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29. Atsushi Momose, Katsutoshi Kamei, and Yoshihiro Nitta : D-Glucuronolactone Derivatives. VII.*1 Synthesis of Anomeric 1-Deoxy-1-halogeno-2,5-di-O-acyl-D-glucofuranurono-γ-lactones.

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The halogeno-substituted derivatives of D-glucuronolactone are of particular importance in the synthesis of glucofuranosiduronic acid derivatives. Neuberg and Neiman[1] prepared in 1905 an "acetobromo-D-glucuronolactone," presumably 1-bromo-1-deoxy-2,5-di-O-acetyl-D-glucuronolactone, by the treatment of D-glucuronolactone with acetyl bromide. Goebel and Babers[2] were unable to confirm this method of synthesis, but found that the reaction of mixture of α- and β-1,2,5-tri-O-acetyl-D-glucuronolactone with acetyl chloride and hydrogen chloride gave 1-chloro-1-deoxy-2,5-di-O-acetyl-β-D-glucuronolactone. The same compound was also obtained recently by the treatment

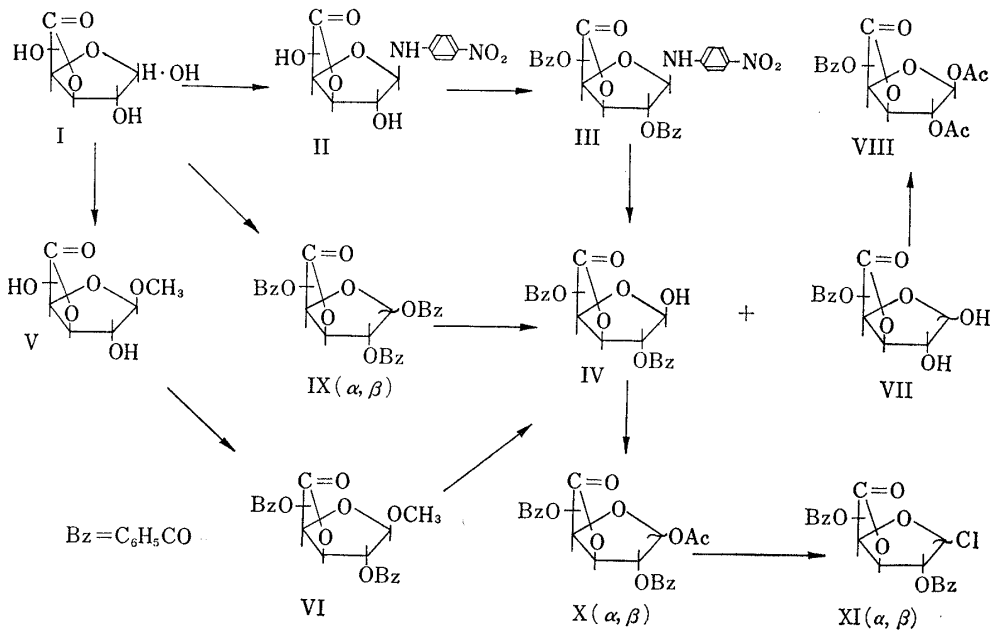


Chart 1.

*1 Part Ⅵ : Yakugaku Zasshi, **85**, 1032 (1965).
*2 Takadaminamicho, Toshima-ku, Tokyo (百瀬 篤, 亀井克利, 新田義博).
1) C. Neuberg, W. Neiman : Z. Physiol. Chem., Hoppe-Seyler's, **44**, 114 (1905).
2) W.F. Goebel, F.H. Babers : J. Biol. Chem., **101**, 173 (1933).

of a triacetate of β-D-glucuronolactone with aluminum chloride in cold chloroform.[3] But, these methods of preparation were not provided for consistent results in the present authors' experiments.

In this paper, we intend to report synthetic procedures for anomeric 1-deoxy-1-halogeno-2,5-diacyl derivatives of D-glucuronolactone and their properties. 2,5-Di-O-benzoyl-β-D-glucuronolactone (Ⅳ), an intermediate compound of the synthesis of 1-chloro-1-deoxy-2,5-di-O-benzoyl-α-(and β)-D-glucuronolactone (Ⅺ), was prepared from D-glucuronolactone by the following three routes as shown in Chart 1.

