UDC 547.459

166. Masuo Akagi, Setsuzo Tejima, and Masanobu Haga : Synthesis of Anomers of 6-O-Tosyl-1,3,4-tri-O-acetyl-N-acetyl-D-glucosamine and 1,6-Anhydro-N-acetyl-β-D-glucosamine.

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Since an exceptional case of Hudson's isorotation rule among certain 2-deoxy-D-ribonucleosides was demonstrated by Lemieux and Hoffer[2] by means of physical methods, there has been displayed considerable interest in the relationship between anomeric configuration and optical rotation.[3]

In the previous paper,[4] the authors reported on the validity of Hudson's isorotation rule in the alkali treatment of anomeric D-glucopyranose derivatives, namely, 6-O-tosyl-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose and 6-deoxy-6-iodo-1,2,3,4-tetra-O-acetyl-α-D-glucopyranose, since the former gave 1,6-anhydro-β-D-glucopyranose (levoglucosan), but the latter did not.

Lemieux *et al.*[5] have already shown that the anomeric configuration of aldoses could be determined by proton magnetic resonance spectroscopy and this result was in agreement with the conclusion derived from the Hudson's rule.

The purpose of this paper is to describe the synthesis of anomeric 6-O-tosyl-1,3,4-tri-O-acetyl-N-acetyl-D-glucosamines in connection with Hudson's isorotation rule. Morel[6] described the synthesis of 6-O-tosyl-1,3,4-tri-O-acetyl-N-acetyl-β-D-glucosamine (IV) by the following series of reactions : N-anisylidene-D-glucosamine ⟶ 6-O-tosyl-1,3,4-tri-O-acetyl-N-anisylidene-β-D-glucosamine ⟶ 6-O-tosyl-1,3,4-tri-O-acetyl-β-D-glucosamine hydrochloride ⟶ 6-O-tosyl-1,3,4-tri-O-acetyl-N-acetyl-β-D-glucosamine (IV), m.p. 174~175°, $[\alpha]_D$ +16.5 (in chloroform). (IV) was assigned the beta configuration from its infrared absorption spectral data.

In the present work, N-benzylidene-D-glucosamine (I)[7] was chosen as a starting material, and 6-O-tosyl-1,3,4-tri-O-acetyl-N-benzylidene-β-D-glucosamine (II) was prepared by the method of Morel.[6] Selective tosylation of the primary hydroxyl group of (I) and subsequent acetylation in pyridine solution furnished (II) in 40% yield. While in the course of this process, N-benzylidene-1,3,4,6-tetra-O-acetyl-β-D-glucosamine (XII) was obtained as a by-product in 6% yield, the anomer of (II) was not isolated from the reaction mixture. (XII) was likewise obtained by acetylation of (I) in 60% yield. Debenzylidenation of (II) was carried out in acetone solution with hydrochloric acid and 6-O-tosyl-1,3,4-tri-O-acetyl-β-D-glucosamine hydrochloride (III) was obtained.

By acetylation of (III) with acetic anhydride and pyridine, 6-O-tosyl-1,3,4-tri-O-acetyl-N-acetyl-β-D-glucosamine (IV) was obtained, which agrees well with the description of Morel.[6]

In view of the failure in the isolation of the anomer of (II), the conversion of (IV) through its glycosyl halide derivative to the alpha form was undertaken. Since it is

