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135. Akira Yamamoto, Chieko Miyashita, and Hisao Tsukamoto: Studies on Amino Sugars. I. Preparation of N-Acyl Derivatives of 2-Acetamido-2-deoxy-β-D-glucosylamine.*1

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In recent years, the structural studies of glycoproteins have been focused to elucidate the nature of the carbohydrate-peptide bond in glycopeptides, which were produced from glycoproteins by the enzymatic or chemical degradation.

Thus, on the basis of the available evidence it was proposed for γ-globulin,[1,2] α_1-acid glycoprotein,[3,4] and ovalbumin[5~7] that the polysaccharide moiety is attached to an aspartyl residue of peptide chain through N-acetylglucosamine and the most likely structure of the linkage is that of a β-aspartyl N-acetylglucosaminylamine, analogous to glycinamide ribotide,[8] an intermediate of purine nucleotide biosynthesis.

The preparation of the derivative having a such structure as model compound may consequently be of use for the elucidation of the nature of the carbohydrate-protein bond in glycoproteins.

The aim of the present work was to develop the general methods for the preparation of the acyl derivatives of 2-acetamido-2-deoxy-β-D-glucosylamine.

In the first place, the preparation of 1-amino-1-deoxy-derivative of N-acetylglucosamine was attempted. The general synthesis of hexosylamine was carried out by Bertho.[9] He prepared a series of 2,3,4,6-tetra-O-acetyl-β-D-hexosylamine by the catalytic hydrogenation over platinum oxide catalyst of the corresponding 1-azido-1-deoxy derivatives. The preparation of hexosylamine by a different procedure, which involved the conversion into 1-amino-1-deoxy sugar of 4,6-O-benzylidene-D-glucose by the methanolic ammonia, was described by Coutsogeorgopoulos and Zervas.[10]

By the same method, Bolton, *et al.*[11] and Yoshimura, *et al.*[12] obtained 2-acetamido-2-deoxy-4,6-O-benzylidene-D-glucosylamine. Bertho, *et al.*[13] also prepared 2-amino-2-deoxy-3,4,6-tri-O-acetyl-β-D-glucosylamine (I) from 1-azido-2-amino-1,2-dideoxy derivatives (II), which was obtained by the treatment of N-acetyl-1-bromo-1-deoxy-glucosamine hydrobromide with silver azide. By the N-acetylation of II, Micheel, *el al.*[14] prepared 2-acetamido-2-deoxy-3,4,6-tri-O-acetyl-β-D-glucosyl azide (III).

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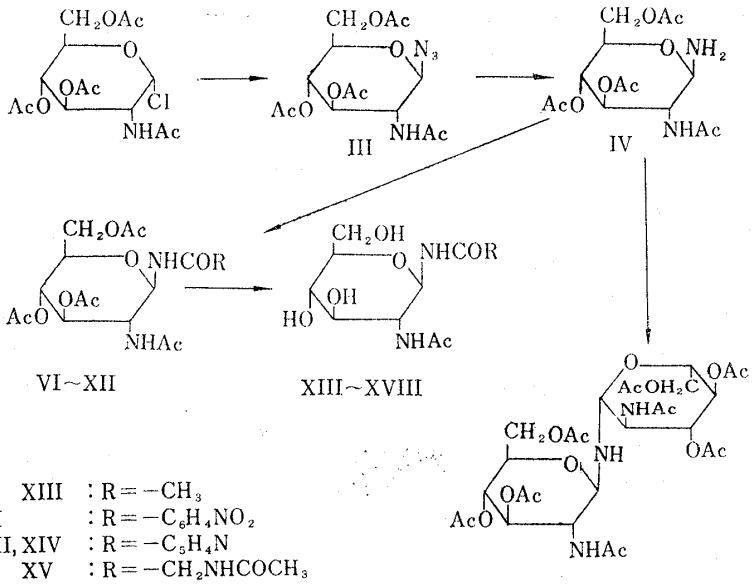

VI, XIII : R=$-CH_3$
VII : R=$-C_6H_4NO_2$
VIII, XIV : R=$-C_5H_4N$
IX, XV : R=$-CH_2NHCOCH_3$
X, XVI : R=$-CH_2NHCOC_6H_5$
XI, XVII : R=$-CH_2NHCOOCH_2C_6H_5$
XII : R=$-C_6H_4NH_2$
XVIII : R=$-CH_2NH_2$

Chart 1.

