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37. Shoji Takitani*1 : Structure of the Condensation Product of Arylamine and Glucofuranuronolactone.

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In the previous papers,[1,2] it was reported that aromatic and aliphatic primary amines easily combine with glucuronic acid or glucuronate to give the amine N-glucuronide of glucopyranoside form, viz. 1-amino-1-deoxyglucopyranuronate.

In this paper, the reaction products of glucofuranurono-γ-lactone (glucurono-γ-lactone) (Ia) with arylamine and their structural investigation are described.

Glucurono-γ-lactone seemed to combine with arylamines more readily than glucuronic acid or sodium glucuronate in a medium of hydrous methanol, acetone, or ether, and the products were easily isolated in higher yield. The crystalline products were thus prepared from aniline, *p*-nitroaniline, *p*-aminoazobenzene, and sulfanilamide.

However, a considerable unstability of the products was observed when compared with the corresponding 1-amino derivative of 1-deoxyglucopyranuronate. The aniline derivative colored redily in the air and the product from stronger basic amine such as *p*-toluidine or anisidine was not isolated.

A chromatographic separation of the condensation products was carried out in a neutral solvent of propanol-butanol-water (2:1:1), when they indicated Rf value of ca. 0.8, while in an acid solvent they immediately decomposed into the two constituents.

Presence of a lactone ring in the molecule of the products was evident from hydroxylamine-ferric chloride reagent on the paper chromatogram.

Kawada[3] observed an interesting fact in his polarographic studies on a series of glucuronic acid that, unlike glucuronate or glucose, glucurono-γ-lactone in an aqueous or a polar solvent seemed to exist predominantly in a state of open-chain form (Ib), holding a lactone ring in it. Taking this into account, two kinds of products are expected in the condensation of glucurono-γ-lactone with arylamine; either 1-arylamino-1-deoxyglucofuranurono-γ-lactone (IIa) or a Schiff base-type (IIb).

In order to verify the alternative structures for the product, the following experiment was carried out. A product from *p*-nitroaniline, as an example, was first acetylated with acetic anhydride in pyridine to give a diacetyl derivative, whose analytical data corresponded to (IIIa). The acetylated derivative was then hydrolysed with 0.5% formic acid solution and the solution was extracted with chloroform after removing *p*-nitroaniline. The substance obtaind by evaporation of chloroform was purified from methanol to needle crystals, and this product was found to be identical in all respects (melting point, optical rotation, and infrared spectrum) with 2,5-di-O-acetylglucofuranurono-γ-lactone (IVa). The compound (IVa) was prepared for comparison from glucofuranurono-γ-lactone through the route (V) and (VI) according to the known method by Korytnyk[4] and Goebel.[5]

Further acetylation of (IVa) with acetic anhydride and boron trifluoride gave a tri-O-acetylated product, which was found to be identical with 1,2,5-tri-O-acetylglucofuranurono-γ-lactone (V) obtained by direct acetylation of glucofuranurono-γ-lactone (Ia) by the same procedure.

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1) M. Ishidate, S. Takitani, T. Kishi : This Bulletin, **7**, 291 (1959).
2) S. Takitani : *Ibid.*, **7**, 845 (1959).
3) A. Kawada : Private communication.
4) W. Korytnyk : J. Chem. Soc., **1959**, 636.
5) W. K. Goebel : J. Biol. Chem., **101**, 173 (1933).

