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102. Shichiro Akiya and Toshiaki Osawa : Nitrogen-containing Sugars. VIII.*2 Acid Hydrolysis and Periodate Oxidation of Methyl N-Acyl-β-D-Glucosaminides.

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In the preceding papers*2,1,2) concerning the replacement reactions at C-1 of N,N-phthaloyl and N,N-succinyl derivatives of D-glucosamine, it was shown that in these derivatives which have bulky groups, phthalimide and succinimide groups at C-2, there were clearly some steric hinderances in the formation of α-anomers.

According to Edward[3] and Foster,[4] the bulky group at C-2 or C-5 retards the rate of hydrolysis of methyl glycoside on account of its steric influence on the formation of intermediate oxonium ion. In fact, acid hydrolysis of methyl pentopyranoside, methyl hexopyranoside, and methyl heptopyranoside proceed with following sequence of rate :

Pentopyranoside > Hexopyranoside > Heptopyranoside

On the other hand, it seemed of interest to examine the steric effect of bulky group at C-2 on the reaction involving neighboring C-3. In general, periodate oxidation of α-glycol is assumed[5,6] to proceed through the five-membered ring involving iodine and glycol grouping. Then, periodate oxidation of carbohydrate which has a bulky group at the neighboring carbon of α-glycol may be expected to proceed relatively slowly on account of the steric influence exerted by the bulky group for the formation of the intermediate five-membered ring. Smith and co-workers[7] attributed the slow consumption of periodate in the cases of phenyl β-D-glucopyranoside and methyl 6-trityl-α-D-glucopyranoside to the steric effect caused by their bulky groups on the oxidation of neighboring α-glycols.

This paper is concerned with both the acid hydrolysis and periodate oxidation of methyl N,N-phthaloyl-β-D-glucosaminide (I) and methyl N,N-succinyl-β-D-glucosaminide (II) in comparison with these reactions of other methyl N-acyl-β-D-glucosaminides.

Deacetylation of methyl N,N-phthaloyl-3,4,6-tri-O-acetyl-β-D-glucosaminide[1] and methyl N,N-succinyl-3,4,6-tri-O-acetyl-β-D-glucosaminide[2] with 2% aqueous methanolic hydrogen chloride gave (I) and (II), respectively. Methyl N-acetyl-β-D-glucosaminide (III), methyl N-anisoyl-β-D-glucosaminide (IV), methyl N-benzoyl-β-D-glucosaminide (V), methyl N-*p*-nitrobenzoyl-β-D-glucosaminide (VI), and methyl N-(3,5-dinitrobenzoyl)-β-D-glucosaminide (VII) were prepared by the treatment of corresponding triacetates with methanolic ammonia.

It has been known that methyl D-glucosaminide shows abnormal resistance for the acid hydrolysis. Moggridge and Neuberger[8] explained this abnormality by the effect of the adjacent positively charged amino group in repelling hydrions from its immediate vicinity.

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*2 Part VII : This Bulletin, 8, 588(1960).

1) S. Akiya, T. Osawa : Yakugaku Zasshi, **77**, 726 (1957).
2) Part VI. *Idem* : This Bulletin, 8, 583(1960).
3) J. T. Edward : Chem. & Ind. (London), **1955**, 1102.
4) A. B. Foster, W. G. Overend : *Ibid.*, **1955**, 566.
5) R. Criegee, L. Kraft, B. Rank : Ann., **597**, 159(1933).
6) C. C. Price, M. Knell : J. Am. Chem. Soc., **64**, 552(1942).
7) E. F. Garner, I. J. Goldstein, R. Montogomery, F. Smith : *Ibid.*, **80**, 1206(1958).
8) R. C. G. Moggridge, A. Neuberger : J. Chem. Soc., **1938**, 745.

Also, it has been known that D-glucosamine is not released quantitatively in the acid hydrolysis of N-substituted methyl β-D-glucosaminides. Foster, Horton, and Stacey[9] suggested that this fact might be due to the presence of two pathways, (A) and (B), in this acid hydrolysis of N-substituted methyl β-D-glucosaminides.

