## Communications to the Editor

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### Isolation of Glucuronide of *p*-Aminosalicylic Acid

In the studies on the metabolic fate of *p*-aminosalicylic acid (PAS) in the animal body, three metabolic products, unchanged PAS, N-acetylated PAS,[1~3] and *p*-aminosalicyluric acid,[4] have been isolated from the urine of man and animals. The occurrence of conjugated glucuronic acids in the urine of man and animals receiving PAS has been reported by several workers,[5~7] but they have never been isolated.

Two monoglucuronides are possible, the ester, (4-amino-2-hydroxybenzoyl)-glucuronide, and the ether, (5-amino-2-carboxyphenyl)-glucuronide. In our present communication, isolation of the ester-type glucuronide is reported.

From the urine of rabbits receiving PAS, crude ester-type glucuronide was obtained by lead acetate separation as a powder which, on methylation and acetylation, yielded a minute amount of a derivative of the ester glucuronide (I) of PAS, as needles, m.p. 192~194°, $[\alpha]_D^5$ −36° (c=1.03 in $CHCl_3$), having the crystal form shown in Fig. 1 (*Anal.* Calcd. for $C_{24}H_{27}O_{14}N$ : C, 52.06; H, 4.91; N, 2.53. Found : C, 51.87; H, 5.08; N, 2.56). It was reducing, showed naphthoresorcinol reaction, and yielded 4-acetamido-2-acetoxybenzoic acid on hydrolysis.

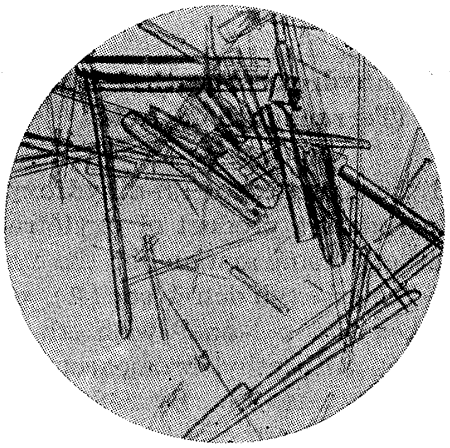

Fig. 1.
Crystals of (I)

To confirm the structure of (I), methyl (4-acetamido-2-acetoxybenzoyl-tri-O-acetyl-β-D-glucopyranosid)uronate (II) was synthesized by O-acetylation of the condensation product (III) of N-acetylated PAS with methyl (tri-O-acetyl-α-glucopyranosyl bromide) uronate, as shown in the accompanying scheme. (II), fine needles, m.p. 193~194°, $[\alpha]_D^5$ −35° (c=1.01 in $CHCl_3$) (*Anal.* Calcd. for $C_{24}H_{27}O_{14}N$ : C, 52.06; H, 4.91; N, 2.53. Found: C, 51.75; H, 4.98; N, 2.62). (I) was identified with (II) by the elemental analyses and by its faliure to depress the melting point of (II).

Further details of these experiments will be reported in a near future.

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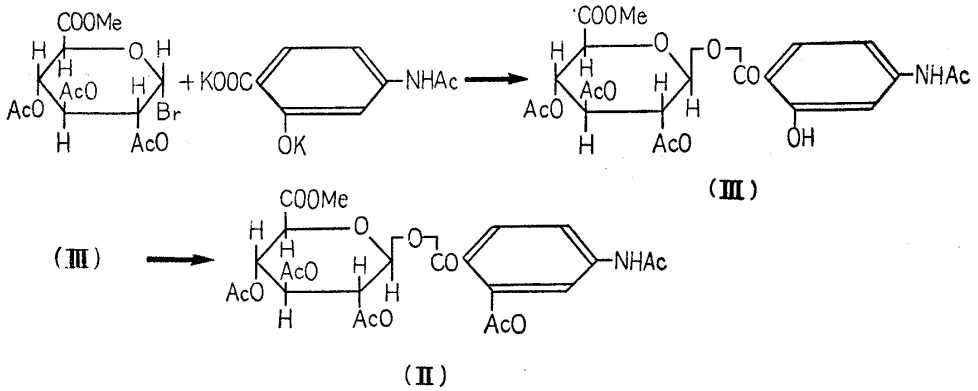

(II)

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## Synthesis of 1,8-Dihydroxy-4-methyl-3-naphthoic Acid (Terranaphthoic Acid)

Hochstein, *et al.*[1] assigned the structure of 1,8-dihydroxy-4-methyl-3-naphthoic acid (I) for terranaphthoic acid, a degradation product of oxytetracycline. The present work was undertaken to provide synthetic confirmation for the structural formula of (I).

2-Ethoxycarbonyl-3-methyl-7-methoxyindan-1-one (II), which was prepared by ester-condensation of 3-methyl-7-methoxyindan-1-one[2] with ethyl carbonate in the presence of NaH, was converted by reaction with ethyl bromoacetate to ethyl 1-oxo-2-ethoxycarbonyl-3-methyl-7-methoxy-2-indanacetate (III). By refluxing (III) with a EtOH-$H_2O$ solution of KOH for 2 hours, ($\alpha$-methyl-2-carboxy-3-methoxybenzyl)succinic acid (IV) was obtained. The trimethyl ester (V), obtained by treatment of (IV) with diazomethane, was subjected to the Dieckmann reaction with sodium in boiling toluene, yielding diethyl 1-oxo-4-methyl-8-methoxy-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylate (VI). Bromination of (VI) with bromine in a mixture of chloroform and ether and subsequent dehydrobromination by heating with 2,4,6-collidine gave diethyl 1-hydroxy-4-methyl-8-methoxy naphthalene-2,3-dicarboxylate (VII). Boiling of (VII) with 48% HBr for 8 hours yielded yellow-tan crystals of (I), m.p. 232~233°(from hot water) (*Anal.* Calcd. for $C_{12}H_{10}O_4$ : C, 66.05; H, 4.62. Found : C, 65.83; H, 4.51), which showed the same melting point and ultraviolet absorption spectrum as those of terranaphthoic acid[1b] (m.p. 233~235°) derived from oxytetracycline.

This has established the structure of terranaphthoic acid. The details of these experiments will be presented in the near future.

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1) *a*) F. A. Hochstein, *et al.* : J. Am. Chem. Soc., **74**. 3706(1952).
*b*) F. A. Hochstein, *et al.* : *Ibid.*, **75**, 5455(1953).
2) L. H. Conover : J. Am. Chem. Soc., **75**, 4017(1953).