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A Route for the Preparation of L-Hygrinic Acid*

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Hygrinic acid was first obtained by the oxidation of hygrine with chromic acid[1]. Later Karrer and Widmer[2] obtained L-hygrinic acid by oxidation of *N*-methyl-nicotone with chromic acid. They determined the configuration of L-hygrinic acid by the permethylation to L-stachydrine obtained also through the permethylation of L-proline. In the present paper the preparation of L-hygrinic acid from L-proline is described. L-Proline is methylated according to the procedure of Sommelet and Ferrand[3] and optically pure anhydrous L-hygrinic acid with $[\alpha]_D$ — 84° and *Rf* 0.37 is obtained.

EXPERIMENTAL

L-Proline (8.7 mmoles, 1 g.) was dissolved in 6*N* hydrochloric acid (10 ml.) and evaporated to dryness. The L-proline hydrochloride thus obtained was dissolved in an aqueous 40% solution of formaldehyde (3 ml.) and heated under reflux on a water bath for 2 hours. Formic acid (83%, 3 ml.) was then added and the refluxing continued for 12 more hours. The reaction mixture was evaporated to dryness under reduced pressure, dissolved in 4 *N* hydrochloric acid (5 ml.), filtered from the undissolved residue and again evaporated to dryness. The oily dry residue (1.27 g.) was dissolved in water (500 ml.), filtered through a column of Amberlite IR-4B (30 × 2 cms., 34 g.) and washed with water. The first 1000 ml. of effluent was evaporated to dryness, and a semi-crystalline, highly hygroscopic residue (0.53 g., 41.5%) was obtained. Recrystallization from absolute ethanol — ether gave L-hygrinic acid (0.5 g.), m. p. 109—117°, showing $[\alpha]_D^{18}$ — 70° (in water). Resublimation at 90—100°/0.05 mm. gave colourless needles of anhydrous L-hygrinic acid showing $[\alpha]_D^{19}$ — 83.7° (c, 0.855 in water).

Anal. 6.956 mg. subst.: 14.190 mg. CO_2, 5.332 mg. H_2O
$C_6H_{11}O_2N$ (129.16) calc'd.: C 55.79; H 8.59%
found: C 55.67; H 8.58%

L-Hygrinic acid monohydrate was obtained by recrystallization from absolute ethanol — ether or by leaving anhydrous hygrinic acid in an open vessel at room temperature.

Anal. 8.200 mg. subst.: 14.810 mg. CO_2, 6.705 mg. H_2O
$C_6H_{11}O_2N \cdot H_2O$ (147.17) calc'd.: C 48.96; H 8.90%
found: C 49.29; H 9.15%

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The m. p. of the monohydrate was 115—116° [lit. m. p. (Karrer): 116°, $[\alpha]_D$ — 80°] $[\alpha]_D^{19}$ — 77.2 (c, 1.02 in water). Paper chromatography was carried out on Whatman No. 1 paper, at 20°, using *n*-butanol-ethanol-water (5:5:2, v/v) as mobile phase, and was developed with a modified Draggendorf reagent[4] for alkaloids. The chromatogram showed an orange spot with *Rf* 0.37.

This preparation of L-hygrinic acid was repeated twice with 5 gram batches of L-proline. An alternative isolation procedure can be the filtration of the reaction mixture through a column of Dowex 50 × 16. L-Hygrinic acid can be eluted from the column with 2% aqueous ammonia.

REFERENCES

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IZVOD

Jedna preparacija L-higrinske kiseline

Metiliranjem L-prolina po Sommeletu i Ferrandu dobivena je L-higrinska kiselina.

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