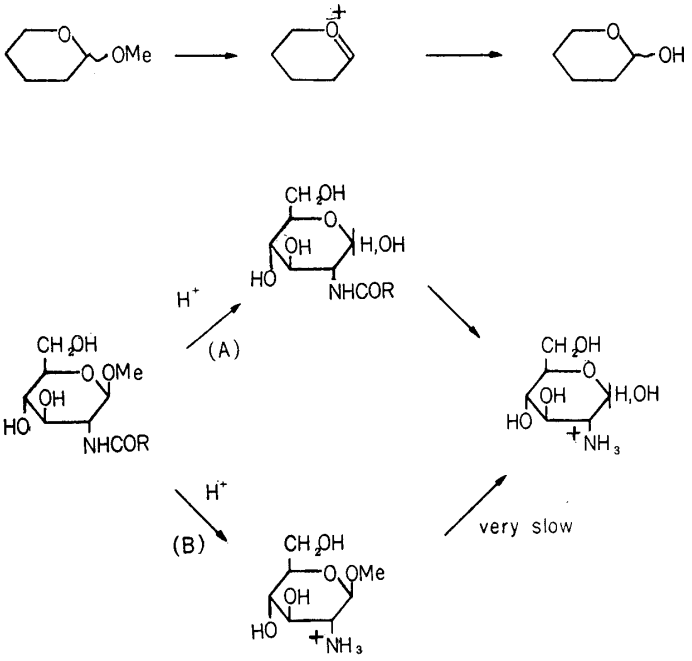

Chart 1.

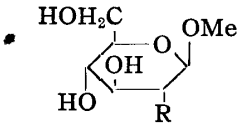

Chart 2.

(I) R = -N(CO)(CO)C6H4

(II) R = -N(CO—CH2)(CO—CH2)

(III) R = -NHCOCH3

(IV) R = -NHCO-C6H4-OMe

(V) R = -NHCO-C6H3(NO2)-OMe

(VI) R = -NHCO-C6H3(NO2)-NO2

(VII) R = -NHCO-C6H3(NO2)2

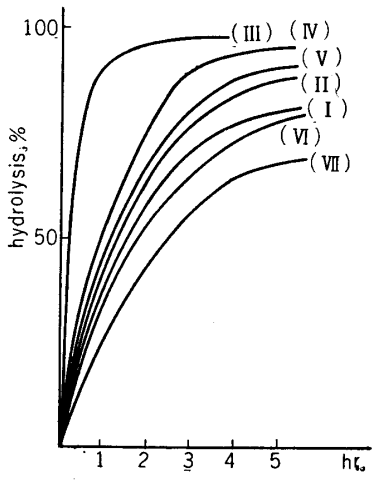

Fig. 1.
Rate of Acid Hydrolysis of Methyl N-Acyl-β-D-glucosaminides with 1.23*N* HCl at 100°

9) A. B. Foster, H. Horton, M. Stacey: *Ibid.*, **1957**, 81.

The compounds (I)~(Ⅶ) were hydrolyzed with 1.23*N* hydrochloric acid at 100° and the released D-glucosamine was followed by the colorimetric method of Belcher, Nutten, and Sambrook.[10] The results are given in Fig. 1.

As shown in Fig. 1, the rates and limits of acid hydrolysis of methyl N-acyl-β-D-glucosaminides, in general, decreased in proportion to the increasing dissociation constants of corresponding acids of N-acyl group. In each case, paper chromatographic examination of final hydrolysate revealed the presence of D-glucosamine hydrochloride and methyl β-D-glucosaminide hydrochloride.

From above experiments, it should be concluded that the acid hydrolysis of methyl N-acyl-β-D-glucosaminides proceeded through the two pathways (A) and (B), as proposed by Foster and co-workers. Thus, in the acid hydrolysis of the glycosidic linkage of the compound which has more stable linkage of acid amide, the pathway (A) is more favorable and the rate and limit of the acid hydrolysis is larger. In contrast, in the hydrolysis of the compound which has more unstable linkage of acid amide, the pathway (B) is more favorable and the rate and limit of the acid hydrolysis is smaller. Contrary to the expectation, in the cases of (I) and (Ⅱ) no remarkable abnormal effects caused by their bulky groups at C-2 for the rate of acid hydrolysis of their glycosidic bonds could be observed.

