Studies on D*-Glucosamine Derivatives. VI. α-1-C-Phenyl-2-acetamido-2-deoxy-*D*-glucopyranoside and its Derivatives*[*]

By Juji YOSHIMURA

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The glucosylation of hydrocarbons with a carbohydrate moiety in which the pyranose ring is preserved has been accomplished by using glycosyl halides in two familiar organic reactions, i. g. the Friedel-Crafts and the Grignard reactions. Both approaches were originated by Hurd and Bonner(1) and extended by them(2). Since then the glycosylation of organometallics has been applied to a variety of carbohydrates(3) and Grignard reagents(3-8) as well as

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[*] Part V, This Bulletin, 33, 1404 (1960).

(1) C. D. Hurd and W. A. Bonner, *J. Am. Chem. Soc.*, **67**, 1664, 1972 (1945).

(2) W. A. Bonner, Friedel-Crafts and Grignard Process, "Advances in Carbohydrate Chemistry" Vol., 6, Academic Press, Inc., New York (1951), p. 251.

(3) C. D. Hurd and R. P. Holysz, *J. Am. Chem. Soc.*, **72**, 1732 (1950).

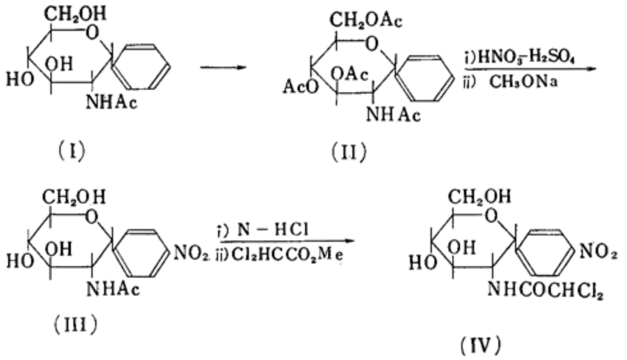
(4) Yu. A. Zhdanov, L. I. Shcherbakova and T. N. Egorova, *Doklady Akad. Nauk S. S. S. R.*, **83**, 403 (1952).

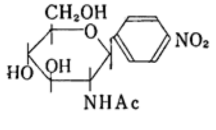
(5) Yu. A. Zhdanov and L. I. Shcherbakova, ibid., **90**, 185 (1953); *Chem. Abstr.*, **48**, 5114 (1954).

(6) Yu. A. Zhdanov, L. I. Shcherbakova and R. V. Golovnya, *Doklady Akad. Nauk S. S. S. R.*, **107**, 259 (1956); *Chem. Abstr.*, **50**, 15476 (1956).

(7) Yu. A. Zhdanov and G. F. Drofeenko, *Doklady Akad. Nauk S. S. S. R.*, **112**, 433 (1957).

(8) R. Zelinski and R. E. Meyer, *J. Org. Chem.*, **23**, 810 (1958).

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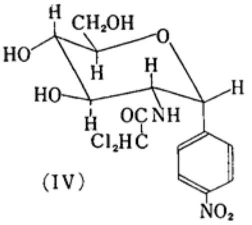
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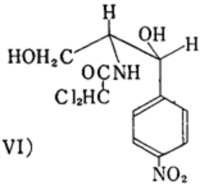
(VI)

to organocadmium[9] and organoalkali[10] compounds. In earlier works of this series, the glycosylation of D-glucosamine was examined by the Friedel-Crafts[11] and Grignard reactions[12], and crystalline β-1-*C*-substituted-2-acetamido-2-deoxy-3, 4, 6-tri-*O*-acetyl-D-glucopyranosides (R; Me, Et, *n*-Pr, *n*-Bu, phenyl, benzyl) were obtained in the latter case. These crystalline substances were designated as β-anomers on the basis of their low rotations, and their pyranose ring systems were confirmed by periodate oxidation. The present investigation centers about the α-1-*C*-phenyl-2-acetamido-2-deoxy-3, 4, 6-tri-*O*-acetyl-D-glucopyranoside (II), produced as a by-product of the crystalline β-anomer when acetobromo-D-glucosamine hydrobromide reacts with phenylmagnesium bromide.

