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Structure of *p*-Ethoxyphenylurea-N-glucuronide

During the studies on the metabolism of *p*-ethoxyphenylurea, three metabolites,[1,2] *p*-ethoxyphenylurea (unchanged), *p*-hydroxyphenylurea, and N-glucuronides of *p*-ethoxyphenylurea, were isolated from the urine of rabbits received single dose (0.5 g./kg.) orally. *p*-Hydroxyphenylurea was isolated as its O,N-diacetate.

N-Glucuronides of *p*-ethoxyphenylurea were isolated as its potassium salt, m.p. 186° (decomp.), $[\alpha]_D^{18}$ −46.8° (c=1.00, H_2O), (*Anal.* Calcd. for $C_{15}H_{19}O_8N_2K$: C, 45.68; H, 4.86; N, 7.10. Found : C, 45.94; H, 4.92; N, 6.98. UV $\lambda_{max}^{H_2O}$ mμ : 241, 280, and ammonium salt, m.p. 135° (decomp.), $[\alpha]_D^{18}$ −46.0° (c=1.00, H_2O) (*Anal.* Calcd. for $C_{15}H_{23}O_8N_3$: C, 48.26; H, 6.00; N, 11.26. Found : C, 48.16; H, 6.10; N, 10.74. UV $\lambda_{max}^{H_2O}$ mμ : 241, 280.

They have been respectively identified as potassium 1-[3-(*p*-ethoxyphenyl)ureido]-1-deoxy-β-D-glucopyranuronate (I) and ammonium 1-[3-(*p*-ethoxyphenyl)ureido]-1-deoxy-β-D-glucopyranuronate (II) by the following synthesis and their mixed melting point, infrared and ultraviolet spectra, and also paper chromatography.

First, on the treatment of *p*-ethoxyphenylurea with D-glucuronic acid[3] in pyridine, followed by neutralization with ammonia, gave II as white needles, m.p. 135° (decomp.) $[\alpha]_D^{20}$ −46.2° (c=1.00, H_2O) (Found : C, 48.41; H, 6.12; N, 10.78).

Secondly, methyl 1-[3-(*p*-ethoxyphenyl)thioureido]-1-deoxy-2,3,4-tri-O-acetyl-β-D-glucopyranuronate[4] was desulfurized with silver nitrate to give methyl 1-[3-(*p*-ethoxyphenyl)-ureido]-1-deoxy-2,3,4-tri-O-acetyl-β-D-glucopyranuronate[5] (III) m.p. 166°, $[\alpha]_D^{13}$ 15.4° (c=1.00, $CHCl_3$) (*Anal.* Calcd. for $C_{22}H_{29}O_{11}N_2 \cdot H_2O$: C, 51.16; H, 6.00; N, 5.42. Found : C, 51.03; H, 5.89; N, 5.73). The compound (III) was deacylated catalytically using barium methoxide, treated with ammonia and ammonium sulfate to give II[6], m.p. 135° (decomp.), $[\alpha]_D^{20}$ −45.0° (c=1.00, H_2O), (Found : C, 48.62; H, 5.77; N, 11.38). I has been also prepared by the similar way, m.p. 186° (decomp.), $[\alpha]_D^{20}$ −46.7° (Found : C, 45.60; H, 5.08; N, 6.90).

Thirdly, 1-[3-(*p*-ethoxyphenyl)ureido]-1-deoxy-2,3,4,6-tetra-O-acetyl-β-D-glucopyranose (VI) m.p. 159°, $[\alpha]_D^{20}$ −8.0° (c=2.00, $CHCl_3$) (*Anal.* Calcd. for $C_{23}H_{30}O_{11}N_2$: C, 54.11;

1) Announced in the Annual Meeting of Pharm. Soc. of Japan, in Sapporo, 20th July 1961.
2) Announced in the Annual Meeting of Pharm. Soc. of Japan, in Yokohama, 8th April 1962.
3) This work was presented at the Hokkaido local meeting of Pharm. Soc. of Japan, in Sapporo, 19th August 1962.
4) M. Kuranari : Yakugaku Zasshi, **81**, 1179 (1961).
5) This work was reported at 16th Annual Meeting of Pharm. Soc. of Japan, in Shizuoka, 3rd November 1962.
6) M. Akagi, *et al.* : Abst. of 17th Annual Meeting of Pharm. Soc. Japan, p. 189 (1963).

