

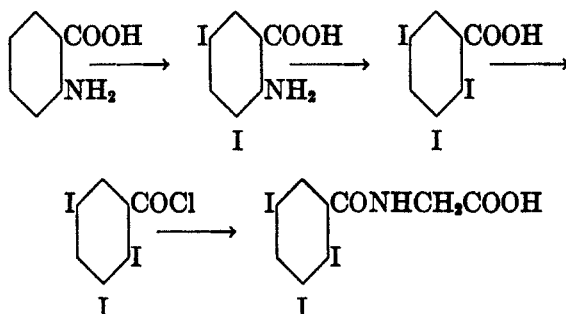
SYNTHESIS OF IODOHIPPURIC ACIDS. II. 2,3,5- AND 3,4,5-TRIIODOHIPPURIC ACIDS¹

CARL J. KLEMME AND JAMES H. HUNTER

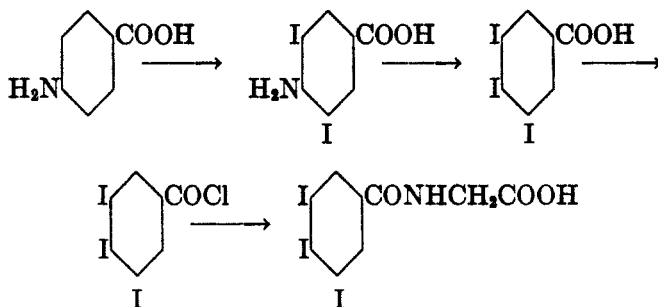
Received May 2, 1940

With the ultimate aim of studying the efficacy of certain iodohippuric acids as contrast agents for clinical radiography, we have recently described the syntheses of three diiodohippuric acids (1). In this second communication we wish to report the syntheses of two more highly iodinated derivatives, *viz.*, 2,3,5- and 3,4,5-triiodohippuric acids.

As indicated below, 2,3,5-triiodohippuric acid was synthesized from *o*-aminobenzoic acid:



and the 3,4,5-triiodo derivative was prepared from *p*-aminobenzoic acid in a similar fashion:



¹ From a portion of a thesis submitted by James H. Hunter in partial fulfillment for the degree of Doctor of Philosophy, August, 1938.

2-Amino-3,5-diiodobenzoic acid was prepared by the action of iodine monochloride on *o*-aminobenzoic acid according to the previously described modification (1) of the procedure of Wheeler and Johns (2). This acid, upon diazotization and treatment with aqueous potassium iodide, gave 2,3,5-triiodobenzoic acid (2). When this acid was warmed with thionyl chloride it readily yielded the corresponding benzoyl chloride. Conversion of the latter into 2,3,5-triiodohippuric acid was effected by treatment with glycine in the presence of dilute sodium hydroxide and subsequent acidification with hydrochloric acid.

Michael and Norton (3), in 1879, described the preparation of 4-amino-3,5-diiodobenzoic acid by the action of iodine monochloride on *p*-aminobenzoic acid. In 1909, Wheeler and Liddle (4) identified 4-amino-3,5-diiodobenzoic acid among the acid hydrolysis products of 4-acetamino-3-iodobenzoic acid. In the same report these authors gave details for the preparation of 4-amino-3,5-diiodobenzoic acid by oxidation of the corresponding acetylated toluide. In our studies we have used an acid prepared by modifying the procedure of Michael and Norton. 4-Amino-3,5-diiodobenzoic acid, when diazotized and treated with aqueous potassium iodide, gave 3,4,5-triiodobenzoic acid as described by Wheeler and Liddle (4). The preparation of 3,4,5-triiodobenzoyl chloride and, from it, 3,4,5-triiodohippuric acid followed the procedure outlined for the foregoing 2,3,5-triiodo derivative.

EXPERIMENTAL

2-Amino-3,5-diiodobenzoic acid was prepared from anthranilic acid and iodine monochloride according to the detailed procedure formerly reported (1).

2,3,5-Triiodobenzoic acid was prepared from the above 2-amino-3,5-diiodobenzoic acid according to the method of Wheeler and Johns (2). It was found to be somewhat more advantageous to purify this compound by dissolving the crude acid, which had been dissolved in dilute alkali and precipitated with dilute hydrochloric acid, in one and one-half volumes of acetone, boiling with a little decolorizing charcoal, filtering, and diluting with water until crystallization began. After thoroughly chilling, eighty per cent recovery was thus obtained.² The purified acid melted at 223–224°.³ Wheeler and Johns reported the melting point as 224–226°.

2,3,5-Triiodobenzoyl chloride. Two and five-tenths grams (0.005 mole) of pure 2,3,5-triiodobenzoic acid (m.p. 223–224°) was gently refluxed with 5 cc. of thionyl chloride (Eastman's "Practical") for forty-five minutes. The excess thionyl chloride was distilled from a steam-bath. The crystalline mass, formed by chilling the residual liquid, was crystallized from carbon tetrachloride; yield, 2.3 g. (85.4%) of a dull yellow solid melting at 85–86° after sintering at 80–84°.

Anal. Calc'd for $C_7H_2ClI_3O$: Cl, 6.84; I, 73.47.

Found: Cl, 7.17; I, 72.01.

² Wheeler and Johns (2) crystallized the crude acid from strong alcohol.

