_2O was kept standing overnight at room temperature. The acetylation mixture was poured into water, 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. 92~95°, $[\alpha]_D^{20}$ +59.1° (c=1.30, $CHCl_3$). Yield, 0.35 g. In admixture with authentic N,N-phthaloyl-1,3,4,6-tetra-O-acetyl-β-D-glucosamine (II), no depression of m.p. was observed.

N,N-Phthaloyl-1-chloro-3,4,6-tri-O-acetyl-1-deoxy-β-D-glucosamine (XI)—a) A solution of 0.5 g. of (III) dissolved in a mixture of 7 cc. of dehyd. benzene and 13 cc. of dehyd. Et_2O, after addition of 2.0 g. of freshly prepared active AgCl, was boiled for 10 min. under stirring, excluding atmospheric moisture. After removal of AgBr, the reaction mixture was concentrated *in vacuo*. The residue was recrystallized from toluene-petr. ether to white needles, m.p. 149°, $[\alpha]_D^{19}$ +61.7° (c=2.22, $CHCl_3$). Yield, 0.32 g. *Anal.* Calcd. for $C_{20}H_{20}O_9NCl$: C, 52.93; H, 4.44; N, 3.09. Found: C, 53.28; H, 4.16; N, 2.99.

b) To a solution of 2.0 g. of (II) dissolved in 20 cc. of pure, dehyd. $CHCl_3$, 1.5 g. of crushed anhyd. $AlCl_3$ was added and the mixture was shaken at room temperature for 40 min. The mixture was then poured into ice-water and the separated aqueous layer was extracted with 20 cc. of $CHCl_3$. The combined $CHCl_3$ solution was dried over $CaCl_2$, evaporated *in vacuo* to a viscous syrup, and this syrup was crystallized from toluene-petr. ether. Recrystallization from toluene gave white needles, m.p. 149°, $[\alpha]_D^{20}$ +61.7° (c=1.51, $CHCl_3$). Yield, 1.3 g. In admixture with the sample obtained in (a), no depression of m.p. was observed.

c) A solution of 3.0 g. of (II) and 0.7 cc. of $TiCl_4$ dissolved in 15 cc. of dehyd. $CHCl_3$ was refluxed for 6.4 hr. The reaction mixture was diluted with $CHCl_3$, washed successively with ice-water, cold $NaHCO_3$ solution, and ice-water, and dried over Na_2SO_4. After filtration, the solution was concentrated *in vacuo* to a viscous syrup and the syrup was crystallized from toluene-petr. ether. Recrystallization from toluene gave white needles, m.p. 149°, $[\alpha]_D^{21}$ +61.7° (c=2.01, $CHCl_3$). Yield, 1.2 g. In admixture with the sample obtained in (a), no depression of m.p. was observed.

d) A solution of 1.0 g. of (II) dissolved in 15 cc. of Ac_2O saturated with HCl at 0° was left to stand for 18 hr. at room temperature. The reaction mixture was diluted with $CHCl_3$ and poured into ice-water. The $CHCl_3$ solution was washed successively with ice-water, cold $NaHCO_3$ solution, and ice-water, dried over $CaCl_2$, and evaporated *in vacuo*. The residue was recrystallized from AcOEt-petr. ether to white needles, m.p. 149°, $[\alpha]_D^{25}$ +61.7° (c=1.32, $CHCl_3$). Yield, 0.55 g. In admixture with the sample obtained in (a), no depression of m.p. was observed.

Reaction of (XI) with MeOH in the Presence of Ag_2CO_3—0.3 g. of (XI) was shaken with a suspension of 0.3 g. of Ag_2CO_3 in 20 cc. of dehyd. MeOH for 4 hr. The reaction mixture was then filtered through charcoal and the halogen-free filtrate was concentrated *in vacuo* to a crystalline mass. Recrystallization from MeOH gave white plates, m.p. 156~157°, $[\alpha]_D^{19}$ +45.5° (c=1.2, $CHCl_3$). Yield, 0.2 g. In admixture with authentic methyl N,N-phthaloyl-3,4,6-tri-O-acetyl-β-D-glucosaminide (IV), no depression of m.p. was observed.

Reaction of (XI) with AcOAg—Under completely anhydrous conditions, 0.7 g. of (XI) dissolved in 20 cc. of benzene was stirred with 0.7 g. of AcOAg under reflux. After filtering through charcoal, the solution was concentrated *in vacuo* to a syrup which was crystallized from EtOH. Recrystallization from EtOH gave white needles, m.p. 92~95°, $[\alpha]_D^{18}$ +59.1° (c=1.8, $CHCl_3$). Yield, 0.5 g. In admixture with authentic N,N-phthaloyl-1,3,4,6-tetra-O-acetyl-β-D-glucosamine (II), no depression of m.p. was observed.

N-Tosyl-1-chloro-3,4,6-tri-O-acetyl-1-deoxy-α-D-glucosamine (VI)—a) A solution of 3.0 g. of N-tosyl-1,3,4,6-tetra-O-acetyl-β-D-glucosamine[9] (V) and 0.7 cc. of $TiCl_4$ dissolved in 20 cc. of dehyd. $CHCl_3$ was refluxed for 6.5 hr. The reaction mixture was diluted with $CHCl_3$ and poured into ice-water. The $CHCl_3$ solution was washed successively with ice-water, cold $NaHCO_3$ solution, and ice-water, dried over $CaCl_2$, and evaporated *in vacuo*. The residue was recrystallized from toluene to

9) A. Neuberger, R. V. Pitt-Rivere: Biochem. J., **33**, 1580(1939).

white needles, m.p. 138°, $[\alpha]_D^{22}$ +106.8° (c=3.07, $CHCl_3$). Yield, 2.4 g. *Anal.* Calcd. for $C_{19}H_{24}O_9NClS$: C, 47.74; H, 5.06; N, 2.93. Found: C, 47.77; H, 5.13; N, 3.02.

b) A solution of 1.0 g. of (V) dissolved in 15 cc. of Ac_2O saturated with HCl at 0° was kept standing for 18 hr. at room temperature. The reaction mixture was diluted with $CHCl_3$ and poured into ice-water. The $CHCl_3$ solution was washed successively with ice-water, cold $NaHCO_3$ solution, and ice-water, dried over $CaCl_2$, and evaporated *in vacuo*. The residue was recrystallized from AcOEt-petr. ether, m.p. 138°, $[\alpha]_D^{21}$ +106.8° (c=2.67, $CHCl_3$). In admixture with the sample obtained in (a), no depression of m.p. was observed.

