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Synthesis of 5-Chloro-7-iodo-8-quinolinol (Chinoform) Glucuronide

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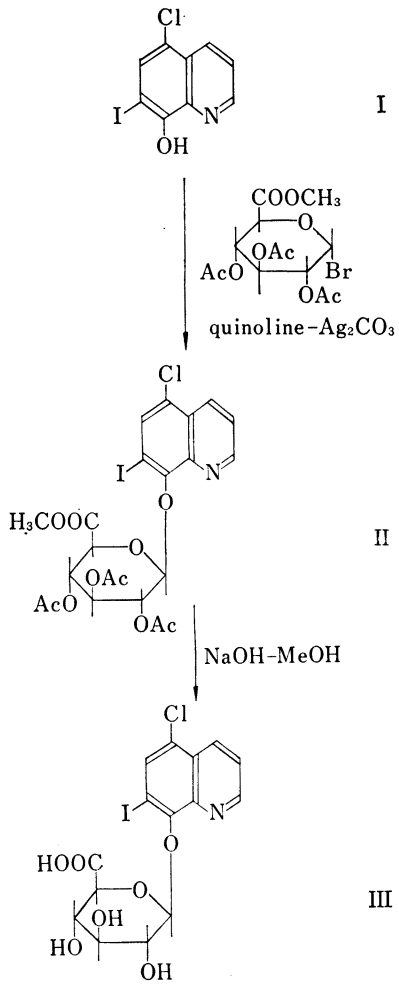

Chart 1

Recently, Chinoform (5-chloro-7-iodo-8-quinolinol, (I)) and its ferric chelate (green pigment) were isolated from the urine and feces of a SMON (subacute myelo-optico-neuro-pathy) patient,[2] and many investigators are studying the relationship between this disease and I. For the purpose of etsablishing the determination of I and its conjugates (glucuronide and sulfate), we projected the synthesis of its glucuronide as an authentic sample.

Haskins, *et al.*[3] fed I to rabbits, and isolated from the urine crude Chinoform glucuronide, but this compound have not been isolated as pure crystals.

The present paper deals with the synthesis of Chinoform glucuronide, 5-chloro-7-iodo-8-quinolyl-β-D-glucopyranosiduronic acid (III). Condensation of glucuronic acid component with I was accomplished by Koenigs-Knorr reaction. When I and methyl 1-bromo-1-deoxy-2,3,4-tri-O-acetyl-α-D-glucopyranosiduronate were stirred in quinoline with freshly prepared silver carbonate, methyl (5-chloro-7-iodo-8-quinolyl-2′,3′,4′-tri-O-acetyl-β-D-glucopyranosid)-uronate (II) was afforded in 40% yield. Removal of the protecting groups in glucuronic acid moiety of II was accomplished by saponification and deacetylation in methanol with aqueous 1 N NaOH at room temperature. Purification of III from sodium ion was achieved by passing through the column of Amberlite CG-120 (H^+) and elution with pyridine–water (1:9). Thus, III was obtained as colorless needles. The infrared (IR) and ultraviolet (UV) spectra of II and III are shown in Fig. 1 and 2.

The evidence of β-glucuronide linkage in III was demonstrated by characterizing I and D-glucuronic acid (respectively 104.8% and 98.5%) by means of gas chromatography after incubation with beef-liver β-glucuronidase.

1) Location: *Hongo 7-3-1, Bunkyo-ku, Tokyo.*
2) M. Yoshioka and Z. Tamura, *Igaku No Ayumi*, **74**, 320 (1970).
3) W.T. Haskins and G.W. Luttermoser, *J. Pharmacol. Exptl. Therap.*, **109**, 201 (1953).

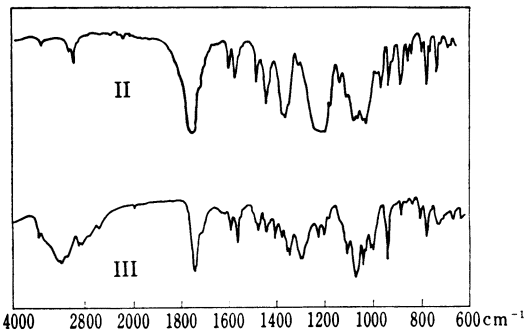

Fig. 1. IR Spectra of II and III (KBr Tab.)