Moreover, it has been known[11] that, in general, the acid hydrolysis of methyl α-D-glycosides proceeds more slowly than that of methyl β-D-glycosides. In both cases of N,N-phthaloyl and N,N-succinyl derivatives of methyl D-glucosaminides, their α- and β-anomers showed no abnormality in acid hydrolysis (Fig. 2).

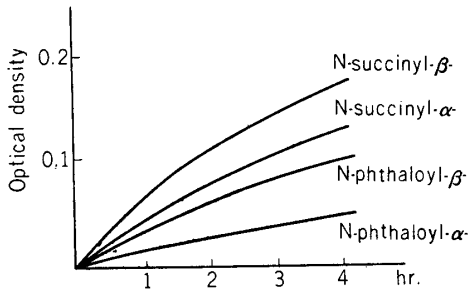

Fig. 2.
Rate of Acid Hydrolysis of Methyl N,N-Phthaloyl(or N,N-Succinyl)-3,4,6-tri-O-acetyl-α(and β)-glucosaminides with 1.23*N* HCl at 100°

In the preceding paper,[1] the obstruction of the formation of α-anomers in the replacement reactions at C-1 position of N,N-phthaloyl derivatives of D-glucosamine was observed and at that time this obstruction was attributed to the resistance caused by the bulky phthalimide group at C-2 for the formation of intermediate oxonium ion. However, as (I) and (Ⅱ) showed normal behavior towards acid hydrolysis, no such remarkable resistance by their bulky group at C-2 for the formation of intermediate oxonium ion as would obstruct the formation of α-anomers could be expected. Then, it seemed to be reasonable to assume that the hindrance for the formation of α-anomer exists in the process of substitution on the once formed intermediate oxonium ion.

On the other hand, it is expected that, in the periodate oxidation of α-glycol grouping (between C-3 and C-4) of (I) and (Ⅱ), the rate of oxidation should be influenced if there is a remarkable steric influence of their bulky group at C-2 for the formation of five-membered ring involving iodine and α-glycol grouping.

The comparative oxidation rates for (I), (Ⅱ), (Ⅲ), (Ⅴ), and (Ⅵ) with 0.1*N* sodium periodate at 25° are shown in Fig. 3.

As illustrated in Fig. 3, although the rates of oxidations of (Ⅲ), (Ⅴ), and (Ⅵ) were

10) R. Belcher, A. J. Nutten, C. M. Sambrook: Analyst, **79**, 201(1954).
11) W.W. Pigman, R.M. Goepp: "Chemistry of the Carbohydrate," 202(1948). Academic Press.

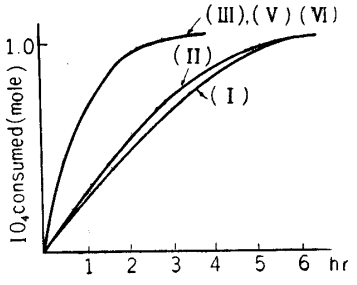

Fig. 3.
Rate of Consumption of Periodate of Methyl N-Acyl-β-D-glucosaminides

almost similar, the oxidation of (I) and (II) proceeded more slowly and the time required for complete oxidation of (I) and (II) was about 2.4 times those of (III), (V), and (VI). Further, the almost similar rate in the oxidation of (III), (V), and (VI) revealed no remarkable electronic influence of C-2 substituent for the oxidation. Thus, the difference in the rates of oxidation between these two groups of compounds might be attributed to the steric influence of the substituents at C-2 on the formation of intermediate five-membered ring involving iodine and α-glycol between C-3 and C-4.

Experimental

Methyl N,N-Phthaloyl-β-D-glucosaminide (I)—A solution of 2.3 g. of methyl N,N-phthaloyl-3,4,6-tri-O-acetyl-β-D-glucosaminide dissolved in 40 cc. of 95% MeOH containing 2% HCl was refluxed for 3 hr. After cool, the reaction mixture was neutralized with $PbCO_3$, filtered. and the filtrate was evaporated *in vacuo* to dryness. The residue was recrystallized from EtOH-AcOEt to white needles, m.p. 191~193°, $[\alpha]_D^{20}$ −11.8° (c=1.53, H_2O). Yield, 1.2 g. *Anal.* Calcd. for $C_{15}H_{17}O_7N$: C, 55.74; H, 5.29; N, 4.33. Found : C, 55.52; H, 5.19; N, 4.35.