For the isolation of II from the crystallization mother liquors of the β-anomer, an attempt was first made to fractionate the sirupy materials obtained by concentration of the mother liquors using a magnesol-celite column. The existence of II was, however, scarcely deduced from the rotation of an effluent, though α- and β-pentaacetyl-D-glucosamine, and the β-anomer were separated in pure crystalline form. Secondly, the sirupy materials were de-*O*-acetylated by treatment with sodium in methanol and chromatographed on the same column. As is shown in Fig. 1, α-1-*C*-phenyl-2-acetamido-2-deoxy-D-glucopyranoside (I), m.p. 113~114°C, $[\alpha]_D^{24}$ 75.3°, was successfully isolated from the β-anomer and *N*-acetyl-D-glucosamine.

The proportions of the β-anomer to the α one, listed in Table II[13], are shown about ten to one in two cases. This is also ture for D-glucose derivatives[13].

On acetylation of I with acetic anhydride and pyridine, II was obtained as a thick sirup. Although all attempts to induce crystallization of this sirupy material failed, the values of elementary analysis were consistent with the theoretical values.

Nitration of II with a mixture of concentrated sulfuric and nitric acid affords again a sirupy material. However, the crystalline α-1-*C*-(*p*-nitrophenyl)-2-acetamido-2-deoxy-D-glucopyranoside (III) was obtained from it, by treating it with sodium methylate and afterwards by fractionation using a magnesol-celite column. The position of the nitro group of III was deduced from its ultraviolet absorption spectrum[14] as shown in Fig. 2.

For purposes of comparison with the compounds to be reported later, the β-anomer of III (V) was also prepared from β-1-*C*-(*p*-nitrophenyl)-2-acetamido-2-deoxy-3, 4, 6-tri-*O*-acetyl-D-glucopyranoside[14] by deacetylation.

Compound III was converted into sirupy *N*-dichloroacetyl derivative (IV) by treating with *N*-hydrochloric acid and methyl dichloroacetate in turn. The conformation at the position of *C*–1 and 2 of IV is very similar to that of chloramphenicol (VI), but IV showed no antibiotic activities.

Having several available anomeric glycosyl

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[9] C. D. Hurd and R. P. Holysz, *J. Am. Chem. Soc.*, **72**, 2005 (1950).

[10] C. D. Hurd and R. P. Holysz, ibid., **72**, 1735 (1950).

[11] J. Yoshimura, A. Kojima, S. Watanabe and T. Sato, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **80**, 1472 (1956).

[12] J. Yoshimura, N. Muramatsu and T. Sato, ibid., **79**, 1503 (1958).

[13] W. A. Bonner and J. M. Craig, *J. Am. Chem. Soc.*, **72**, 3480 (1950).

[14] J. Yoshimura, T. Nakagawa and T. Sato, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **80**, 1475 (1959).

TABLE I. ISOROTATION RULE VALUES FOR ANOMERIC GLUCOSAMINE DERIVATIVES

D-Glucosamine pyranoside-derivatives		$[M]_D$	T, °C	Approx. concn. g./100 ml.	Solvent	*A*	*B*
α-1-*C*-Phenyl-*N*-acetyl-		21180	24	0.65	EtOH	8790	12390
β-1-*C*-Phenyl-*N*-acetyl-		3600	20	1.0	EtOH		
α-1-*C*-(*p*-Nitrophenyl)-*N*-acetyl-		31940	22	1.0	MeOH	19395	12545
β-1-*C*-(*p*-Nitrophenyl)-*N*-acetyl-		−6850	23	0.9	MeOH		
α-1-*C*-(*p*-Nitrophenyl)-*N*-dichloroacetyl-		23710	23	0.9	MeOH	13040	10670
β-1-*C*-(*p*-Nitrophenyl)-*N*-dichloroacetyl-		−2370	27	0.8	EtOH		
N-Acetyl-α-	b)	18200	22	1.5	H_2O	11475	6725
N-Acetyl-β-	a)	−4750	22	0.054	H_2O		
Methyl *N*-acetyl-α-	c)	30800	25	1.0	H_2O	20450	10350
Methyl *N*-acetyl-β-	d)	−10100	22	2.0	H_2O		
Phenyl *N*-acetyl-α-	e)	63320	25	1.0	H_2O	33160	30130
Phenyl *N*-acetyl-β-	e)	−3060	25	1.3	H_2O		
α-1-*C*-Phenyl-*N*, *O*-tetraacetyl-		27900	25	0.7	$CHCl_3$	21650	6250
β-1-*C*-Phenyl-*N*, *O*-tetraacetyl-		−15400	20	1.2	$CHCl_3$		
N, *O*-Pentaacetyl-α-	f)	36400	20	5.0	$CHCl_3$	17965	18435
N, *O*-Pentaacetyl-β-	f)	470	20	4.3	$CHCl_3$		
Methyl *N*, *O*-tetraacetyl-α-	d)	31790	22	2.0	$CHCl_3$	19690	12100
Methyl *N*, *O*-tetraacetyl-β-	g)	−7590	20	0.3	EtOH		
Phenyl *N*, *O*-tetraacetyl-α-	e)	58330	25	2.0	$CHCl_3$	33610	24720
Phenyl *N*, *O*-tetraacetyl-β-	e)	−8890	25	2.0	$CHCl_3$		