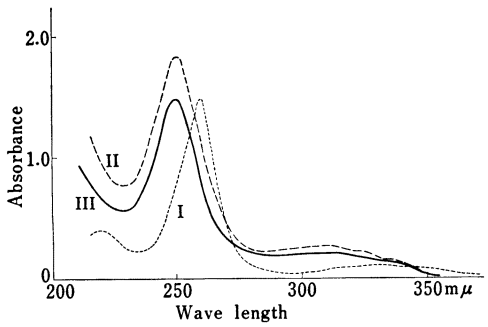

Fig. 2. UV Spectra of I, II and III

I: 3.24×10^{-5}M in dioxane
II: 5.63×10^{-5}M in dioxane
III: 4.57×10^{-5}M in MeOH

Experimental[4]

Methyl (5-Chloro-7-iodo-8-quinolyl-2′,3′,4′-tri-O-acetyl-β-D-glucopyranosid) uronate (II)——A mixture of I (2.8 g, 9 mmole), methyl 1-bromo-1-deoxy-2,3,4-tri-O-acetyl-α-D-glucopyranosiduronate (3.6 g, 9 mmole), $CaSO_4\cdot1/2\ H_2O$ (2 g) and quinoline (50 ml) was stirred at room temperature for 20 min. Freshly prepared Ag_2CO_3 (2 g) was added to the reaction mixture and the suspended solution was stirred at room temperature for 24 hr in the dark. The reaction mixture was diluted with $CHCl_3$ (300 ml), filtered, subsequently washed with aq. 3N HCl (200 ml×2), aq. 1N NaOH (300 ml×2) and finally with H_2O (200 ml×2) and dried over anhyd. Na_2SO_4. After evaporation of the solvent, the crude product obtained was recrystallized from EtOH to give II (2.3 g, 40%) as colorless needles. mp 213—214°, $[\alpha]_D^{28}-5.0°$ ($c=0.35$, dioxane), UV $\lambda_{max}^{dioxane}$ mμ (ε): 250 (32300), 305 (4260). *Anal.* Calcd. for $C_{22}H_{21}O_{10}NClI$: C, 42.50; H, 3.40; N, 2.25. Found: C, 42.34; H, 3.28; N, 2.27.

5-Chloro-7-iodo-8-quinolyl-β-D-glucopyranosiduronic Acid (III)——II (1 g) was suspended in MeOH (10 ml). Aq. 1N NaOH (10 ml) was added to the solution under cooling with ice–H_2O. After 30 min at room temperature, the reaction mixture was passed through a column of Amberlite CG-120 (H^+), washed with H_2O and eluted with pyridine–H_2O (1:9) from the column. After evaporation, the crystals liberated were washed with benzene and the residue was recrystallized from EtOH to give III (692 mg, 89.6%) as colorless needles. mp 176—177° (decomp.), $[\alpha]_D^{21}-11.4°$ ($c=0.22$, MeOH), UV λ_{max}^{MeOH} mμ (ε): 250 (31900), 305 (4470). *Anal.* Calcd. for $C_{15}H_{13}O_7NClI$: C, 37.41; H, 2.72; N, 2.91. Found: C, 37.50; H, 2.73; N, 2.94.

Hydrolysis of III with β-Glucuronidase——After III (10 mg) was dissolved in 0.4 M acetate buffer (pH 4.5, 10 ml), beef-liver β-glucuronidase (Tokyo Zōki, Co., Ltd.) (13000 Fishman Unit/ml, 0.5 ml) was added and the mixture was incubated at 37° for 20 hr. The incubated fluid was extracted with benzene (50 ml×2). The organic layer was dried and concentrated *in vacuo*. Recrystallization of the residue from EtOH yielded 6.3 mg of I, yield 100%. mp 175—175.5° (decomp.). Completion of the hydrolysis was also confirmed by gas chromatography. Namely, after incubation for 40 min, I and D-glucuronic acid were analyzed as respectively 104.8% and 98.5% by gas chromatographic methods.[5,6]

4) All melting points are uncorrected.
5) T. Imanari and Z. Tamura, *Igaku No Ayumi*, **75**, 547 (1970).
6) I. Matsunaga, T. Imanari and Z. Tamura, *Chem. Pharm. Bull.* (Tokyo), **18**, 2535 (1970).