Methyl N,N-Succinyl-β-D-glucosaminide (II)—A solution of 0.8 g. of methyl N,N-succinyl-3,4,6-tri-O-acetyl-β-D-glucosaminide dissolved in 15 cc. of 95% MeOH containing 2% HCl was refluxed for 3 hr. After cool, the reaction mixture was neutralized with $PbCO_3$, filtered, and the filtrate was evaporated *in vacuo* to dryness. The residue was recrystallized from EtOH-AcOEt to white needles, m.p. 185~187°, $[\alpha]_D^{27}$ −23.0° (c=0.61, C_2H_5OH). Yield, 0.25 g. *Anal.* Calcd. for $C_{11}H_{17}O_7N$: C, 49.00; H, 6.23; N, 5.09. Found : C, 48.65; H, 5.78; N, 4.97.

Methyl N-Benzoyl-β-D-glucosaminide (V)—A solution of 0.55 g. of methyl N-benzoyl-3,4,6-tri-O-acetyl-β-D-glucosaminide[12] dissolved in 30 cc. of MeOH saturated with dry ammonia at 0° was kept overnight at room temperature. The reaction solution was evaporated *in vacuo* to dryness and the residue was recrystallized from MeOH to white needles, m.p. 223~224°, $[\alpha]_D^{27}$ −16.2° (c=1.17, H_2O). Yield, 0.25 g. *Anal.* Calcd. for $C_{14}H_{19}O_6N$: C, 56.54; H, 6.46; N, 4.71. Found : C, 56.33; H, 6.39; N, 4.56.

Methyl N-Anisoyl-β-D-glucosaminide (IV)—A solution of 0.75 g. of methyl N-anisoyl-3,4,6-tri-O-acetyl-β-D-glucosaminide[13] dissolved in 30 cc. of MeOH saturated with dry ammonia at 0° was kept standing overnight at room temperature. The reaction solution was evaporated *in vacuo* to dryness and the residue was recrystallized from MeOH to white needles, m.p. 220°, $[\alpha]_D^{22}$ −18.9° (c=1.06, MeOH). Yield, 0.36 g. *Anal.* Calcd. for $C_{15}H_{21}O_7N$: C, 55.06; H, 6.47; N, 4.28. Found : C, 54.70; H, 6.05; N, 4.59.

Methyl N-*p*-Nitrobenzoyl-β-D-glucosaminide (VI)—A solution of 1.5 g. of methyl N-*p*-nitrobenzoyl-3,4,6-tri-O-acetyl-β-D-glucosaminide[13] dissolved in 50 cc. of MeOH saturated with dry ammonia at 0° was kept overnight at room temperature. The reaction solution was evaporated *in vacuo* to dryness and the residue was recrystallized from MeOH to white needles, m.p. 231~232°, $[\alpha]_D^{18}$ −15.9° (c=0.44, H_2O). Yield, 0.8 g. *Anal.* Calcd. for $C_{15}H_{20}O_9N_2$: C, 49.11; H, 5.29; N, 8.18. Found : C, 48.70; H, 5.17; N, 7.90.

N-(3,5-Dinitrobenzoyl)-1-chloro-3,4,6-tri-O-acetyl-1-deoxy-α-D-glucosamine—A solution of 1.0 g. of N-(3,5-dinitrobenzoyl)-1,3,4,6-tetra-O-acetyl-β-D-glucosamine[14] dissolved in 15 cc. of Ac_2O saturated with HCl at 0° was kept overnight 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* to a syrup

12) F. Micheel, F.-P. van de Kamp, H. Petersen : Ber., **90**, 521(1957).
13) Part IX. T. Osawa : This Bulletin, **8**, 597(1960).
14) F. Micheel, F.-P. van de Kamp, H. Wulff : Ber., **88**, 2011(1955).

which was crystallized from AcOEt-petr. ether to pale yellow needles, m.p. 144°, $[\alpha]_D^{30}$ +133.3°(c=0.63, $CHCl_3$). Yield, 0.7 g. *Anal.* Calcd. for $C_{19}H_{20}O_{12}N_3Cl$: C, 44.07; H, 3.90 N, 8.11. Found : C, 43.71; H, 3.62; N, 7.90.

