335. Morizo Ishidate* and Masashi Okada**: An Improved Preparation of Glucuronic Acid from Glucose.

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Glucuronic acid was obtained synthetically from glucose by Zervas, et al.¹⁾, by the oxidation and the subsequent hydrolysis of monoacetone-benzylidene-glucose. The yield, however, was found unsatisfactory, because the intermediate products, monoacetone-glucose and monoacetone-benzylidene-glucose, are freely soluble in water, so that they are hardly capable of being isolated in a pure state. Though Akiya and Watanabe²⁾ later endeavoured to improve the preparation by purifying the products through 6-acetyl-monoacetone-benzylidene-glucose, the yields have not been much improved.

Recently, Hockett, et al.³⁾, reported the preparation of 1,2-monocyclohexylidene-glucofuranose, which in contrast to acetone-glucose is only slightly soluble in water and easily obtainable in pure crystalline condition.

We have now found that, by using 1,2-cyclohexylidene-glucofuranose (I) as the starting material, instead of monoacetone-glucose, the preparation of pure glucuronic acid was improved.

By the condensation of 1,2-monocyclohexylidene-glucofuranose (I) with benzaldehyde in the presence of anhydrous zinc chloride, 1,2-monocyclohexylidene-3,5-benzylidene-glucose (II) was formed, which was easily isolated as ether soluble crystals in pure state. By a subsequent oxidation with permanganate, 1,2-monocyclohexylidene-3,5-benzylidene-glucuronic acid (IV) was obtained in a good yield, and the following catalytic reduction or acid hydrolysis gave 1,2-monocyclohexylidene glucuron (V) or glucuron (VI), respectively.

From these facts the structure and the location of semiacetal ring in (II) should be beyond question. On the condensation of (I) with boric acid and the subsequent benzylation, 1,2-cyclohexylidene-glucofuranosemonoboric ester (III) and its benzoate were respectively formed. By hydrolysis of this compound, 1,2-cyclohexylidene-6-benzoylglucose was formed, which coincided with the product obtained from 1,2-cyclohexylidene-3,5-benzylidene-6-benzoyl-glucose.

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1) L. Zervas, P. Sessler: Ber., **66**, 1326 (1933).

2) S. Akiya, T. Watanabe: This Journal, **67**, 99 (1947).

3) R.C. Hockett, et al.: J. Am. Chem. Soc., **71**, 3072 (1949).

Experimental

1,2-Cyclohexylidene-D-glucufuranose (I) and its acid hydrolysis—This material was prepared from 1, 2, 5, 6-cyclohexylidene-D-glucufuranose, according to Hockett, et al.³⁾, which after recrystallisation melted at 152.5° (cor.). For reference to preparation of glucuron from the compound (III) or (IV) the optimal condition of hydrolysis of 1,2-cyclohexylidene-D-glucose in D-glucose was examined. A certain amount of the compound (I) was heated in 0.2N, 0.1N and 0.05N ethanolic hydrochloric acid solution at 100° for various duration of time, and the liberated glucose was measured after Bertrand's methode. The hydrolysis was found to be completed when it was heated at 100° for one hour in 0.05N hydrochloric solution.

1, 2-Cyclohexylidene-D-glucufuranose-3, 5-monoboric acid ester (III)—1, 2-Cyclohexylidene-D-glucufuranose (1.6 g.) was dissolved in acetone (15 cc.) and boric acid (0.4 g.), and then conc. sulfuric acid (0.6 cc., $d=1.84$) added. The reaction mixture was shaken at room temperature for 3 hours, and anhydrous sodium carbonate then added to neutralisation. After filtration, the solution was concentrated at a reduced pressure to a yellow syrup. The syrup was shaken up in hot ethyl acetate, petroleum then added, and allowed to cool. Prismatic crystals separated which melted at 145–148° (cor.) after recrystallization from ethyl acetate and petroleum. *Anal.* Calcd. for $C_{10}H_{20}O_5B$: C, 47.39; H, 6.91. Found: C, 46.47%; H, 6.76. This coincides better with the formula (III) of tetravalence form of boron-atom according to Vargha.⁴⁾ When this compound was dissolved in methanol and the methanol evaporated on a water bath, 1, 2-cyclohexylidene-D-glucose was obtained.

1, 2-Cyclohexylidene-6-benzoyl-D-glucose — 1, 2-Cyclohexylidene-D-glucose-3, 5-monoboric acid ester (0.3 g.) was treated with benzoyl chloride (0.45 g.) in anhydrous pyridine (2 cc.) The reaction product was recrystallized from ethanol to m.p. of 182° (cor.). This was identical with 1, 2-cyclohexylidene-6-benzoyl-D-glucose prepared by partial hydrolysis of 1, 2-cyclohexylidene-3, 5-benzylidene-6-benzoyl-D-glucose. *Anal.* Calcd. for $C_{19}H_{24}O_7$: C, 62.64; H, 6.59. Found: C, 62.23; H, 6.68.