1) Treatment of 1-deoxy-1-*p*-nitroanilino-D-glucuronolactone[4] with benzoyl chloride in pyridine afforded a 2,5-di-O-benzoyl derivative (Ⅲ) in 75% yield, which was hydrolyzed with formic acid solution to give Ⅳ in 52% yield. This compound was considered to be in a β-configuration, because it showed a mutalotation of +26°→+36° after 20 hours.

2) Benzoylation of methyl β-D-glucuronolactone (Ⅴ)[5] gave the 2,5-di-O-benzoyl derivative (Ⅵ) in a good yield. Hydrolysis of Ⅵ with hydrochloric acid or sulfuric acid in aqueous acetic acid produced a mixture of two compounds as shown in Fig. 1. Recrystallization from ethanol had a good effect on the isolation of main product (Ⅳ), which was identified by the melting point of admixture with the product prepared from Ⅲ. The mother liquor of Ⅳ was purified by a column chromatography on silicagel, a syrup (Ⅶ) being obtained. Attempts to crystallize the syrup were unsuccessful, but the acetylation gave a crystalline substance, 1,2-di-O-acetyl-5-O-benzoyl derivative (Ⅷ). The structure of Ⅷ was proved by the elemental analysis and infrared absorption bands at 1810 (γ-lactone), 1760 (benzoyl) and 1730 cm^{-1} (acetyl) which were characterisic of carbonyl groups, and also at 976 and 956 cm^{-1}, characteristic of β-furanosyl compounds.[6]

3) Benzoylation of D-glucuronolactone (1) gave a mixture of α- and β-1,2,5-tri-O-benzoyl derivatives (Ⅸ). Both α- and β-anomer were hydrolyzed well to give Ⅳ and Ⅵ in a similar method to that described for Ⅵ.

Acetylation of Ⅳ with acetic anhydride and pyridine gave a mixture of α- and β-anomer of 1-O-acetyl-2,5-di-O-benzoyl derivatives (X). On the other hand, treatment of Ⅳ with acetic anhydride and sulfuric acid led to yield only the β-anomer in an excellent yield. The infrared spectrum of α-anomer showed absorption bands at 945 and 934 cm^{-1}, characteristic of α-furanosyl compounds, whereas the β-anomer gave absorptions at 973 and 956 cm^{-1}, characteristic of β-furanosyl compounds.[6]

The β-anomer of X gave the desired 1-chloro-1-deoxy-2,5-di-O-benzoyl-β-D-derivatives (Ⅺ) in 75% yield when treated with aluminum chloride in chloroform at a room temperature. On the other hand, it gave α- and β-anomers of Ⅺ, in the yields of 5.8 and 70%, respectively when treated with titanium tetrachloride in boiling chloroform for 3 hours. These results suggested that the anomerization of β-chloride was more difficult than the case of acylated glycosyl chloride,[7] and this stability might be due to the electronic and steric effects.[3]

Now, we are going to describe the synthesis of 1-deoxy-1-halogeno-2-O-acetyl-5-O-benzoyl derivatives.

3) W. Korytnyk, J. A. Mills : J. Chem. Soc., **1959**, 636.
4) S. Takitani : This Bulletin, **9**, 222 (1961).
5) E. M. Osman, K. C. Hobbs, W. E. Walston : J. Am. Chem. Soc., **73**, 2726 (1951).
6) Y. Nitta, J. Ide, A. Momose, Y. Nakajima : Yakugaku Zasshi, **82**, 578 (1962).
7) R. L. Whistler, M. L. Wolfrom : "Method in Carbohydrate Chemistry," Vol. Ⅱ, 223, 379 (1963), Academic Press, New York.

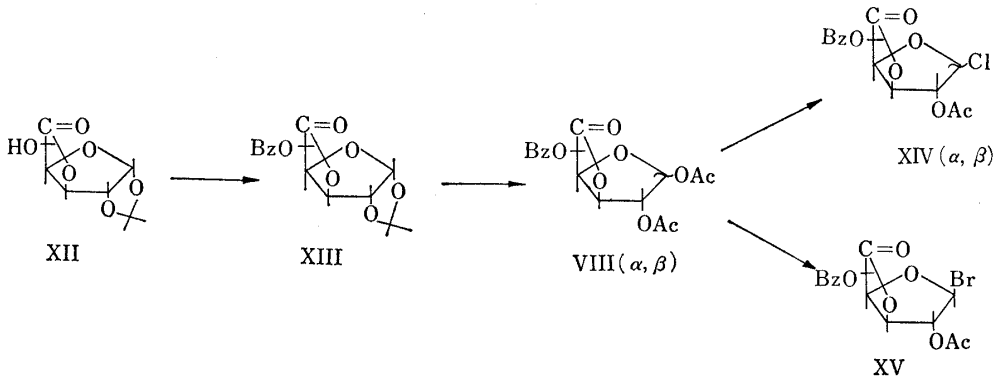


Chart 2.