a) R. Kuhn and F. Haber, *Ber.*, **86**, 722 (1953).
b) C. Niemann and J. T. Hays, *J. Am. Chem. Soc.*, **67**, 1302 (1945).
c) R. Kuhn, *Ber.*, **86**, 466 (1953).
d) A. Neuberger and R. P. Rivers, *J. Chem. Soc.*, **1939**, 122.
e) S. Roseman and A. Dorfman, *J. Biol. Chem.*, **191**, 609 (1951).
f) C. S. Hudson and J. K. Dale, *J. Am. Chem. Soc.*, **38**, 1431 (1916).
g) W. H. Myers and G. J. Robertson, ibid., **56**, 8 (1943).

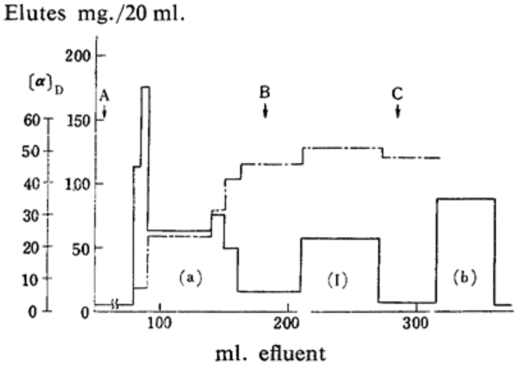

Fig. 1. Chromatographic separation of I on a magnesol-celite column.
A, B and C are a mixture of benzene and ethanol used for elution in which the ratios of benzene to ethanol are 10, 5 and 1, respectively.; ----- rotation of elutes, —— weight of elutes, (a) the β anomer of I, (b) *N*-acetyl-D-glucosamine.

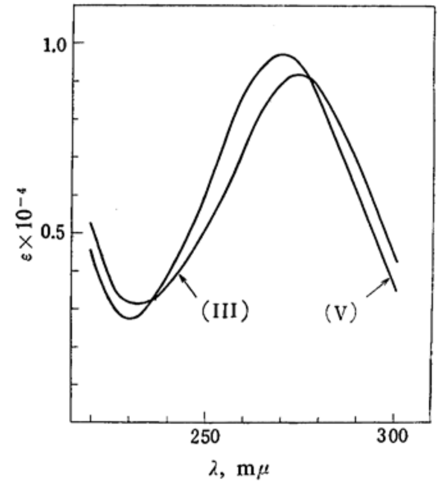

Fig. 2. Ultraviolet absorption spectra of III and V in methanol.

derivatives of D-glucosamine, it is interesting to apply Hudson's rules[15] of isorotation to them. The *A* values, referring to the molecular rotatory contribution of *C*-1 containing the phenyl group, and the *B* values, referring to the free or substituted remainder of the molecule, are presented in Table I.

For comparative purposes we have included in Table I, *B* values for other appropriately substituted anomeric D-glucosamine derivatives. Table I shows that the *A* and *B* values of glucosyl derivatives of D-glucosamine are very

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[15] C. D. Hudson, *J. Am. Chem. Soc.*, **31**, 66 (1909).