In this work, a highly explosive property of silver azide led us to prepare III from N-acetyl-1-chloro-1-deoxy-glucosamine,[15] heating the latter with sodium azide in formamide[16] at 85°. III contained a strong absorption band assignable to azide at 2130 cm^{-1} in the infrared absorption spectrum. III was hydrogenated in dioxane over Adams' platinum oxide catalyst to give about 80% yield of 2-acetamido-2-deoxy-3,4,6-tri-O-acetyl-β-D-glucosylamine (IV), m.p. 147~149°, which was free of azide absorption at 2130 cm^{-1} in the infrared absorption spectrum. Marks, *et al.*[7] and Bolton, *et al.*[11] prepared IV independently of us, recorded m.p. 152~153° and 225~230°, respectively. The reduction was also carried out in ethyl acetate or tetrahydrofuran, serving as good solvent.

From the mother liquor of the reduction of III, fine silky needles (V), m.p. 222°, were isolated. Furthermore, it was found that IV is converted to V in boiling methanol. The by-product (V) had analytical values in agreement with the formula $C_{28}H_{41}O_{16}N_3$ and was tentatively identified as bis(2-acetamido-2-deoxy-tri-O-acetyl-D-glucosyl)amine, possibly formed by the elimination of a molecule of ammonia from two molecules of IV, analogous to bis(tetra-O-acetyl-D-glucosyl)amine,[17] although no further studies were carried out on the chemical structure.

Treatment of V with acetic anhydride in pyridine effected no acetylation, but IV was readily acetylated to give N-acetyl-2-acetamido-2-deoxy-3,4,6-tri-O-acetyl-β-D-glucosylamine (VI). Although a series of 2-acylamino-2-deoxy-D-glucose[18~20] or 1-acylamino-1-deoxy-D-glucose derivatives[10,21] have been prepared by the action of acid anhydride or chloride on amino sugar derivatives in the presence of a strong base, Kocheto-

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kov, *et al.*[22] and several workers[23] found that carbodiimide method is more satisfactory for the condensation of further complicated compounds bearing a carboxylic function with the amino group of amino sugar derivatives.

The latter method was now applied and 2-acetamido-2-deoxy-3,4,6-tri-O-acetyl-β-D-glucosyl-amides of *p*-nitro-benzoic acid (Ⅵ), isonicotinic acid (Ⅶ), and of suitably protected amino acids, *e.g.*, aceturic acid (Ⅸ), hippuric acid (Ⅹ) and N-benzyloxycarbonylglycine (Ⅺ) were synthesized. *p*-Aminobenzoyl derivative (Ⅻ) of Ⅳ was obtained by catalytic hydrogenation over Adams' catalyst of Ⅵ.

Finally, 1-acyl derivatives of Ⅳ were freed from the acetyl groups by de-O-acetylation. In the studies of the condition for de-O-acetylation of the alkali-sensitive glucosaminide acetates, Whitaker, *et al.*[24] found that magnesium methoxide is the most suitable de-O-acetylating agent, for it is capable of maintaining anhydrous condition by the removal of hydroxyl ion from the reaction system as insoluble magnesium hydroxide. In the present work, 1-acyl derivatives of Ⅳ were de-O-acetylated in the same way, but a prolonged time of reaction was found to be necessary.