³ All melting points are uncorrected.

2,3,5-Triiodohippuric acid. One and three-tenths grams of glycine was dissolved in 22 cc. of approximately 3% sodium hydroxide. The solution was warmed to about 85° and treated with 0.9 g. (0.00173 mole) of 2,3,5-triiodobenzoyl chloride. The mixture was shaken until most of the acid chloride had dissolved. The amber colored supernatant liquid was filtered, the residue washed with a little water, and the combined filtrate acidified with concentrated hydrochloric acid. The bulky, white precipitate was collected, washed with water, and dried in air; yield, 0.9 g. (93.3%). The crude, dry product was repeatedly extracted with ether to remove any 2,3,5-triiodobenzoic acid present. The ether-insoluble residue weighed 0.72 g. (74.5%). Crystallization from a mixture of 50 cc. of acetone and 80 cc. of water gave 0.32 g. (33.2%) of white platelets melting at 255.5–257° after darkening at 250–255°.

Anal. Calc'd for $C_9H_6I_3NO_3$: I, 68.38; N, 2.51; M.w. 556.8.

Found: I, 66.80; N, 2.70; M.w. 580.3.

4-Amino-3,5-diiodobenzoic acid. With efficient mechanical stirring, 10 g. (0.073 mole) of recrystallized *p*-aminobenzoic acid (m.p. 184°) (5) was dissolved in 450 cc. of warm (75°) 12.5% hydrochloric acid contained in a 2 l. beaker. Forty-eight grams (0.295 mole) of iodine monochloride (6) in 40 cc. of 25% hydrochloric acid was added, and the mixture stirred for one minute. During this time a yellow precipitate began to appear. The reaction-mixture was then diluted with 1 l. of water, whereupon a copious precipitate was deposited. The temperature of the well-stirred mixture was raised gradually, and held at about 90° for fifteen minutes. After the contents of the beaker had cooled to room temperature, the precipitate was collected, thoroughly washed with water and dried in air; yield, 24.0 g. (84.5%).⁴ Purification by dissolving in dilute sodium hydroxide and precipitating with dilute hydrochloric acid gave 22.8 g. (82.4%) of a product of sufficient purity for the preparation of 3,4,5-triiodobenzoic acid. The product was not crystallized because of its slight solubility. Its melting point lies above 350° (4).

3,4,5-Triiodobenzoic acid was prepared according to the procedure of Wheeler and Liddle (4). The crude product was directly crystallized from dilute alcohol. The purified acid melted at 289–290°. Wheeler and Liddle found 288°.

3,4,5-Triiodobenzoyl chloride. Five grams (0.01 mole) of 3,4,5-triiodobenzoic acid (m.p. 289–290°) was gently refluxed for two hours with 10 cc. of thionyl chloride. Excess thionyl chloride was distilled from a steam-bath, and the residue crystallized from a carbon tetrachloride-petroleum ether mixture with the use of a little decolorizing charcoal. The bright yellow needles thus obtained weighed 3.8 g. (73.4%) and melted at 136–138°. Recrystallization from the carbon tetrachloride-petroleum ether mixture gave 2.7 g. (52.1%) of yellow needles melting at 138–139°.

Anal. Calc'd for $C_7H_2ClI_3O$: Cl, 6.84; I, 73.47.

Found: Cl, 7.05; I, 72.28.

3,4,5-Triiodohippuric acid. Two and nine-tenths grams of glycine (Eastman) was dissolved in 50 cc. of 1% sodium hydroxide and the solution warmed to 90°. Two grams (0.00386 mole) of 3,4,5-triiodobenzoyl chloride was added and the temperature held at 90–100° for about ten minutes with frequent shaking. The clear, yellow solution was cooled slightly, acidified with concentrated hydrochloric acid, and again cooled. The somewhat yellow precipitate was collected, washed with water and air-dried; yield, 2.2 g. (quantitative). The crude compound was freed from any 3,4,5-triiodobenzoic acid by repeated extraction with ether. The dry,

⁴ The yield obtained by Michael and Norton (3) was not reported.

ether-insoluble residue weighed 1.95 g. (90.6%). One crystallization from dilute alcohol gave pure, white crystals melting at 242-243°.

Anal. Calc'd for $C_9H_5I_3NO_3$: I, 68.38; N, 2.51; M.w. 556.8.

Found: I, 66.76; N, 2.85; M.w. 580.1.

SUMMARY

Details are given for a four-step synthesis of 2,3,5-triodohippuric acid, and its isomer, the 3,4,5-triiodo derivative, from *o*- and *p*-aminobenzoic acids, respectively.

LAFAYETTE, IND.

REFERENCES

- (1) KLEMM AND HUNTER, *J. Org. Chem.*, **5**, 227 (1940).
- (2) WHEELER AND JOHNS, *Am. Chem. J.*, **43**, 405 (1910).
- (3) MICHAEL AND NORTON, *Am. Chem. J.*, **1**, 264 (1879).
- (4) WHEELER AND LIDDLE, *Am. Chem. J.*, **42**, 454 (1909).
- (5) FISCHER, *Ann.*, **127**, 142 (1863).
- (6) "Organic Syntheses," John Wiley and Sons, New York City, 1934, Vol. 14, p. 53.