Confirmation of the structure of imidazoleacetic acid riboside by synthesis*

Following the administration of either histamine or imidazoleacetic acid to rats, a compound identified as imidazoleacetic acid riboside was isolated from the urine[1-3]. For confirmation of the structure assigned by the authors to this nucleoside, imidazoleacetic acid riboside was synthesized by (1) condensation of the HgCl-complex[4] of cyanomethylimidazole[5] with 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide[6] in boiling xylene solution, (2) debenzoylation with barium methoxide, and (3) hydrolysis of the cyano group with aqueous barium hydroxide. This synthesis does not indicate which of the two nitrogen atoms of the imidazole ring is the site of the substitution by ribose. It may be designated as 1-β-D-ribofuranosylimidazole-4(5)-acetic acid. By analogy with comparable reactions, it is assumed that the configuration in this case is trans or β[7].

The mercuric chloride complex[4] was prepared in aqueous solution from 2.14 g cyanomethylimidazole, 2.12 g Na_2CO_3 and 5.43 g (0.02 mole) $HgCl_2$ with the addition of 3 g "Celite"[8]. It was dried by azeotropic distillation with xylene, mixed with a xylene solution of tri-O-benzoyl-D-ribofuranosyl bromide[6] and refluxed with stirring for 2 h. The filtered solution was dried *in vacuo;* the residue consisted of 10 g of a light-brown oil which became partly solid upon successive treatment with ethanol, ether and petroleum ether. The compound was a mercuric chloride complex of cyanomethylimidazole tribenzoylriboside.

Calcd. for $C_{31}H_{24}N_3O_7 \cdot Hg_{0.5}Cl \cdot C_2H_5OH$: C, 54.12; H, 4.13; N, 5.74; Hg, 13.70; Cl, 4.84.
Found: C, 53.51; H, 3.70; N, 5.77; Hg, 13.63; Cl, 5.00.

Removal of the mercury with H_2S gave cyanomethylimidazole tribenzoylriboside as a hydrochloride (from CCl_4 + petroleum ether).

Calcd. for $C_{31}H_{25}N_3O_7 \cdot HCl$ 1.5 C_2H_5OH: C, 62.14; H, 5.37; N, 6.40; Cl, 5.40.
Found: C, 62.19; H, 4,81; N. 6.13; Cl, 5.38.

Following debenzoylation with barium methoxide[6], hydrolysis[5] of the cyano group to the carboxylic group was effected by boiling with 2 *N* barium hydroxide. After removing excess barium with CO_2, the solution was placed on a Dowex-1 acetate column and the product was eluted by gradient elution with 3 *N* acetic acid. The fractions containing the product, as determined by drying aliquots, were acidified with HCl and evaporated. White crystals (1.5 g) of 1-β-D-ribofuranosylimidazole-4(5)-acetic acid hydrochloride were obtained which, after recrystallization from water–acetone, melted at 185°. The product isolated from urine[2] was recrystallized from water–acetone and melted at 185°. The mixed m.p. was 185°.

Calcd. for $C_{10}H_{15}N_2O_6Cl$: C, 40.75; H, 5.13; N, 9.51; Cl, 12.03.
Found: C, 41.03; H, 5.37; N, 9.29; Cl, 12.24.

The infrared spectra (nujol mull) of the urinary and the synthetic nucleosides proved to be identical**.

Urinary product: $[\alpha]_D^{20}$ —36.6° (water, $c = 1$); —52.5° (methanol[3], $c = 0.7$).
Synthetic product: $[\alpha]_D^{20}$ —37.0° (water, $c = 1$); —49.7° (methanol, $c = 0.7$).

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** Dr. J. BADDILEY has recently informed us (personal communication) that he has independently synthesized a riboside of imidazoleacetic acid, and that this material is identical with a sample of urinary imidazoleacetic acid riboside supplied by Drs. TABOR AND HAYAISHI.