Thus, Ⅵ～Ⅺ were deacetylated with 1% $Mg(OCH_3)_2$ in methanol containing 2% of acetate at 0°, until only traces of ferric-hydroxamate-positive material were present. The results showed the reaction to be complete in 1 to 3 hr. The excess of magnesium ions were removed by Dowex 50 (H^+) resin to give desired products. It was unsuccessful to obtain crystalline material of Ⅻ by the de-O-acetylation.

N-(N-Benzyloxycarbonylglycyl)-2-acetamido-2-deoxy-β-D-glucosylamine (XVⅡ) prepared by the deacetylation of Ⅺ was catalytically hydrogenated over palladium on charcoal by the usual method to give N-glycyl-2-acetamido-2-deoxy-β-D-glucosylamine (XVⅢ).*3[3,12]

Ⅲ and Ⅳ were very readily hydrolyzed, especially by dilute alkali, and these reacted with the Morgan-Elson reagent and reduced ammoniacal silver nitrate reagent and Ⅳ turned brown after about 2 months at room temperature, and it was identified to be Ⅴ after recrystallization from ethanol. On the other hand, 1-acyl derivatives of Ⅳ and its de-O-acetylated products failed to react with two above-reagents, unless preheated with dilute alkali and did not mutarotate for 16 hr. These behaviors are in agreement with similar observations for N-acetyl-2-acetamido-2-deoxy-α-D-glucosylamine.[25] Therefore, these facts indicate that the acylation of Ⅳ tend to stabilize the molecule.

According to the general rules of substitution for N-acetyl-1-chloro-1-deoxy-α-D-glucosamine, the azide (Ⅲ) probably possesses the β-configuration. The structure of glucosylamine prepared by reduction from the corresponding β-azide is known to be β-configuration. In this respect, it was considered that the amine (Ⅳ) is also consistent with the β-D-structure. The negative rotation observed in Ⅴ supports this consideration. Furthermore, N-acylation of Ⅳ stabilized the molecule as described above. These assumptions were also supported by the facts that 1,2-diacetamido-derivative (Ⅵ), $[\alpha]_D$ +22.8°, is assignable to the β-D-isomer in contrast to the specific rotation, $[\alpha]_D$ +92.2°,[25] of the corresponding α-anomer. Consequently, it seems reasonable to assign the configuration of β-D-isomers to low dextrorotatory substances as listed in Table Ⅰ and Ⅱ.

*3 Most recently, Yoshimura, *et al.*[12] communicated the preparation of hydrochloride of XVⅢ in the different method, which involves the condensation of N-benzyloxycarbonylglycine with 2-acetamido-2-deoxy-4,6-O-benzylidene-D-glucosylamine, followed by the removal of protecting groups.

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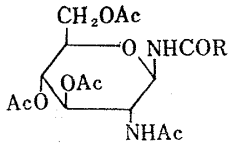
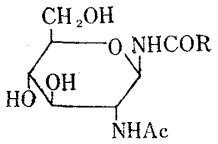
TABLE I. Analytical and Physical Data



Compd. (No.)	Formula	Substituent (R)	React.[a] solv.	m.p. (°C)	Yield[b] (%)	Recryst. solv.	$[\alpha]_D$[c]	Analysis (%) Calcd. C	H	N	Found C	H	N
VI	$C_{16}H_{24}O_9N_2$	$-CH_3$	P	241	62	MeOH	+22.8	49.48	6.23	7.21	49.52	6.42	7.21
VII	$C_{21}H_{25}O_{11}N_3$	$-C_6H_4NO_2$	T	260～263[d]	71	MeOH	−46.2	50.91	5.09	8.48	50.91	5.24	8.58
VIII	$C_{20}H_{25}O_9N_3$	$-C_5H_4N$	P	226	58	iso-PrOH	−35.2	53.21	5.58	9.31	53.34	5.70	8.86
IX	$C_{18}H_{27}O_{10}N_3$	$-CH_2NHCOCH_3$	P	198	74	EtOH-ether	+28.2	48.54	6.11	9.43	48.37	6.33	9.43
X	$C_{23}H_{29}O_{10}N_3$	$-CH_2NHCOC_6H_5$	T	198	81	iso-PrOH	+ 8.7	54.43	5.76	8.28	54.61	5.81	8.20
XI	$C_{24}H_{31}O_{11}N_3$	$-CH_2NHCO_2CH_2C_6H_5$	T	196	75	EtOH	+13.9	53.63	5.82	7.84	53.52	5.91	7.64

a) P: pyridine; T: tetrahydrofuran *b*) yield for analytical pure materials *c*) determined in pyridine *d*) decomposed