H, 5.92. Found : C, 54.20; H, 6.05) was synthesized by the reaction of 2,3,4,6-tetra-O-acetyl-β-D-glucosylisocyanate[7] with *p*-phenetidine in pyridine-chloroform, then deacetylated with ammonia in methanol to give 1-[3-(*p*-ethoxyphenyl)ureido]-1-deoxy-β-D-glucopyranose (V) m.p. 211° (decomp.), $[\alpha]_D^{22}$ −7.0° (c=1.00, pyridine) (*Anal.* Calcd. for $C_{15}H_{28}O_7N_2$: C, 52.62; H, 6.48; N, 8.18. Found : C, 52.54; H, 6.58; N, 8.23). IV has been also obtained from the product (VI), m.p. 151°, $[\alpha]_D^{20}$ −8.0° (c=2.00, $CHCl_3$) (*Anal.* Calcd. for $C_{23}H_{30}O_{10}N_2S$: C, 52.43; H, 5.75; N, 5.32. Found : C, 52.24; H, 6.02; N, 5.34) on the condensation of 2,3,4,6-tetra-O-acetyl-β-D-glucosylisothiocyanate with *p*-phenetidine, followed by desulfurization with silver nitrate. V was catalytically oxidized[8] to I, m.p. 186° (decomp.), $[\alpha]_D^{20}$ −46.0° (c=1.00, H_2O) (Found : C, 45.42; H, 5.05; N, 6.71), using platinum carbon catalyst, oxygen and potassium bicarbonate.

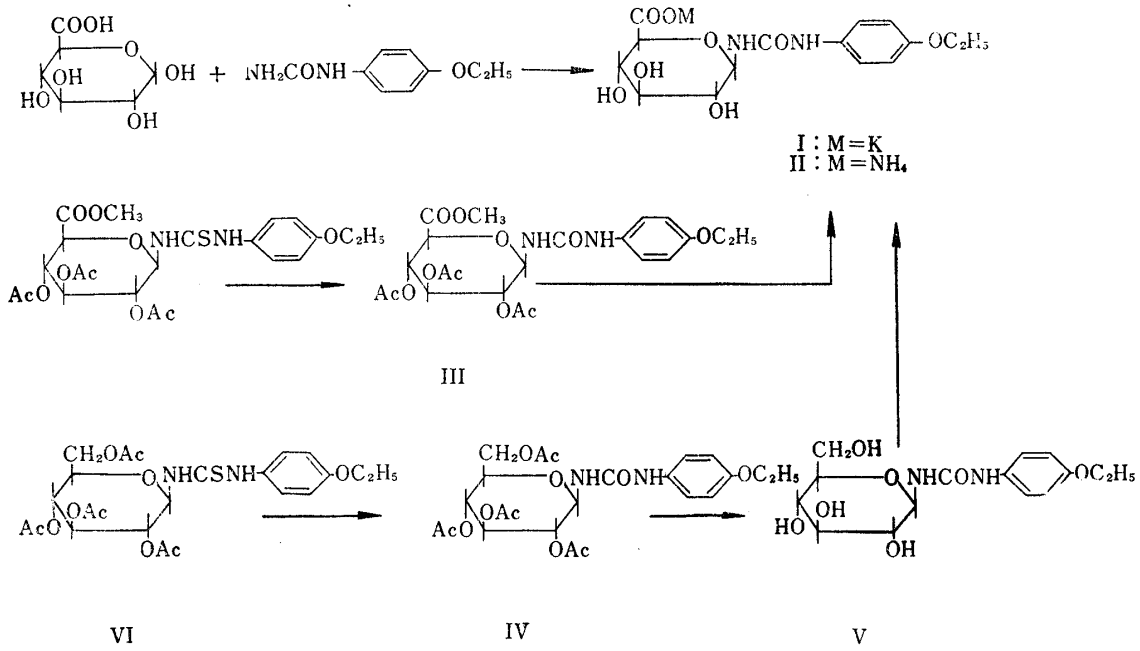

Chart 1.

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7) E. Fischer, *et al.* : Ber., **47**, 1377 (1914).
8) C.A. Marsh : J. Chem. Soc., 1578 (1952).