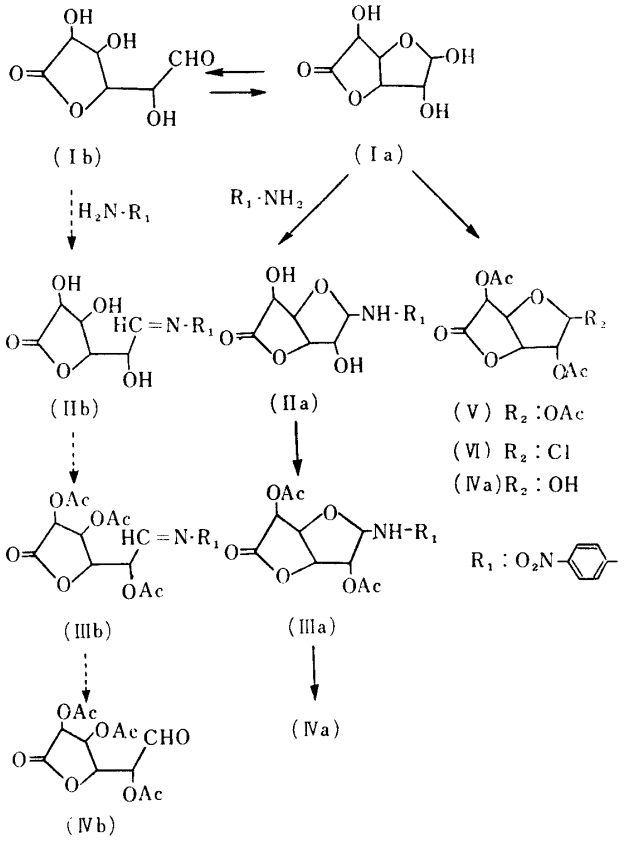

Chart 1.

It has consequently been proved that the condensation product of glucurono-γ-lactone and *p*-nitroaniline has the structure of 1-arylamino-1-deoxyglucofuranurono-γ-lactone (IIa). The same conclusion might apply to all arylamine homologs in general.

When the compound (IIa) in acetone solution was carefully treated with an equimolar amount of sodium hydroxide under cooling and followed by addition of ether, yellowish hygroscopic crystals of m.p. 170~180°(decomp.) were obtained after recrystallization from hydrous methanol. This product showed Rf 0.46 on paper chromatogram developed with propanol-butanol-water(2:1:1), which differed from that of sodium 1-*p*-nitroanilino-1-deoxyglucopyranuronate (VIII)(m.p. 240°, Rf 0.31). Moreover, this new product differed from (VIII) not only in the character of optical rotation (Fig. 1) but also in its higher unstability to acidic medium. From these facts, it might be concluded that the unstable product is sodium 1-*p*-nitroanilino-1-deoxyglucofuranuronate (VII).

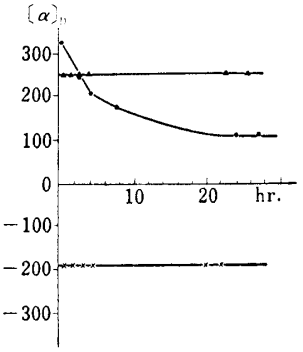

Fig. 1. Optical Rotation

—×— Na 1-*p*-nitroanilino-1-deoxyglucopyranuronate

—•— Reaction product obtained from 1-*p*-nitroanilino-1-deoxyglucofuranurono-γ-lactone and NaOH

—▲— 1-*p*-Nitroanilino-1-deoxyglucofuranurono-γ-lactone

On the other hand, treatment of the compound (IIa) with ammonia-saturated methanol for 48 hours at 0° afforded, after recrystallization from methanol-ether, yellow prismatic crystals which were unexpectedly identified with 1-*p*-nitroanilino-1-deoxyglucopyranuronamide (XI) in every respect. The latter compound was directly synthesized from glucopyranuronamide and *p*-nitroaniline for comparison. The ring transformation of the amide from furanoside to pyranoside form is only explainable by the formation of intermediates (IX) and (X), as illustrated in Chart 2.