TABLE II. Analytical and Physical Data



Compd. (No.)	Formula	Substituent (R)	Recryst. solv.	m.p.[e] (°C)	$[\alpha]_D$[a]	IR[b] (cm^{-1})	Rf[c]	Yield[d] (%)	Analysis (%) Calcd. C	H	N	Found C	H	N
XIII	$C_{10}H_{18}O_2N_2 \cdot H_2O$	$-CH_3$	MeOH-acetone	240～243	+43.7	892	0.45	77	42.85	7.14	10.00	42.83	7.17	10.46
XIV	$C_{14}H_{19}O_6N_3 \cdot 2H_2O$	$-C_5H_4N$	H_2O-EtOH	258～259	+33.9	892	0.53	61	46.54	6.41	11.62	47.09	6.37	11.82
XV	$C_{12}H_{21}O_7N_3 \cdot H_2O$	$-CH_2NHCOCH_3$	H_2O-EtOH	247～249	+54.7	894	0.37	72	42.73	6.87	12.46	42.39	7.31	12.25
XVI	$C_{17}H_{23}O_7N_3 \cdot 2H_2O$	$-CH_2NHCOC_6H_5$	MeOH	235～236	+15.0	893	0.61	69	48.92	6.48	10.07	48.57	6.34	10.21
XVII	$C_{18}H_{25}O_8N_3$	$-CH_2NHCOOCH_2C_6H_5$	MeOH	231～232	+43.4	897	0.68	75	52.55	6.13	10.21	52.29	6.10	10.39
XVIII	$C_{10}H_{19}O_6N_3 \cdot 2.5H_2O$	$-CH_2NH_2$	H_2O-EtOH	187～192	+30.5	890	0.21	80	37.29	7.45	13.05	37.03	7.03	13.03

a) determined in H_2O *b*) type-2b absorption of β-D-glucopyranose structure *c*) Solvent: BuOH-AcOH-H_2O(12:3:5), chlorine-iodide-starch reagent
d) yield for analytical pure materials *e*) decomposed

Experimental

2-Acetamido-2-deoxy-3,4,6-tri-O-acetyl-β-D-glucosyl Azide (III)——a) To a suspension of AgN_3 (prepared from 1 g. of NaN_3 and 2.5 g. of $AgNO_3$ according to Bertho[9]) in 20 ml. of $CHCl_3$, was added 1.83 g. of N-acetyl-1-chloro-1-deoxy-glucosamine.[15] The reaction mixture was refluxed with mechanical stirring for 3 hr. under protection from light. After cooling, the mixture was filtered, evaporated under reduced pressure to a crystalline material. This was recrystallized from AcOEt-petr. ether to colorless, needles m.p. 159~160.5°(decomp.); yield 1.0 g. Micheel, *et al.*[14] and Marks, *et al.*[7] recorded m.p. 160~161° and 166~167°, respectively.

b) The suspension of 2.5 g. of NaN_3 in 50 ml. of dry $HCONH_2$ was stirred with 5 g. of N-acetyl-1-chloro-1-deoxy-glucosamine for 3 hr. at 80~85°. After cooling, the mixture was poured into 200 ml. of ice-cold water and extracted 3 times with $CHCl_3$. The combined $CHCl_3$ extracts were washed with water, dried over anhyd. Na_2SO_4, and evaporated to dryness under reduced pressure to yield crystalline residue. It was recrystallized from AcOEt-petr. ether to give 3.8 g. of the colorless needles, m.p. 160~161°(decomp.), undepressed when mixed with the product from (a), $[\alpha]_D^{30}$ −40°(c=1.0. $CHCl_3$). *Anal.* Calcd. for $C_{14}H_{20}O_8N_4$: C, 45.16; H, 5.41; N, 15.05. Found: C, 44.98; H, 5.52; N, 14.87.