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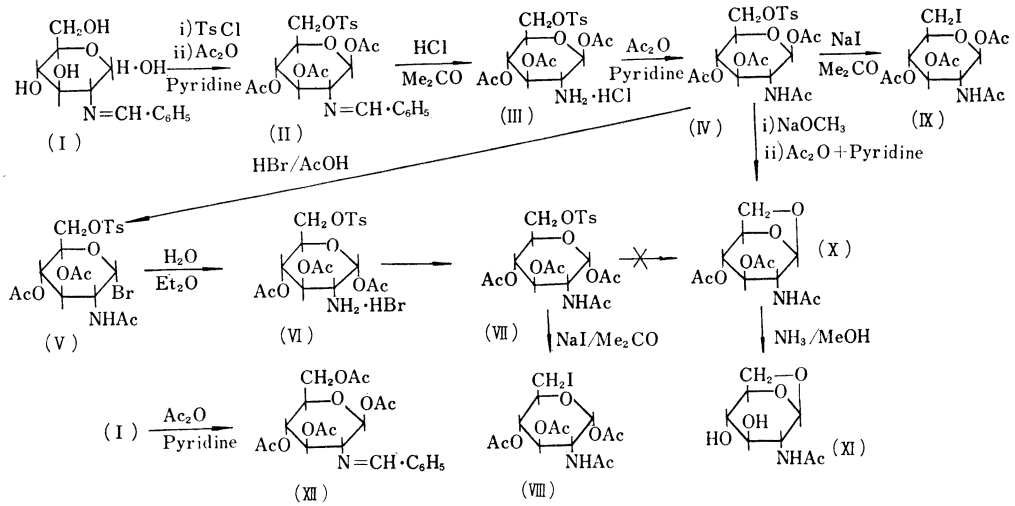
well established[8] that the halide of acylated glucosamine is readily rearranged to acylated α-glucosamine hydrohalide through an oxazolone derivative, this procedure was applied to the preparation of the pure α-anomer of pentabenzoyl-D-glucosamine.[9] By treatment of (IV) with hydrogen bromide in acetic acid, (IV) was converted to the bromide (V), which, without isolation, was directly led to 6-O-tosyl-1,3,4-tri-O-acetyl-α-D-glucosamine hydrobromide (VI).

Acetylation of (VI) with acetic anhydride and pyridine gave 6-O-tosyl-1,3,4-tri-O-acetyl-N-acetyl-α-D-glucosamine (VII), m.p. 151~153°, $[\alpha]_D$ +116.5° in chloroform. On treatment of (VII) with sodium iodide in acetone at 100°, 6-deoxy-6-iodo-1,3,4-tri-O-acetyl-N-acetyl-α-D-glucosamine (VIII), m.p. 196~197° (decomp.), $[\alpha]_D$ +92.2° in chloroform, was obtained in 95% yield. Similarly (IV) gave 6-deoxy-6-iodo-1,3,4-tri-O-acetyl-N-acetyl-β-D-glucosamine (IX), m.p. 193~194°, $[\alpha]_D$ +9.0° in chloroform, in agreement with the description of Morel.[6]

From the reason discussed in our previous paper,[4] it is expected that (IV) gives 1,6-anhydride by the action of alkali while (VII) does not form an anhydride. As might have been expected, 1,6-anhydro-3,4-di-O-acetyl-N-acetyl-β-D-glucosamine (X) was obtained from (IV) by the action of sodium methoxide and reacetylation, but the α-anomer (VII) gave a dark syrup and no 1,6-anhydride (X) could be isolated. These facts agree with the Hudson's isorotation rule because only in the case of β-configuration[4] 1,6-anhydride can be formed.

Deacetylation of (X) with methanolic ammonia gave 1,6-anhydro-N-acetyl-β-D-glucosamine (XI). (X) and (XI) are levorotatory and do not reduce a hot Benedict's solution. The rapid consumption of approximately one mole of periodate and no formation of formaldehyde under the usual condition[10] indicate the presence of a vicinal glycol group and hence (XI) should be 1,6-anhydro-pyranose.

It is pertinent to note that as regards the 1,6-anhydride of D-glucosamine Micheel *et al.*[11] prepared 1,6-anhydro-N-tosyl-β-D-glucosamine and its diacetate from 3,4,6-tri-O-acetyl-N-tosyl-α-D-glucosaminyl fluoride by the action of sodium methoxide.



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Experimental

6-O-Tosyl-1,3,4-tri-O-acetyl-N-benzylidene-β-D-glucosamine (II)——A solution of 13.5 g. of N-benzylidene-D-glucosamine[7] in 150 cc. of dry pyridine was cooled in tap water and treated by the dropwise addition of 9.5 g. of tosyl chloride, while the temperature was held below 40°. Then the mixture was allowed to stand overnight at 5~10°. To this mixture was added dropwise 40 cc. of Ac_2O, while the temperature was maintained below 40°. After standing overnight at 5~10°, the mixture was then poured into 1 L. of ice-water, and a syrupy product precipitated, which solidified on standing for several hr. This was filtered, washed with water, and air dried. Yield, 12 g. The product was dissolved in 100 cc. of EtOH, and allowed to crystallize at room temperature. The yield of the crude product, m.p. 170~180° was 10.5 g. (From this mother liquor 2 g. of 1,3,4,6-tri-O-acetyl-N-benzylidene-β-D-glucosamine (XII) was isolated instead of the α-anomer of (II).)