Methyl N-(3,5-Dinitrobenzoyl)-3,4,6-tri-O-acetyl-β-D-glucosaminide—0.50 g. of N-(3,5-dinitrobenzoyl)-1-chloro-3,4,6-tri-O-acetyl-1-deoxy-α-D-glucosamine was shaken with suspension of 0.5 g. of Ag_2CO_3 in 30 cc. of anhyd. MeOH. After filtration, the filtrate was evaporated *in vacuo* to dryness. The residue was recrystallized from EtOH to pale yellow needles, m.p. 206~208°, $[\alpha]_D^{30}$ +35.8°(c=0.81, $CHCl_3$). Yield, 0.25 g. *Anal.* Calcd. for $C_{20}H_{23}O_{13}N_3$: C, 46.79; H, 4.51; N, 8.18. Found : C, 46,48; H, 4.81; N, 8.45.

Methyl N-(3,5-Dinitrobenzoyl)-β-D-glucosaminide (VII)—A solution of 1.5 g. of methyl N-(3,5-dinitrobenzoyl)-3,4,6-tri-O-acetyl-β-D-glucosaminide dissolved in 40 cc. of anhyd. MeOH saturated with dry ammonia at 0° was kept overnight at room temperature. The reaction mixture was evaporated *in vacuo* to dryness and the residue was recrystallized from MeOH to pale yellow needles, m.p. 250°(decomp.), $[\alpha]_D^{30}$ +15.1°(c=0.53, H_2O). Yield, 0.7 g. *Anal.* Calcd. for $C_{14}H_{17}O_{10}N_3$: C, 43.41; H, 4.43; N, 10.85. Found : C, 43.45; H, 4.13; N, 11.16.

Hydrolysis of Methyl N-Acyl-β-D-glucosaminide—To each 1 cc. of aqueous solutions of methyl N-acyl-β-D-glucosaminides, 1 cc. of 2.46*N* HCl was added and the solutions were heated in a boiling water bath. At suitable times the reaction solution was cooled, treated with 2 cc. of *N* Na_2CO_3 solution, and diluted exactly to 10 cc. with distilled water. One cc. of this aliquot was taken and examined for D-glucosamine content by the method of Belcher, Nutten, and Sambrook. From the standard graph prepared simultaneously, percentage of hydrolysis was calculated. The results are illustrated in Fig. 1.

Hydrolysis of Methyl N,N-Phthaloyl- and N,N-Succinyl-α-D-glucosaminides—Owing to the syrupy nature of methyl N,N-phthaloyl-α-D-glucosaminide, methyl N,N-phthaloyl- and N,N-succinyl-3,4,6-tri-O-acetyl-α-D-glucosaminides were used. 0.040 g. of methyl N,N-phthaloyl(or N,N-succinyl)-3,4,6-tri-O-acetyl-α-D-glucosaminide was dissolved in 25 cc. of anhyd. EtOH. 1 cc. of this solution was diluted with 1 cc. of 2.46 *N* HCl and the mixture was heated on a boiling water bath. At suitable times, the reaction solution was cooled, treated with 2 cc. of *N* Na_2CO_3 solution, and diluted exactly to 10 cc. with distilled water. 1 cc. of this solution was taken and examined for D-glucosamine content by the method of Belcher, Nutten, and Sambrook. Under exactly the same conditions, methyl N,N-phthaloyl- and N,N-succinyl-3,4,6-tri-O-acetyl-β-D-glucosaminides were hydrolyzed and the results were compared with those of α-anomers (Fig. 2).

Chromatographic Examination of the Hydrolysates—The hydrolysates obtained by the acid treatment of methyl N-acyl-β-D-glucosaminides were evaporated *in vacuo* to dryness and examined chromatographically. In each case, spots corresponding to D-glucosamine and methyl β-D-glucosaminide were observed using benzidine-periodic acid as the color reagent. Rf values were as follows:

	H_2O-saturated BuOH	BuOH-EtOH-NH_3(40:10:1)
D-Glucosamine	0.03	0.22
Methyl β-D-glucosaminide	0.06	0.40

Periodate Oxidations of Methyl N-Acyl-β-D-glucosaminides—Approximately 0.25 m.mole of sample was accurately weighed. To this were added 10 cc. of water and 5 cc. of 0.25*M* $NaIO_4$ solution, and this mixture was brought exactly to 25 cc. by the addition of distilled water. On the other hand, the blank solution was prepared by mixing 20 cc. of distilled water and 5 cc. of 0.25*M* $NaIO_4$ solution. These two solutions were kept at 25°. At suitable times, to 1 cc. of each of these two solutions, 10 cc. of distilled water, 10 cc. of boric acid-borax buffer, and 0.2 g. of KI were added, and each mixture was titrated with 0.1*N* As_2O_3 solution in the usual way.