The benzoylation of 1,2-O-isopropylidene-D-glucuronolactone (XII)[8] gave a 5-O-benzoyl-1,2-O-isopropylidene derivative (XIII) in 80% yield. Treatment of XIII with acetic acid, acetic anhydride and sulfuric acid at a room temperature gave α- and β-anomers of the acetate (VIII), in the yields of 0.7 and 70%, respectively. This β-anomer undepressed the melting point of an admixture with VIII. Treatment of β-anomer of VIII with aluminum chloride in chloroform gave anomeric 1-chloro-1-deoxy-2-O-acetyl-5-O-benzoyl derivatives (XIV), in which the β-anomer in 70% yield and the α-anomer in a few percent yield. The same result was obtained when aluminum chloride was replaced by titanium chloride, and the reaction mixture was boiled for 6~8 hours. Attempts to anomerize the β-anomer by aluminum chloride or titanium tetrachloride were unsuccessful. Treatment of VIII with hydrogen bromide in acetic acid at a room temperature for 1 week gave a 1-bromo-1-deoxy-2-O-acetyl-5-O-benzoyl derivative (XV) in 61% yield. This compound was considered to be in a β-configuration from the fact that it showed $[\alpha]_D^{22}$ +103°, and absorbed at 950 cm^{-1} in infrared spectrum, which was characteristic of β-furanosyl compounds.[6] Moreover, the nuclear magnetic resonance spectra supported our conclusion as shown later.

The anomeric O-substituted halogeno compounds, XI, XIV, and XV are very stable, and can be kept for many weeks in a desiccator without any decomposition.

Nuclear Magnetic Resonance Evidence for Configuration of Glucuronolactone Derivatives

Recently, many conformational studies on carbohydrate derivatives have been made on the basis of nuclear magnetic resonance (NMR) spectra. In the usual carbohydrate derivatives, the anomeric proton (H-1) signal was observed in a lower field and split into a doublet owing to coupling

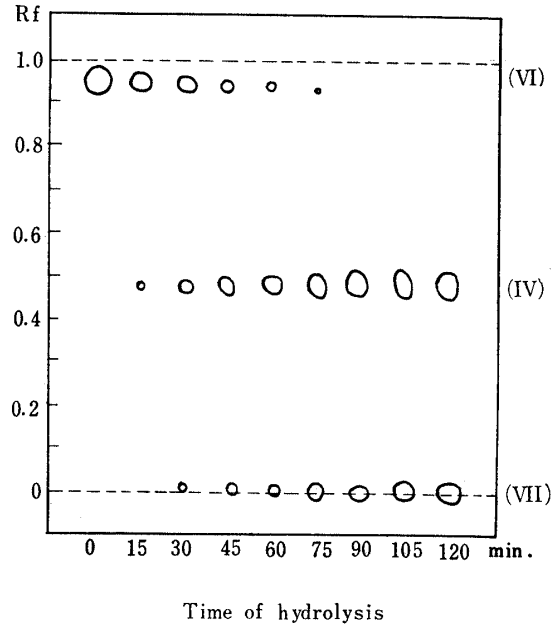
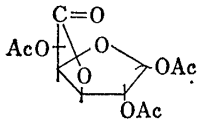
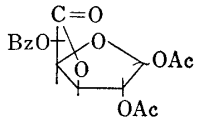
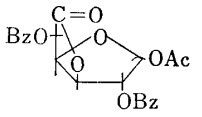
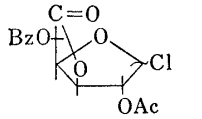
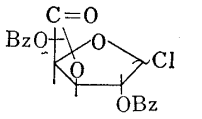
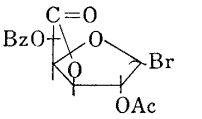
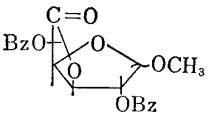


Fig. 1. Thin-layer Chromatogram of the Hydrolyzate of VI

Adsorbent: Silicagel G
Developing solvent: 3% Methanol-benzene
Detection: Ferric hydroxamate reaction

8) R. U. Lemieux, R. K. Kulling, H. J. Bernstein, W. G. Schneider: J. Am. Chem. Soc., 79, 1005 (1957); 80, 6098 (1958).