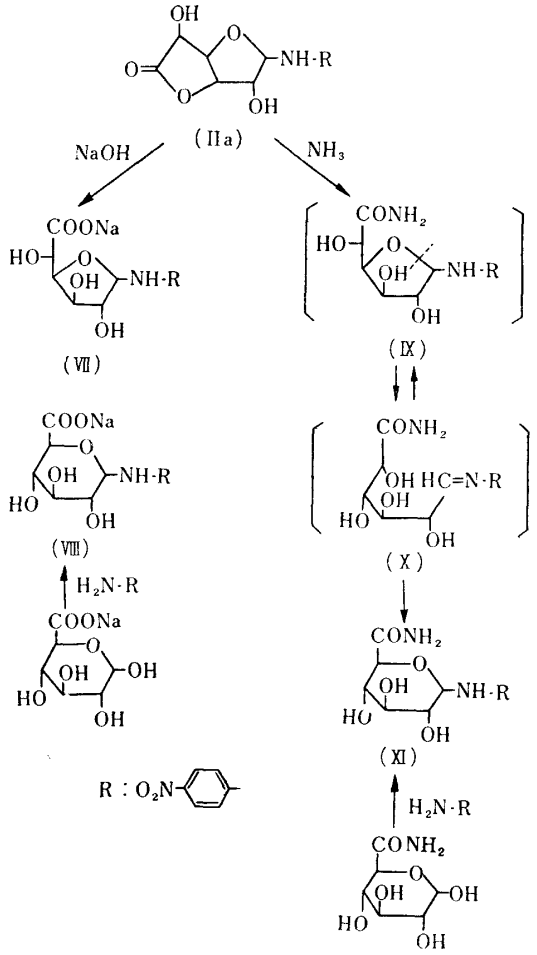

Chart 2.

Experimental

1-Anilino-1-deoxyglucofuranurono-γ-lactone—A mixture of a solution of aniline (3 g.) in Et_2O (15 cc.) and aqueous solution (10 cc.) of glucofuranuronolactone (2 g.) was left for 2 hr. The separated crystalline product was washed with Et_2O and recystallization from MeOH gave fine needles, m.p. 75~80°(decomp.); yield, 1.6 g. *Anal.* Calcd. for $C_{12}H_{13}O_5N$: C, 57.37, H, 5.22; N, 5.58. Found : C, 57.18; H, 5.83; N, 5.34.

1-Sulfanilamido-1-deoxyglucofuranurono-γ-lactone—A mixture of a solution of sulfanilamide (25 g.) in Me_2CO (250 cc.) and aqueous solution (20 cc.) of glucofuranuronolactone (20 g.) was left at room temperature (or heated for 0.5~1 hr.). By concentration of the solution *in vacuo* and addition of EtOH under cooling, a crystalline product separated, which was further washed with cold EtOH and Et_2O. Yield, 35 g. Recrystallization from EtOH-MeOH gave needles, m.p. 96~100°(decomp.). $[\alpha]_D^{10}$ +133.3° → +86.7°(c=3.0, MeOH). *Anal.* Calcd. for $C_{12}H_{14}O_7N_2S$: C, 43.63; H, 4.27; N, 8.48. Found : C, 43.44; H, 4.55; N, 7.91.

1-*p*-Nitroanilino-1-deoxyglucofuranurono-γ-lactone (IIa)—A mixture of a solution of *p*-nitroaniline (10 g.) in MeOH (50 cc.) and Me_2CO (40 cc.) and aqueous solution (20 cc.) of glucofuranurono-

lactone (10 g.) was refluxed for 3 hr. on a water bath and left at room temperature. The separated crystalline product gave yellow needles from MeOH-Me_2CO (8.5 g.), m.p. 128~130° (decomp.), $[\alpha]_D^{14}$ +255.4° (c=0.83, Me_2CO). *Anal.* Calcd. for $C_{12}H_{12}O_7N_2 \cdot H_2O$: C, 46.02; H, 4.47; N, 8.92; H_2O, 5.73. Found : C, 46.27; H, 4.47; N, 9.11; H_2O (Karl-Fischer) 5.78.

Sodium 1-*p*-Nitroanilino-1-deoxyglucopyranuronate (VIII)—A mixture of a solution of *p*-nitroaniline (10 g.) in dimethylformamide (10 cc.) and MeOH (20 cc.), and Na glucuronate (3 g.) in ethylene glycol (30 cc.) and HCl (0.2 cc.) was refluxed for 2 hr. on a water bath and left at room temperature. The separated crystalline product was washed with MeOH and Me_2CO. Yield, 3.3 g. Recrystallization from 30% MeOH gave yellow needles, m.p. 235~240° (decomp.). $[\alpha]_D^{14}$ −198.4° (c=1.25, H_2O). *Anal.* Calcd. for $C_{12}H_{13}O_8N_2Na$: C, 42.88; H, 3.90; N, 8.32. Found : C, 42.77; H, 3.76; N, 8.03.