2-Acetamido-2-deoxy-3,4,6-tri-O-acetyl-β-D-glucosylamine (IV)——A solution of 1.5 g. of III in 30 ml. of dioxane (25 ml. of tetrahydrofuran or 60 ml. of AcOEt) was catalytically hydrogenated with 0.15 g. of Adams' PtO_2 for 3.5 hr. at atmospheric pressure. The catalyst was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. After several recrystallization of the white residue from EtOH, 1.2 g. of colorless needles, m.p. 147~149° (decomp.), $[\alpha]_D^{30}$ −14° (c=1.0, $CHCl_3$), separated. *Anal.* Calcd. for $C_{14}H_{22}O_8N_2$: C, 48.55; H, 6.40; N, 8.06. Found: C, 48.34; H, 6.50; N, 8.09.

The combined mother liquor was evaporated to dryness. The residue was recrystallized from boiling AcOEt to give silky needles of bis(2-acetamido-2-deoxy-tri-O-acetyl-D-glucosyl)amine (V), 222~224° (decomp.), $[\alpha]_D^{16}$ −25°(c=1.0, $CHCl_3$). *Anal.* Calcd. for $C_{28}H_{41}O_{16}N_3$: C, 49.80; H, 6.10; N, 6.22. Found: C, 49.79; H, 6.24; N, 6.17.

N-Acetyl-2-Acetamido-2-deoxy-3,4,6-tri-O-acetyl-β-D-glucosylamine (VI)——IV, 0.1 g. was acetylated with 0.25 ml. of Ac_2O and 0.8 ml. of pyridine overnight at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. The residue was recrystallized from EtOH to give 0.07 g. of colorless needles, m.p. 241°, $[\alpha]_D^{36}$ +22.8°(c=1.2, pyridine). *Anal.* Calcd. for $C_{16}H_{24}O_9N_2$: C, 49.48; H, 6.23; N, 7.21. Found: C, 49.52; H, 6.42; N, 7.21.

General Procedure of N-Acylation of IV by Dicyclohexylcarbodiimide (DCC)——To a solution of 0.01 mole of IV and 0.01 mole of acids in dry tetrahydrofuran or pyridine was added 0.12 mole of DCC. The solution was stirred for 2 hr. at room temperature and allowed to stand overnight. A 3 drops of AcOH were added to the reaction mixture and stirred for a short time. Dicyclohexylurea separated was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized from suitable solvent to give crystalline compounds. The data for the compounds are listed in Table I.

N-(*p*-Aminobenzoyl)-2-acetamido-2-deoxy-3,4,6-tri-O-acetyl-β-D-glucosylamine (XII)——A solution of 0.35 g. of VII in 70 ml. of AcOEt was catalytically hydrogenated with 0.07 g. of Adams' PtO_2 at atmospheric pressure. The hydrogenation was continued for 160 min., until the theoretical amounts of H_2 were used. The catalyst was removed by filtration and the solvent was removed under reduced pressure. Recrystallization of the residue from MeOH gave 0.27 g. of colorless needles, m.p. 258~263° (decomp.), $[\alpha]_D^{35}$ −64.2 (c=1.2, pyridine). This substance gave a yellow color with Ehrlich's reagent (*p*-dimethylaminobenzaldehyde). *Anal.* Calcd. for $C_{21}H_{27}O_9N_3$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.39; H, 6.00; N, 8.93.