Table I. Nuclear Magnetic Resonance Spectral Data

Compound	Anomer	Anomeric Proton	
		τ	$J_{1,2}$(c./sec.)
	α	3.51	5.0
	β	3.83	0
	α	3.44	4.4
	β	3.72	0
	α	3.29	5.2
	β	3.62	0
	α	3.45	4.7
	β	3.94	0
	α	3.33	5.2
	β	3.77	0
	β	3.70	0
	α	4.30	5.0
	β	4.49	0

with C_2-hydrogene (H-2).[8~11] The NMR data of the D-glucuronolactone derivatives synthesized are listed in Table I. The typical spectra are also shown in Fig. 1.

In each compound the anomeric proton signal was observed in a lower field, and the signal appeared as a doublet in the α-anomer compounds, and as a singlet in the β-anomer compounds. The anomeric proton signal was reported by Hall[12] and Iwai, *et al.*[13] as a singlet. The spectrum of 1-bromo-1-deoxy derivatives showed singlet signals, and supported the β-configuration.

9) C. D. Jardetzky : J. Am. Chem. Soc., **84**, 62 (1962).
10) N. Mori, S. Omura, O. Yamamoto, T. Suzuki, Y. Tsuzuki : Bull. Chem. Soc. Japan, **36**, 1047 (1963).
11) D. Horton, W. N. Turner : Chem. Comm., **6**, 113 (1965).
12) L. D. Hall : Chem. & Ind., **1963**, 950.
13) T. Hiraoka, T. Iwashige, I. Iwai : This Bulletin, **13**, 285 (1965).