After several recrystallizations from $CHCl_3$–EtOH (1:20), (II) was obtained as colorless crystals, m.p. 183~184°, $[\alpha]_D^{20}$ +85.6 (c=1.1, $CHCl_3$). *Anal.* Calcd. for $C_{26}H_{29}O_{10}NS$: C, 57.03; H, 5.34; N, 2.56; S, 5.84. Found : C, 56.99; H, 5.21; N, 2.75; S, 5.57.

6-O-Tosyl-1,3,4-tri-O-acetyl-β-D-glucosamine Hydrochloride (III)——A solution of 25 g. of (II) in 200 cc. of Me_2CO was heated to boiling. To this solution, 10 cc. of 5*N* HCl was added and the resulting precipitates were collected after cooling.

Recrystallization from MeOH gave 20.5 g. of crystals, m.p. 205~207° (decomp.), $[\alpha]_D^{20}$ +46.3 (c=0.7, MeOH). *Anal.* Calcd. for $C_{19}H_{26}O_{10}NSCl$: C, 45.83; H, 5.26; N, 2.81. Found : C, 45.58; H, 5.34; N, 3.04.

6-O-Tosyl-1,3,4-tri-O-acetyl-N-acetyl-β-D-glucosamine (IV)——Twenty grams of (III) was acetylated as usual by 100 cc. of pyridine and 40 cc. of Ac_2O. After standing for several hr. at room temperature, the mixture was poured into 500 cc. of ice-water, the product crystallized out; yield of the crude procuct was 16.2 g. (80%).

After several recrystallizations from EtOH, the material was obtained as needles, m.p. 174~175°, $[\alpha]_D^{20}$ +14.8 (c=1.2, $CHCl_3$); reported[6] m.p. 174~175°, and $[\alpha]_D$ +16.5 in $CHCl_3$. *Anal.* Calcd. for $C_{21}H_{27}O_{11}NS$: C, 50.29; H, 5.43; N, 2.79; S, 6.38. Found : C, 50.22; H, 5.49; N, 3.06; S, 6.34.

6-O-Tosyl-1,3,4-tri-O-acetyl-N-acetyl-α-D-glucosamine (VII)——Six grams of the β-anomer (IV) was dissolved in AcOH containing 30% (W/V) of HBr under stirring. This solution was allowed to stand at room temperature for 2 hr. Then the solvent was removed by distillation under reduced pressure. The syrupy residue (V) was taken up in 10 cc. of $CHCl_3$ and, to this solution, 100 cc. of moistened Et_2O was added. (IV) was immediately precipitated with slight evolution of heat. (VI) was obtained as a hygroscopic amorphous powder, which, without purification, was acetylated with 30 cc. of pyridine and 10 cc. of Ac_2O. By the usual treatment, (VII) was obtained as needles; yield, 5.2 g. (85%). After recrystallization from EtOH, it showed m.p. 151~153°, $[\alpha]_D^{20}$ +116.5 (c=2.4, $CHCl_3$). *Anal.* Calcd. for $C_{21}H_{27}O_{11}NS$: C, 50.29; H, 5.43; N, 2.79; S, 6.38. Found : C, 49.95; H, 5.54; N, 2.82; S, 6.36.

1,6-Anhydro-3,4-di-O-acetyl-N-acetyl-β-D-glucosamine (X)——Ten grams of (IV) was added portion wise to 100 cc. of MeOH containing 0.9 g. of Na under stirring at room temperature. The reaction mixture turned light amber and, after standing for 10 hr. at room temperature, was neutralized with AcOH.

The solvent was removed by distillation under reduced pressure to dryness and the resulting crystalline residue was acetylated with 40 cc. of pyridine and 20 cc. of Ac_2O. After standing overnight at room temperature, the precipitated sodium tosylate was removed by filtration and the filtrate was concentrated under reduced pressure to a syrupy residue, which was taken up in $CHCl_3$ (100 cc.) and washed with water. On removal of the $CHCl_3$ by distillation under reduced pressure, (X) was obtained as crystalline; yield, 3.1 g. (55%). After several recrystallizations from EtOH–Et_2O (1:10), the product was obtained as prisms, which did not reduce Benedict's solution, m.p. 137~138°, $[\alpha]_D^{20}$ −88.4 (c=1.1, MeOH). *Anal.* Calcd. for $C_{12}H_{17}O_7N$: C, 50.17; H, 5.97; N, 4.88. Found : C, 50.20; H, 5.73; N, 5.20.