1-(4-Phenylazoanilino)-1-deoxyglucofuranurono-γ-lactone—A mixture of a solution of *p*-aminoazobenzene (0.8 g.) in Me_2CO (10 cc.) and glucofuranuronolactone (0.5 g.) in H_2O (10 cc.) was refluxed for 1 hr. on a water bath, Me_2CO was distilled off *in vacuo*, and benzene added. The separated crystalline product was washed with Et_2O and recrystallization from MeOH-Me_2CO gave yellow crystals, m.p. 124~127° (decomp.). *Anal.* Calcd. for $C_{18}H_{17}O_5N_3$: C, 60.84; H, 4.82; N, 11.82. Found : C, 60.98; H, 4.62; N, 12.27.

1-Sulfanilamido-1-deoxy-2,5-di-O-acetylglucofuranurono-γ-lactone—To a solution of Ac_2O (4 cc.) and pyridine (7 cc.), 1.4 g. of 1-sulfanilamido-1-deoxyglucofuranurono-γ-lactone was added gradually at 0°, the mixture was left at 0° for 2 hr., and poured into 100 cc. of cold water. The precipitate was recrystallized from MeOH to 1.4 g. of needles, m.p. 192~195° (decomp.), $[\alpha]_D^{10}$ −26.6° (c=3.0, Me_2CO). *Anal.* Calcd. for $C_{16}H_{18}O_9N_2S$: C, 46.38; H, 4.38; N, 6.76. Found : C, 46.29; H, 4.36; N, 6.60.

1-*p*-Nitroanilino-1-deoxy-2,5-di-O-acetylglucofuranurono-γ-lactone (IIIa)—To a solution of Ac_2O (18 cc.) and pyridine (23 cc.), 4.6 g. of (II a) was added at 0°, the mixture was left at 0° for 2 hr., and poured into 300 cc. of cold water. The precipitate was recrystallized from EtOH to 2.5 g. of colorless needles, m.p. 142~145°, $[\alpha]_D^{18}$ −68.5° (c=2.0, Me_2CO). *Anal.* Calcd. for $C_{16}H_{16}O_9N_2$: C, 50.54; H, 4.24; N, 7.36. Found : C, 50.65; H, 3.90; N, 7.31.

2,5-Di-O-acetylglucofuranurono-γ-lactone (IVa)—To a solution of Me_2CO (10 cc.) and 0.5% formic acid solution (40 cc.), 0.9 g. of (III a) was added, the mixture was refluxed for 3 hr., and concentrated to 25 cc. After cool, separated *p*-nitroaniline was filtered off, the filtrate was added with 1.5 cc. of 5% formic acid, and extracted eight times with $CHCl_3$. The $CHCl_3$ fraction was dried over Na_2SO_4 and distilled *in vacuo*. The resulting brown substance was recrystallized from EtOH. A small amount of the same compound was obtained from aqueous layer. Total yield, 0.3 g. of needles, m.p. 129~132°, $[\alpha]_D^{18}$ +124° → +60° (c=1.0, MeOH). It showed no m.p. depression on admixture with 2,5-di-O-acetylglucofuranurono-γ-lactone, obtained by the usual method from glucofuranurono-γ-lactone, and optical rotation and IR spectrum of the two substance were identical. *Anal.* Calcd. for $C_{10}H_{12}O_8$: C, 46.15; H, 4.64. Found : C, 46.37; H, 4.44.

1,2,5-Tri-O-acetylglucofuranurono-γ-lactone (V)—To a solution of Ac_2O (1.0 cc.) and 47% Et_2O solution of BF_3 (0.1 cc.), 0.5 g. of (IV a) was added, the mixture was stirred at room temperature for 2 hr., and poured into 10 cc. of ice water. The precipitate was recrystallized from EtOH-AcOH (4:1) to 0.3 g. of long needles, m.p. 190°, $[\alpha]_D^{18}$ +97.5° (c=2.0, $CHCl_3$). It showed no m.p. depression on admixture with 1,2,5-tri-O-acetylglucofuranurono-γ-lactone, obtained by the same method from glucofuranurono-γ-lactone and optical rotation of the two substances was identical. *Anal.* Calcd. for $C_{12}H_{14}O_9$: C, 47.68; H, 4.64. Found : C, 47.67; H, 4.75.