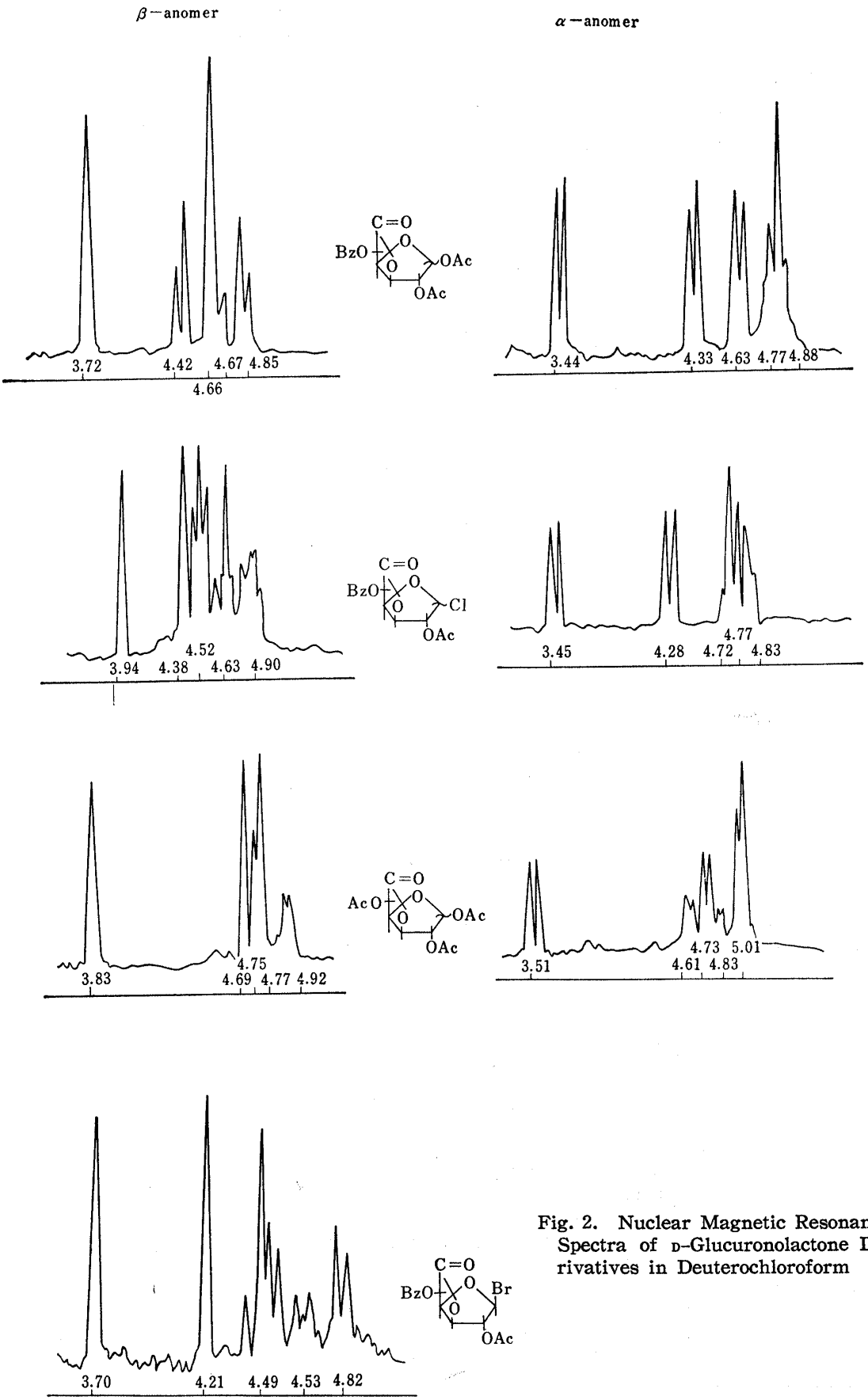


Fig. 2. Nuclear Magnetic Resonance Spectra of D-Glucuronolactone Derivatives in Deuterochloroform

These results of the studies on NMR spectra lend some support to our assignment of infrared spectra of D-glucuronolactone derivatives.[6]

Reaction of β-Anomer of XI with Alcohol

Recrystallization of β-anomer of XI from ethanol afforded an unexpected compound of m.p. 182~184°, which differed from the original compound, m.p. 142~144°. On the other hand, the α-anomer unchanged by the same recrystallization. The new compound had no chlorine atom. From the molecular formula of $C_{22}H_{19}O_8$, the compound was assumed to assign to ethylorthoester (XVI) or ethyl glucoside (XVII) derivatives. Therefore, the following reactions were carried out to confirm the structure of the changed substance.

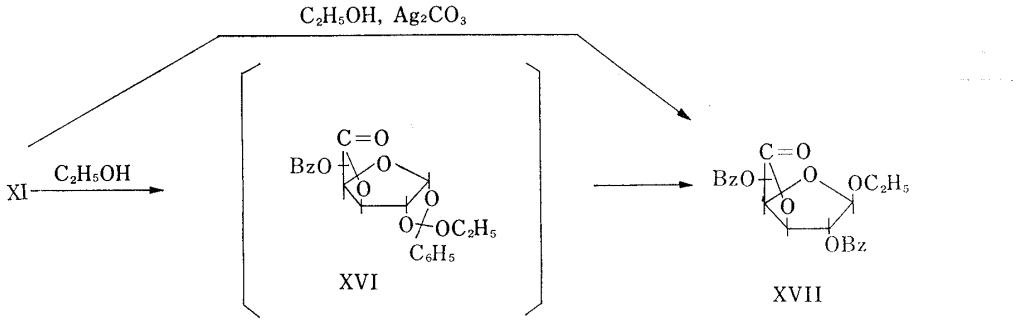


Chart 3.

Treatment of β-anomer of XI with silver carbonate in ethanol yielded ethyl 2,5-di-O-benzoyl derivative (XVII). XVII was also obtained by reaction of I with ethanol in the presence of cation exchange resine and followed by benzoylation. This substance proved to be identical with the above-mentioned changed substance from the comparision of infrared spectra and an undepressed mixed melting point.

Similarly, recrystallization of β-anomer of XI from methanol afforded methyl glucoside derivative (VI), but the α-anomer was unchanged by the same treatment.

Experimental*3

Thin-layer chromatography was carried out by the usual technique employing either Silica Gel G (E. Merk, Germany) or Silicagel B-5 (Wako) as adsorbing materials, using the solvent systems such as benzene-methanol. Detection of spots was carried out by the ferric hydroxamate reaction.

The NMR spectra of the compounds were obtained by Varian HR-100 spectrometer at 100 Mc./sec. The compounds were dissolved in $CDCl_3$ and tetramethylsilan was used as an internal reference.