General Procedure of De-O-acetylation of 1-Acyl Derivatives of IV——To a 4% solution of 1-acyl derivatives of IV in dry MeOH was added an equal amounts of 2% solution of $Mg(OCH_3)_2$ in dry MeOH at 0°. The reaction was continued until ferric-hydroxamate test became negative. After being kept at 0° for 1 to 3 hr., a few ml. of water were added to the reaction mixture and then the solution was neutralized by the addition of Dowex 50 (H^+) resin. The resin was filtered and washed with water until the filtrate gave a negative test for chlorine-iodide-starch reagent.[31] The filtrate and washings were combined, evaporated to dryness under reduced pressure. The residue was recrystallized from suitable solvent to give crystalline compounds.

N-Glycyl-2-acetamido-2-deoxy-β-D-glucosylamine (XVIII)——A solution of 0.37 g. of XVII in 40 ml. of MeOH was catalytically hydrogenated with 2.6 g. of 1% Pd-C at atmospheric pressure. Evolution of CO_2 stopped after 7 hr. The solution was filtered from the catalyst, which was washed with MeOH until the filtrate showed a negative ninhydrine test. The filtrate and washings were combined, evaporated under reduced pressure to give crystalline residue. Several recrystallization of the residue from aqueous

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EtOH gave 0.2 g. of colorless plates, m.p. 187~192° (decomp.), $[\alpha]_D^{16}$ +30 (c=0.5, H_2O). *Anal.* Calcd. for $C_{10}H_{19}O_6N_3 \cdot 2.5H_2O$: C, 37.29; H, 7.45; N, 13.05. Found : C, 37.03; H, 7.03; N, 13.03.

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Summary

2-Acetamido-2-deoxy-3,4,6-tri-O-acetyl-β-D-glucosylamine (Ⅳ) was prepared by the hydrogenation of 2-acetamido-2-deoxy-3,4,6-tri-O-acetyl-β-D-glucosyl azide (Ⅲ) which was obtained by the treatment of acetochloroglucosamine with NaN_3 in formamide at 85°. Ⅳ was characterized by the acetylation as N-acetyl-2-acetamido-2-deoxy-3,4,6-tri-O-acetyl-β-D-glucosylamine (Ⅵ). Ⅳ in tetrahydrofuran or pyridine was condensed in the presence of dicyclohexylcarbodiimide with *p*-nitrobenzoic acid, isonicotinic acid, aceturic acid, hippuric acid and N-benzyloxycarbonyl glycine to yield the corresponding amides, followed by the removal of the protecting groups. N-(*p*-Aminobenzoyl)2-acetamido-2-deoxy-3,4,6-tri-O-acetyl-β-D-glucosylamine was obtained by the hydrogenation of the corresponding *p*-nitrobenzamido derivative over Adams' catalyst.

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136. Akira Yamamoto, Chieko Miyashita, and Hisao Tsukamoto : Studies on Amino Sugars. II.*1 Preparation of N-[L-α (and β)-Aspartyl]-2-acetamido-2-deoxy-β-D-glucosylamine and N-(L-γ-Glutamyl)-2-acetamido-2-deoxy-β-D-glucosylamine.*2

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It has recently been proposed[1] for the structure of the carbohydrate-peptide bond in natural glycoproteins that the polysaccharide moiety would be attached to the amide group of asparagine residue of peptide chain through the reducing end of N-acetylglucosamine. In the previous paper of this series,*1 the preparation of six acyl derivatives of 2-acetamido-2-deoxy-β-D-glucosylamine, which was of interest in connection with the above-proposed structure, has been described. They were 2-acetamido-2-deoxy-β-D-glucosyl-amides of acetic, *p*-nitrobenzoic, isonicotinic, aceturic, hippuric acid and glycine. This paper, furthermore, reports the synthesis of three N-acyl, *i.e.*, β-aspartyl (Ⅷ), α-aspartyl (Ⅸ) and γ-glutamyl (Ⅹ) derivatives of 2-acetamido-2-deoxy-β-D-glucosylamine that were considered to be the most likely structure in the natural glycoproteins.

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1) See the Part Ⅰ of this series.