1,6-Anhydro-N-acetyl-β-D-glucosamine (XI)——A solution of 2 g. of (X) in 30 cc. of MeOH saturated with NH_3 at 0° was allowed to stand in a refrigerator overnight. The solution was evaporated under reduced pressure to a syrupy residue, which by trituration with a small amount of dehyd. EtOH, gave 1.3 g. (90%) of crystals. Recrystallization from EtOH–Et_2O (1:5) gave colorless prisms, m.p. 190~191° which decomposed at 207°, $[\alpha]_D^{20}$ −45.2 (c=2.3, H_2O). *Anal.* Calcd. for $C_8H_{13}O_5N$: C, 47.29; H, 6.45; N, 6.89. Found : C, 47.36; H, 6.40; N, 6.98. The substance did not reduce a hot Benedict's solution and did not show mutarotation.

A solution of (XI) (0.113 g.) in water was treated with 0.25*M* sodium metaperiodate solution (20 cc.) and the volume adjusted to 50 cc. The consumption of the oxidant was determined by the standard arsenite procedure on aliquots withdrawn at given intervals.

The consumption of the oxidant (moles per mole) was as follows :

Time (hr.)	0.5	1.0	2.0	3.0	24.0
Moles of $NaIO_4$	0.78	0.98	0.98	0.98	1.12

6-Deoxy-6-iodo-1,3,4-tri-O-acetyl-N-acetyl-α-D-glucosamine (VIII)——Two grams of (VII) and 1 g. of NaI were dissolved in 10 cc. of Me_2CO and the resulting solution was heated in a sealed tube at 100° for 6 hr. When the tube was cooled, the solution was poured into 50 cc. of water. Yield, 1.7 g. (95%). Recrystallizations from EtOH gave needles, m.p. 196~197° (decomp.), $[\alpha]_D^{20}$ +92.2°(c=1.2, $CHCl_3$). *Anal.* Calcd. for $C_{14}H_{20}O_8NI$: C, 36.87; H, 4.41; N, 3.06; I, 27.75. Found : C, 36.87; H, 4.52; N, 2.94; I, 27.98.

6-Deoxy-6-iodo-1,3,4-tri-O-acetyl-N-acetyl-β-D-glucosamine (IX)——Two grams of (IV) were treated in a similar manner. Yield, 1.6 g. (90%), m. p. 192~193°, $[\alpha]_D^{20}$ +8.8 (c=1.0, $CHCl_3$); reported[6] m.p. 193~194°, $[\alpha]_D$ +9.4 in $CHCl_3$. *Anal.* Calcd. for $C_{14}H_{20}O_8NI$: C, 36.87; H, 4.41; N, 3.06; I, 27.75. Found : C, 36.50; H, 4,63; N, 3.36; I, 27.64.

1,3,4,6-Tetra-O-acetyl-N-benzylidene-β-D-glucosamine (XII)——Two grams of (I) were dissolved in 10 cc. of pyridine, followed by the dropwise addition of Ac_2O, and the solution was kept below 40°. After standing overnight at room temperature, the solution was poured into 50 cc. of ice-water. The precipitates were filtered and washed with water. Yield, 2.7 g. (60%). Several recrystallizations from EtOH gave needles, m.p. 147~148°, $[\alpha]_D^{20}$ +85.6 (c=2.3, $CHCl_3$).

By debenzylidenation with HCl, followed by acetylation, (XII) gave a known pentaacetyl-β-D-glucosamine,[12] and consequently the configuration of (XII) is a beta-form. *Anal.* Calcd. for $C_{21}H_{25}O_9N$: C, 57.93; H, 5.79; N, 3.22. Found : C, 58.11; H, 5.87; N, 3.16.

The authors wish to thank Chugai Pharmaceutical Co. Ltd., for a supply of glucosamine hydrochloride. Acknowledgment is also made to Mr. K. Narita, Hokkaido University, and Mrs. K. Iwata, Kyoto University for the microanalysis.

Summary

Anomeric 6-O-tosyl-1,3,4-tri-O-acetyl-N-acetyl-D-glucosamines and 6-deoxy-6-iodo-compounds were prepared from N-benzylidene-D-glucosamine. By alkali treatment of the β-anomer of the 6-tosylate, 1,6-anhydro-N-acetyl-β-D-glucosamine was synthesized, but no anhydride of the α-anomer was obtained.

(Received September 7, 1961)

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