Opening of the Lactone Ring in 1-*p*-Nitroanilino-1-deoxyglucofuranurono-γ-lactone (IIa) by Treatment with NaOH or NH_3—i) With NaOH : The aqueous solution (5 cc.) of NaOH (0.135 g.) was added to Me_2CO solution (60 cc.) of (II a) (1 g.) with stirring at 0°. Et_2O was added to the resulting solution and the mixture was left to stand overnight in an ice box. The precipitate was recrystallized from hydr. MeOH, m.p. 170~180° (decomp.), $[\alpha]_D^{14}$ +324.6° → +111.4° (c=1.14, H_2O). *Anal.* Calcd. for $C_{12}H_{13}O_8N_2Na$: N, 8.32. Found : N, 7.90.

ii) With NH_3 : To MeOH solution (250 cc.) saturated with NH_3, 2 g. of (II a) was added and the solution was left at 0° for 2 days. After distilling off MeOH *in vacuo*, the yellow residue was washed with Et_2O and recystallized from hydr. MeOH-Et_2O to yellow prismatic crystals, m.p. 181° (decomp.), $[\alpha]_D^{14}$ −191° (c=0.33, MeOH). Yield, 1.8 g. There was no m.p. depression on admixture with 1-*p*-nitroanilino-1-deoxyglucopyranuronamide obtained from *p*-nitroaniline and glucopyranuronamide, and IR spectrum and optical rotation of the two substances were identical. *Anal.* Calcd. for $C_{12}H_{15}O_7N_3$: C, 46.01; H, 4.83; N, 13.42. Found : C, 45.97; H, 4.63; N, 13.53.

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Summary

The condensation products of arylamine (aniline, *p*-nitroaniline, *p*-aminoazobenzene, and sulfanilamide) with glucofuranurono-γ-lactone were prepared. It was established that the condensation product should have a structure of 1-arylamino-1-deoxyglucofuranurono-γ-lactone (IIa). It was found that the opening of the lactone ring in (IIa) by treatment with sodium hydroxide afforded 1-arylamino-1-deoxyglucofuranuronate, while it gave 1-arylamino-1-deoxyglucopyranuronamide with ammonia-saturated methanol.

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38. Seitaro Saeki: Quaternization of the Ring Nitrogen of Hexahydrojulolidine and its Related Compounds. II.[1] Quaternization of the Ring Nitrogen of Stereoisomers of Perhydro-1*H*,5*H*-naphtho[1,2,3-*i*,*j*]quinolizine.

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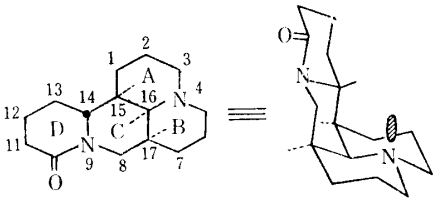
Tsuda and Mishima[2] reported that matrine (I) reacted neither with cyanogen bromide nor with methyl iodide on refluxing in ether because the ring junctures of A/C and B/C in matrine were all *cis*, and that allomatrine (II), in which the concerned junctures were all *trans*, reacted with these reagents to afford its bromocyanamide and methiodide, respectively.

Furthermore, it was found by Tsuda and Saeki[1] that *cis-cis*-hexahydrojulolidine (III) did not react with methyl iodide when refluxed in ether, but that the *trans-trans*-isomer (IV) reacted easily under the same condition to give the methiodide.



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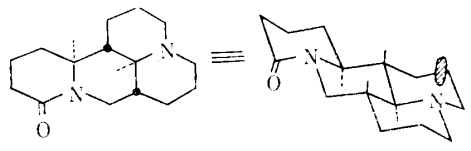

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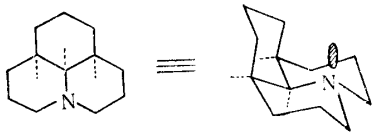

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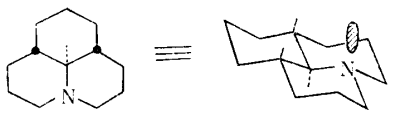

(IV)

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