1, 2-Cyclohexylidene-3, 5-benzylidene-D-glucose (II)—The dried powder of 1, 2-cyclohexylidene-D-glucose (6 g.) was shaken with pure benzaldehyde (25 cc.) and anhydrous zinc chloride (8 g.) for 20 hours. The product was mixed with water and distilled to remove benzaldehyde, and the residual suspension extracted with ether. The substance isolated from the ether extract was recrystallized from ethanol as fine needles (3.5 g.), m.p. 140–141° (cor.), $[\alpha]_D^{27}+31.0$ (c=2, in ethanol). *Anal.* Calcd. for $C_{19}H_{24}O_6$: C, 65.52; H, 6.90. Found: C, 65.71; H, 6.90.

1, 2-Cyclohexylidene-3, 5-benzylidene-6-benzoyl-D-glucose—The benzoyl derivative was prepared in the usual way and was recrystallized from ethanol, giving m.p. 139–140° (cor.). *Anal.* Calcd. for $C_{26}H_{32}O_7$: C, 69.03; H, 6.19. Found: C, 68.84; H, 6.35.

1, 2-Cyclohexylidene-6-benzoyl-D-glucose — 1, 2-Cyclohexylidene-3, 5-benzylidene-6-benzoyl-D-glucose (0.3 g.) was dissolved in 0.1N ethanolic hydrochloric acid solution, and the mixture kept for one hour at 40–50°. The product was recrystallized from ethanol, giving needles, m.p. 182° (cor.). The same substance was also obtained by the catalytic reduction with palladium-charcoal and hydrogen.

1, 2-Cyclohexylidene-3, 5-benzylidene-D-glucuronic acid (IV)—The ground powder of 1, 2-Cyclohexylidene-3, 5-benzylidene-D-glucose (2 g.) was suspended in 0.2N sodium hydroxide solution (30 cc.) and stirred vigorously with powdered potassium permanganate (1.4 g.) for 5 hours, whereupon manganese dioxide was removed by filtration and washed with hot water. The filtrate gathered was acidified with hydrochloric acid to Congo red. The separated substances were purified by precipitation from the bicarbonate solution with hydrochloric acid, m.p. 174–175° (cor.). The yield, 88%. *Anal.* Calcd. for $C_{19}H_{22}O_7$: C, 62.98; H, 6.08. Found: C, 62.80; H, 5.73. $[\alpha]_D^{27}+40^\circ$. (c=2, in ethanol).

D-Glucuron (VI)—The acid (IV) (1 g.) was sealed in a glass tube with a mixture of ethanol (5 cc.) and 0.2N hydrochloric acid solution (5 cc.) and heated for 1 hour at 100°. The solution was evaporated in vacuo at 40° to leave a syrup which, after drying in a desiccator, was dissolved in dioxane, allowed to cool, whereupon the acid slowly crystallized. It was recrystallized from dioxane, having m.p. 175–177° (decomp.). $[\alpha]_D^{27}+19.5^\circ$ (c=2 in water). The semicarbozone, prepared in the usual way, crystallized from water in fine needles, m.p. 188–189° (decomp.), identical with an authentic specimen. *Anal.* Calcd. for $C_7H_{11}O_6N_3$: C, 36.05; H, 4.72; N, 18.03. Found: C, 36.12; H, 5.01; N, 17.73.

* The shortage of carbon was found due to the formation of boroncarbide.

4) L.v. Vargha: Ber., 66, 704 (1933).

1,2-Cyclohexylidene-glucuron (V)—(i) The acid (IV) (1 g.) was hydrogenated in the presence of palladium-charcoal for 5 hours in ethanol solution, and then the filtrate condensed to a syrup. To remove benzaldehyde, it was distilled with water under reduced pressure, whereupon the residue crystallized. It was recrystallized from water to m.p. 147–148° (uncor.) It is insoluble in bicarbonate, but soluble in alkali hydroxide with yellow coloration. *Anal.* Calcd. for $C_{12}H_{16}O_6$: C, 56.25; H, 6.25. Found: C, 56.04; H, 6.41.

(ii) The acid (IV) (1 g.) was hydrolysed by heating at 60–70° for 2 hours in 0.1*N* ethanolic hydrochloric acid solution. The product was purified in the similar way as above, the obtained crystals giving m.p. 147° from water, identical with 1,2-cyclohexylideneglucuron.

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