1-Deoxy-1-*p*-nitroanilino-2,5-di-O-benzoyl-β-O-glucofuranuronolactone (III)——To a solution of 37.0 g. of II in 300 ml. of pyridine was added 60 ml. benzoyl chloride at 5° and the mixture was kept for 16 hr. at a room temperature. The pyridine was removed under reduced pressure, the residue was poured into ice-H_2O, and extracted with $CHCl_3$. The solution was washed with $NaHCO_3$ solution, then with H_2O, dried, and the solvent was removed. The residue was crystallized from MeOH. Recrystallization from MeOH gave 48 g. (75%) of the product, melting at 115~116°, as white needles. *Anal.* Calcd. for $C_{26}H_{20}O_9N_2$: C, 61.90; H, 4.00; N, 5.55. Found : C, 61.54; H, 4.11; N, 5.40. $[\alpha]_D^{22}$ −129.0°(c=1, acetone).

(Methyl 2,5-di-O-benzoyl-β-D-glucofuranosid)urono-γ-lactone (VI)——The benzoylation of V[4] was carried out according to the procedure described above. m.p. 149~150°, yield of 90%. *Anal.* Calcd. for $C_{21}H_{17}O_8$: C, 63.47; H, 4.31. Found : C, 63.77; H, 4.59. $[\alpha]_D^{28}$ +80°(c=2, $CHCl_3$).

1,2,5-Tri-O-benzoyl-α(and β)-D-glucofuranurono-γ-lactone (IX)——Benzoylation of I was worked up in the usual manner. The resulting crystal was recrystallized from MeOH to give β-anomer of IX in 50% yield as colorless needles, m.p. 184~185°. Recrystallization of β-anomer from MeOH raised the m.p. to 185~186°. *Anal.* Calcd. for $C_{27}H_{19}O_9$: C, 66.53; H, 3.93. Found : C, 66.65; H, 4.15. $[\alpha]_D^{23}$ +50.0°(c=1.0, $CHCl_3$). When the mother liquor was concentrated to one-half volume, α-anomer of IX

*3 Melting points are uncorrected.

crystallized as colorless needles, m.p. 145~146°. Recrystallization of α-anomer from EtOH raised the m.p. to 150~151°. *Anal.* Found : C, 66.79; H, 4.24. $[\alpha]_D^{23}$ +100.0°(c=1.0, $CHCl_3$).

2,5-Di-O-benzoyl-β-D-glucofuranurono-γ-lactone (IV)——A) A solution of 5 g. of III in 150 ml. of acetone was added to 100 ml. of 5% HCOOH solution. After refluxing for 5 hr., 100 ml. of acetone was removed under reduced pressure. Yellow crystals were isolated by decantation. Recrystallization from MeOH gave 2 g. (52%) of product, melting at m.p. 189~190°, as colorless needles. *Anal.* Calcd. for $C_{20}H_{15}O_8$: C, 62.66; H, 3.94. Found : C, 62.75; H, 4.16. $[\alpha]_D^{23}$ +26.0° after 20 hr. (c=3.0, acetone).

B) To a solution of 10.0 g. of VI in 120 ml. of AcOH was added 20 ml. of 6*N* HCl solution, and the mixture was heated for 1.5 hr. at 75~80° in a water-bath. The solution showed three spots on thin-layer chromatography in 3% MeOH-benzene : Rf 0.98 (VI), Rf 0.47 (IV), and Rf 0.01 (V). This solution was poured into ice-H_2O and the precipitated product was collected by filtration. Recrystallization from EtOH gave 2.9 g. (30%) of colorless needles, m.p. 189~190°, undepressed on admixture with IV obtained by method A.

1-O-Acetyl-2,5-di-O-benzoyl-α(and β)-D-glucofuranurono-γ-lactone (X)——Two grams of IV was acetylated with Ac_2O (10 ml.) and pyridine (10 ml.) for 2 hr. at a room temperature. The solution was poured into ice-H_2O to give a white crystalline product. Recrystallization from MeOH gave 1.5 g. of colorless needles, m.p. 150~160° which were recrystallized from MeOH to raise the m.p. to 170~171°. *Anal.* Calcd. for $C_{22}H_{17}O_9$: C, 62.11; H, 4.02. Found : C, 62.36; H, 4.16. $[\alpha]_D^{23}$ +93.0°(c=1, $CHCl_3$).