Reaction of (VI) with MeOH in the Presence of Ag_2CO_3—0.2 g. of (VI) was shaken with a suspension of 0.2 g. of Ag_2CO_3 in 20 cc. of dehyd. MeOH for 3 hr. The reaction mixture was filtered through charcoal and the filtrate was concentrated *in vacuo* to a crystalline mass. Recrystallization from MeOH gave white needles, m.p. 151~152°, $[\alpha]_D^{20}$ −26.1° (c=2.00, $CHCl_3$). In admixture with authentic sample,[3] no depression of m.p. was observed. Yield, 0.1 g.

N,N-Phthaloyl-1,3,4,6-tetra-O-acetyl-α-D-glucosamine (XVI)—A solution of 0.7 g. of 1,3,4,6-tetra-O-acetyl-α-D-glucosamine[10] (XV) and 0.3 g. of phthalic anhydride dissolved in 5 cc. of pyridine was heated for 30 min. at 90°. Then, 5 cc. of Ac_2O was added and heated for an additional 1 hr. at 90°. The reaction mixture was poured into ice-water, extracted with $CHCl_3$, and the $CHCl_3$ solution was washed successively with ice-water, 5% HCl, and ice-water. After drying over $CaCl_2$, the solution was concentrated to a syrup which crystallized from 30% EtOH to white needles, m.p. 124~126°, $[\alpha]_D^{25}$ +116.1° (c=1.80, $CHCl_3$). Yield, 0.55 g. *Anal.* Calcd. for $C_{22}H_{23}O_{11}N$: C, 55.34; H, 4.86; N, 2.93. Found: C, 54.86; H, 5.22; N, 3.12.

Reaction of (XVI) with HBr in AcOH-Ac_2O Mixture—A solution of 0.2 g. of (XVI) dissolved in AcOH-Ac_2O mixture (2:1) saturated with HBr at 0° was left to stand for 4 hr. at room temperature. The reaction mixture was poured into ice-water, extracted with $CHCl_3$, and the $CHCl_3$ extract was washed three times with ice-water. After drying over $CaCl_2$, the solution was concentrated *in vacuo*. The residue was recrystallized from toluene-petr. ether, m.p. 136~137°, $[\alpha]_D^{28}$ +51.0°*3 (c=1.49, $CHCl_3$). Yield, 0.1 g. In admixture with authentic sample of (III), no depression of m.p. was observed.

Methyl N,N-Phthaloyl-3,4,6-tri-O-acetyl-α-D-glucosaminide (XVIII)—A solution of 3.3 g. of methyl N-benzyloxycarbonyl-α-D-glucosaminide[11] (XVII) dissolved in 50 cc. of MeOH was catalytically hydrogenated over 2.0 g. of 20% Pd-C. After consumption of 1 mole of H_2, the catalyst was filtered off and the filtrate was concentrated to a syrup. This syrup and 1.7 g. of phthalic anhydride were dissolved in 20 cc. of pyridine and heated for 30 min. at 90°. After addition of 20 cc. of Ac_2O the mixture was heated for an additional 1 hr. at 90°. The reaction mixture was poured into ice-water and extracted with $CHCl_3$. The $CHCl_3$ solution was dried over $CaCl_2$ and evaporated *in vacuo*. The residue was recrystallized from EtOH to white needles, m.p. 159~161°, $[\alpha]_D^{25}$ +180.3° (c=1.27, $CHCl_3$). Yield, 2.4 g. *Anal.* Calcd. for $C_{21}H_{23}O_{10}N$: C, 56.12; H, 5.16; N, 3.12. Found: C, 56.02; H, 5.92; N, 3.48.

Acetolysis of (IV) or (XVIII)—A solution of 1.25 g. of (IV) or (XVIII) 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., from both (IV) and (XVIII) the same reaction mixture, having the same final rotation, was obtained. 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-$CHCl_3$ (2:1), put on the top of a column of silica gel (26.5×1.5 cm.), and eluted with the same solvent. From the eluate needles of m.p. 92~95° (0.73 g.) were obtained, which, on admixture with authentic sample of (II), gave no depression of m.p.

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Summary

N,N-Phthaloyl-1-bromo-3,4,6-tri-O-acetyl-1-deoxy-β-D-glucosamine (III) reported in Part IV[1] of this series is the first example of 1,2-*trans*-acetobromo-sugar obtained in glucose and glucosamine series. Several replacement reactions at C-1 position of (III) as well as properties of several new N,N-phthaloyl derivatives of D-glucosamine were described in the present paper. From the results of these reactions, it was concluded that the replacement reaction at C-1 position of N,N-phthaloyl derivatives of D-glucosamine gave β-anomers and there was some steric hinderance for the formation of α-anomers.

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10) F. Micheel, F.-P. van de Kamp, H. Wulff: Ber., 88, 2011(1955).
11) A. B. Foster, D. Horton, M. Stacey: J. Chem. Soc., 1957, 81.