Table II. Yields and ratio of products

Starting material g.	Crude yield g. (%)	Acetylderivative of the β-anomer, g.	Residual syrup, g. (β, α)	Ratio of β to α
Acetobromo-D-glucosamine hydrobromide (5.0)	2.9 (64.0)	2.1	0.5 (0.2, 0.18)	12.8
〃 (45.0)	24.1 (59.3)	12.6	11.0 (3.69, 1.65)	9.9
α-Acetochloro-D-glucose[13] (27.4)	19.5 (63.6)	15.0	4.2 (1.98, 1.58)	10.7

similar to that of the corresponding glucosyl derivatives of D-glucose[13], and behave almost normally.

It is interesting to compare the values A_{ph} and A_{pho} for 1-*C*-phenyl derivatives and phenyl glycosides, substances differing only in the presence or absence of an oxygen atom at *C*-1. The A_{pho} value is seen to be higher than the A_{ph} by a factor of about two to four.

Apparently, the conjugation with the aromatic nucleus of the unshared electrons on the glycosidic oxygen in the phenyl glycosides produces a considerably higher partial rotatory contribution of the *A*-portion of the molecule than is the case when the aromatic nucleus alone is present.

The substitution of the *p*-nitro group in the aromatic nucleus of 1-*C*-phenyl derivative, however, leads to an anomalously high *A* value which is analogous to that of phenyl glucosides[16].

Experimental

Reaction of Acetobromo-D-glucosamine Hydrobromide with Phenylmagnesium Bromide. — The reaction was performed in the manner described previously[12], using a ninefold increase (45 g.) in the quantities of starting material. The crude product was isolated, after acetylation, as a thick brown sirup in about 60% yield. It was crystallized from a minimum of 2-propanol, yielding β-1-*C*-phenyl-2-acetamido-2-deoxy-3, 4, 6-tri-*O*-acetyl-D-glucopyranoside. The mother liqors were concentrated to dryness, leaving a sirup which contains the α-anomer.

In Table II are tabulated two results of such preparations.

α-1-*C*-Phenyl-2-acetamido-2-deoxy-D-glucopyranoside (I).—The entire residual sirup from the second run in Table II was deacetylated with sodium in methanol. Evaporation of methanol affords 7.2 g. of sirupy materials. A part of the sirup (2.5 g.) was dissolved in 10 ml. of benzene-ethanol (10 : 1 mixture) and insoluble *N*-acetyl-D-glucosamine (0.29 g.) was filtered off. The filtrate was chromatographed at room temperature on a column packed with 25 g. of magnesol-celite (5 : 1 mixture). The solvents used for elution were benzene and ethanol of successively increasing concentrations in benzene. The effluents were examined as to the weight of elutes and their rotation. As is shown in Fig. 1, 0.98 g. of the β-anomer, 0.51 g. of the α-anomer and 0.51 g. of crystalline *N*-acetyl-D-glucosamine were obtained. The α and β anomers were again chromatographed, and 0.395 g. and 0.88 g. of pure crystals were obtained respectively. The α-anomer had m. p. 113～114°C, $[\alpha]_D^{24}$ 75.3° (*c* 0.65, chloroform).

Found: C, 59.93; H, 7.02; N, 4.63. Calcd. for $C_{14}H_{19}O_5N$(281.3): C, 59.77; H, 6.81; N, 4.98%.

α-1-*C*-Phenyl-2-acetamido-2-deoxy-3, 4, 6-tri-*O*-acetyl-D-glucopyranoside (II).—Compound I (200 mg.) was acetylated with acetic anhydride (10 ml.) and pyridine (5 ml.) at 25°C for one day. Processing in the usual manner gave 290 mg. of a clear sirup. $[\alpha]_D^{25}$ 68.5° (*c* 0.69, ethanol).

Found: C, 58.36; H, 6.45; N, 3.34. Calcd. for $C_{20}H_{25}O_8N$(407.4): C, 58.69; H, 6.18; N, 3.44%.