Concentration of the foregoing mother liquor gave 400 mg. of another product, m.p. 123~125° as colorless needles. Recrystallization from EtOH raised the m.p. to 129~130°. *Anal.* Found : C, 62.35; H, 4.37. $[\alpha]_D^{23}$ +3.5°(c=2, $CHCl_3$).

1-Chloro-1-deoxy-2,5-di-O-benzoyl-α(and β)-D-glucofuranurono-γ-lactone (XI)——β-Anomer : One gram of $AlCl_3$ was added to a solution of 5.0 g. of β-anomer of X in 80 ml. of dry $CHCl_3$ and the mixture was shaken at a room temperature for 2 hr. The mixture was then added to 500 ml. of benzene, and the resulting precipitate was removed by filtration. Evaporation of the $CHCl_3$ and benzene under reduced pressure afforded a solid which was crystallized from ether and petr. ether to give 3.5 g. (75%) of colorless needles, m.p. 142~144°. *Anal.* Calcd. for $C_{20}H_{15}O_7Cl$: C, 59.64; H, 3.75. Found : C, 59.51; H, 3.74. $[\alpha]_D^{23}$ +48.0°(c=1.0, $CHCl_3$). α-Anomer : One milliliter of $TiCl_4$ was added to a solution of 1.0 g. of β-anomer (X) in 20 ml. of $CHCl_3$, and the mixture was refluxed for 3 hr. with shaking. The mixture was poured into ice-H_2O, and 20 ml. of $CHCl_3$ was added. The $CHCl_3$ layer was separated, washed successively with cold water, $NaHCO_3$ solution, and cold H_2O, dried, and evaporated under reduced pressure. The residue was crystallized from ether to give 400 mg. of the product. The product was recrystallized from ether and then from EtOH to give 50 mg. (5.8%) of white needles, m.p. 196~198°. *Anal.* Found : C, 59.78; H, 3.84, $[\alpha]_D^{23}$ +135.0°(c=0.46, $CHCl_3$).

The mother liquor of their ether was concentrated to a syrup, which was crystallized from petr. ether. Further recrystallization from ether-petr. ether yielded 150 mg. (33%) of β-anomer, m.p. 142~144°, which was identical with that obtained by the treatment of $AlCl_3$.

1,2-O-Isopropylidene-5-O-benzoyl-D-glucofuranurono-γ-lactone (XIII)——The benzoylation of XII was worked up in the usual manner. The residue (syrup) was crystallized from MeOH. Recrystallization from MeOH gave the desired product, colorless plates, m.p. 89~90°, in 80% yield. *Anal.* Calcd. for $C_{16}H_{16}O_7$: C, 60.00; H, 5.04. Found : C, 59.77; H, 5.06.

5-O-Benzoyl-1,2-di-O-acetyl-α(and β)-D-glucofuranurono-γ-lactone (VIII)——A) A solution of 200 g. of XIII in a mixture of 1 L. of AcOH and 200 ml. of Ac_2O was cooled at 5°, and 280 ml. of H_2SO_4 was added to the solution. After allowing to stand in a room temperature for 16 hr., the solution was poured into ice-H_2O, and the precipitated crystals were collected and washed with H_2O. Recrystallization from EtOH gave colorless needles of β-anomer. 170 g. (70%). m.p. 155~156°. *Anal.* Calcd. for $C_{17}H_{16}O_9$: C, 56.04; H, 4.43. Found : C, 56.17; H, 4.52. $[\alpha]_D^{23}$ +74°(c=2.0, $CHCl_3$).

The mother liquor was evaporated and the residue was crystallized with MeOH. The crystal was recrystallized from benzene for six times, and gave colorless needles of α-anomer 1.7 g. (0.7%). *Anal.* Found : C, 56.21; H, 4.42. $[\alpha]_D^{23}$ +140°(c=2, $CHCl_3$).

B) The mother liquor of IV was concentrated to dryness under reduced pressure. The residue was diluted with benzene and the solution was passed through a column of silica gel. The column was eluted with benzene, 1% MeOH-benzene, 3% MeOH-benzene, and 5% MeOH-benzene, successively. The fraction of 5% MeOH-benzene was concentrated to dryness under reduced pressure. Its purity was checked by thin-layer chromatography on silica gel using 10% MeOH-benzene. The residual syrup was acetylated with Ac_2O and H_2SO_4 for 2 hr. at a room temperature. The solution was poured into ice-H_2O to give a syrup by the usual extraction procedure. Recrystallization from EtOH yielded colorless needles of β-anomer in 5% yield based on IV, m.p. 155~156°, undepressed on admixture with the product obtained in Method A.