(a) With methyl N-acetyl-β-D-glucosaminide

Time (min.)	20	40	80	120	150	210	270
$NaIO_4$ consumed (mole)	0.35	0.50	0.80	0.95	1.00	1.05	1.05

(b) With methyl N-benzoyl-β-D-glucosaminide

Time (min.)	20	45	120	180	210
$NaIO_4$ consumed (mole)	0.40	0.50	1.00	1.05	1.10

(c) With methyl N-*p*-nitrobenzoyl-β-D-glucosaminide

Time (min.)	20	40	80	100	140	180
$NaIO_4$ consumed (mole)	0.40	0.50	0.80	0.90	1.00	1.00

(d) With methyl N,N-phthaloyl-β-D-glucosaminide

Time (min.)	45	90	180	240	300	360	420
$NaIO_4$ consumed (mole)	0.20	0.40	0.70	0.85	0.95	1.00	1.00

(e) With methyl N,N-succinyl-β-D-glucosaminide

Time (min.)	45	90	150	240	330	420
$NaIO_4$ consumed (mole)	0.20	0.45	0.65	0.90	1.00	1.00

The authors are indebted to the members of Central Analysis Room of Faculty of Pharmaceutical Sciences, University of Tokyo, for elementary analyses.

Summary

Comparative studies on the acid hydrolysis and periodate oxidation of methyl N-acyl-β-D-glucosaminides were carried out. Results of these reactions were discussed in relation to the properties of N-acyl groups.

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103. Toshiaki Osawa: Nitrogen-containing Sugars. IX.*2 Influence of the Substituent at C-2 on the Chlorination at C-1 in N-Acyl-1,3,4,6-tetra-O-acetyl-β-D-glucosamines.

(*Tokyo Medico-Dental University*[*1])

The two methods most usually used for the preparation of glycosyl chloride from C-1-acylated sugars are treatment of acylated sugar with hydrogen chloride in acetic acid or acetic anhydride, and that with titanium tetrachloride in refluxing chloroform. These methods give the stable form of the poly-O-acylglycosyl chloride as the final product, irrespective of the anomeric configuration of the starting material. For example, α-glycosyl chlorides are obtained from both α- and β-acylated glucose derivatives by either of these methods.

In 1926, Schlubach[1] found that a brief treatment of the normal α-acetobromo-D-glucose in ether with freshly prepared silver chloride yielded the unstable acetochloro-β-D-glucose. This reaction has been commonly used to obtain unstable β-glycosyl chlorides. In 1954, Zémplen and co-workers[2] found that the reaction of penta-O-acetyl-β-D-glucose with anhydrous aluminium chloride in cold chloroform gave acetochloro-β-D-glucose. Recently, Korytnyk and Mills[3] applied this reaction on several 1,2-*trans*-acetylated sugars and found that this reaction was a convenient method for the preparation of 1,2-*trans*-acetylglycosyl chlorides from 1,2-*trans*-acetylated sugars. Lemieux and Brice[4] have recently found that the reaction of penta-O-acetyl-β-D-glucose with titanium tetrachloride at 40° results in a rapid formation of acetochloro-β-D-glucose followed by a relatively much slower rearrangement of the latter to the α-anomer.

In the preceding papers of this series,[5,6] several methods of chlorination were applied on both N,N-phthaloyl and N,N-succinyl derivatives of D-glucosamine and only β-glycosyl chlorides were obtained. In this paper, several new observations on the chlorination at C-1 of other N-acyl-1,3,4,6-tetra-O-acetyl-β-D-glucosamines will be de-

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3) W. Korytnyk, J. A. Mills: J. Chem. Soc., **1959**, 636.
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6) Part. Ⅶ. *Idem*: *Ibid.*, 8, 588(1960).