α-1-*C*-(*p*-Nitrophenyl)-2-acetamido-2-deoxy-D-glucopyranoside (III).—A sirupy material of II (1.5 g.) was dissolved in a mixture of 7 ml. of concentrated sulfuric acid (sp. gr. 1.8) and 7 ml. of concentrated nitric acid (sp. gr. 1.38) on cooling with ice-salt bath. After 30 min. the reaction mixture was left to stand for 1 hr. at 0°C, and for 15 min. at room temperature. About 20 ml. of dry chloroform were added and the mixture was poured gradually into ice-water including an excess amount (about 20 g.) of sodium carbonate. The chloroform layer was separated from the water layer, and the latter was extracted with chloroform in the usual manner. Evaporation of the solvent afforded about 1.5 g. of a pale yellow sirup. A small grain of sodium was added to the solution of this sirup and 15 ml. of methanol, and was left to stand for 3 hr. at room temperature. The methanol solution was diluted with 10 ml. of water and treated with 15 ml. of cation-exchanger (IRA 120) and concentrated in vacuo to dryness. The residual sirup was chromatographed on 10 g. of magnesol-celite column (5 : 1 mixture) in a manner similar to that of I shown in Fig. 1. The fractions eluted with benzene-ethanol mixtures the ratios of which were five to one and two to one were crystallized. Yield 200 mg., m. p. 170～171°C, $[\alpha]_D^{22}$ 97.5° (*c* 1.0, methanol).

Found: C, 51.18; H, 5.23; N, 8.25. Calcd. for $C_{14}H_{18}O_7N_2$(326.3): C, 51.53; H, 5.56; N, 8.59%.

α-1-*C*-(*p*-Nitrophenyl)-2-dichloroacetamido-2-deoxy-D-glucopyranoside (IV).—A mixture of 1.3 g. of III, 10 ml. of 2 N hydrochloric acid and 10 ml. of

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[16] W. W. Pigman, *J. Research Natl. Bur. Standards*, 33, 129 (1944).

ethanol was refluxed 3 hr. on a steam bath. The reaction mixture was concentrated in vacuo, and the residual sirup (ca. 1 g.) was neutralized with about 0.072 g. of sodium in methanol. The solution was filtered and concentrated in vacuo, and the residual sirup was refluxed in 8 ml. of *n*-butanol and 3 ml. of methyl dichloroacetate for 5 hr. The precipitate (a small amount) was filtered off, and the filtrate was concentrated to a thick sirup. An attempt was made to fractionate this on a magnesol-celite column, but no crystalline material could be obtained. The main fraction was about 0.8 g., $[\alpha]_D^{23}$ 60.0° (*c* 0.9, methanol).

Found: C, 42.88; H, 4.25; N, 7.34; Cl, 17.32. Calcd. for $C_{14}H_{16}O_7N_2Cl_2$ (395.2): C, 42.52; H, 4.08; N, 7.09; Cl, 17.94%.

β-1-*C*-(*p*-Nitrophenyl)-2-acetamido-2-deoxy-D-glucopyranoside (V).—β-1-*C*-(*p*-Nitrophenyl)-2-acetamido-2-deoxy-3, 4, 6-tri-*O*-acetyl-D-glucopyranoside (0.5 g.) was deacetylated with sodium in methanol. Processing in the usual manner gave 0.3 g. of crystals. m. p. 269~271°C, $[\alpha]_D^{27}$ −21.0° (*c* 0.8, ethanol).

Found: C, 51.33; H, 5.47; N, 8.52. Calcd. for $C_{14}H_{18}O_7N_2$ (326.3): C, 51.53; H, 5.56; N, 8.59%.

Summary

The sirup obtained as a by-product with β-1-*C*-phenyl-2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-D-glucopyranoside by the action of phenylmagnesium bromide on acetobromo-D-glucosamine hydrobromide has been deacetylated and chromatographed to yield the α-anomer. Several α-derivatives have been described, among which, α-1-*C*-(*p*-nitrophenyl)-2-dichloroacetamido-2-deoxy-D-glucopyranoside which is a chloramphenicol derivative showed no antibiotic activities. The application of Hudson's rules of isorotation to the anomeric compounds in this series is discussed.

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Laboratory of Organic Chemistry
Tokyo Institute of Technology
Meguro-ku, Tokyo