1-Chloro-1-deoxy-2-O-acetyl-5-O-benzoyl-α(and β)-D-glucofuranurono-γ-lactone (XIV)——To a solution of 150 g. of β-anomer of VIII in 750 ml. of dry $CHCl_3$ was added 75 g. of $AlCl_3$, the mixture was shaken at room temperature for 3 hr., and the product was isolated in the usual procedure. It was

washed with cold ether and recrystallized from ether and petr. ether to give colorless needles of β-anomer, 105 g. (70%), m.p. 169~171°. *Anal.* Calcd. for $C_{15}H_{13}O_7Cl$: C, 52.87; H, 3.84. Found : C, 52.71; H, 4.12. $[\alpha]_D^{22}$ +129° (c=1.0, $CHCl_3$).

The washed ether solution was evaporated to a syrup which dissolved in a small amount of fresh ether and left in a refrigerator for 1 week. The crystal was recrystallized from ether to give colorless plates of α-anomer, 2.2 g. (1.5%), m.p. 151~153°, $[\alpha]_D^{22}$ +196° (c=1.0, $CHCl_3$). *Anal.* Found : C, 52.80; H, 3.67.

1-Bromo-1-deoxy-2-O-acetyl-5-O-benzoyl-β-D-glucofuranurono-γ-lactone (XV)——A solution of β-anomer of Ⅷ in 30~32% HBr-AcOH was stirred at a room temperature for 1 week. The precipitated crystals were filtered, washed with ice-water, and recrystallized from ether to give colorless plates. 1.2 g. (61%). m.p. 172~173° (decomp.). *Anal.* Calcd. for $C_{15}H_{13}O_7Br$: C, 47.01; H, 3.40. Found : C, 46.97; H, 3.47. $[\alpha]_D^{22}$ +103° (c=1.0, $CHCl_3$).

(Ethyl 2,5-di-O-benzoyl-β-D-glucofuranosid)urono-γ-lactone (XVII)——a) Two grams of Ag_2CO_3 was added to a solution of 2.5 g. of Ⅺ in 100 ml. of dry EtOH and the mixture was shaken at a room temperature for 24 hr. The solid was filtered and the filtrate was evaporated under reduced pressure. The residue was dissolved in EtOH and the solution was chilled in a refrigerator. The crystalline was recrystallized from EtOH to give 1.3 g. of colorless needles, m.p. 182~184°, $[\alpha]_D^{22}$ +10° (c=1.0, $CHCl_3$). *Anal.* Calcd. for $C_{22}H_{19}O_8$: C, 64.07; H, 4.89. Found: C, 64.21; H, 4.91.

b) β-Anomer of Ⅺ (2.0 g.) was recrystallized from EtOH to give colorless needles, m.p. 167~170°. More recrystallization from EtOH raised the m.p. to 182~184°, undepressed on admixture with the product obtained by method (a).

c) A mixture of D-glucuronolactone (15 g.) and Amberlite IR-120 (H) (15 g.) in 250 ml. of EtOH was refluxed for 10 hr. The mixture was filtered and the filtrate was evaporated under reduced pressure to give a sirup. This sirup was treated with 100 ml. of C_5H_5N and 25 ml. of C_6H_5COCl at a room temperature for 12 hr. The pyridine was removed and the residue was poured into ice-water, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with $NaHCO_3$ solution and then with H_2O followed by dryness. The solvent was removed. The residue was crystallized from EtOH. Recrystallization from EtOH gave 15 g. of colorless needles, m.p. 182~184°; on admixture with an authentic sample obtained by method (a), the product melted at 183~184°.

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Summary

Treatment of 1-O-acetyl-2,5-di-O-benzoyl- and 5-O-benzoyl-1,2-di-O-acetyl-β-D-glucuronolactones with aluminum chloride or titanium tetrachloride afforded the corresponding anomeric 1-chloro-1-deoxy derivatives, respectively. 1-Bromo-1-deoxy-2-O-acetyl-5-O-benzoyl derivative was obtained from reaction of 1-O-acetyl-2,5-di-O-benzoyl-β-D-glucuronolactone with hydrogen bromide. These compounds are very stable.

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