SYNTHESIS OF α-AMINOPHENYLACETIC ACID.

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α-Aminophenylacetic acid is the basic raw material for the preparation of Ampicillin which is one of the most important semi-synthetic penicillins having a wide area of application [1].

The two methods for its preparation of practical interest are: 1) from phenylacetic acid via α-bromophenylacetic acid with the substitution of the amino group for bromine, and 2) from benzaldehyde, sodium cyanide, and ammonium chloride with a subsequent saponification of the nitrile of α-aminophenylacetic acid [2-7]. In the development of a method for the preparation of α-aminophenylacetic acid we have preferred the first method since the second one gave a yield not exceeding 37%.

α-Bromophenylacetic acid has been prepared by us by the well known method [8]. Several methods have been proposed for the substitution of the amino group for bromine: heating with a threefold amount of aqueous ammonia solution at 100-110° in sealed tubes [9], treatment with 35% aqueous ammonia solution, or with liquid ammonia and various saturated alcoholic solutions at 0-18° for 8-15 days. The yields of α-aminophenylacetic acid varied from 21 to 57% [10].

For the substitution of the amino group for bromine we treated α-bromophenylacetic acid with various amounts of 25% aqueous ammonia solution. The molar ratios of the reagents and the yield (in parentheses) were: 1:15 (43-44%), 1:30 (53-54%), 1:45 (53-56%), 1:60 (59-61%), 1:100 (62-64%).

With the increase of the relative amount of ammonia the yield of α-aminophenylacetic acid gradually increased; however, it was expedient to use only a 30-fold molar amount of ammonia. The substitution of the amino group for bromide in α-bromophenylacetic acid was practically completed in 24 hours.

Recently a new method was proposed for the preparation of α-aminoalkylcarboxylic acids from α-chloro- or α-bromoalkylcarboxylic acids, formaldehyde, and NH_4OH [11]; this method was used for the synthesis of glycine from monochloroacetic acid. The reaction was found to be fairly convenient for the synthesis of α-aminophenylacetic acid from α-bromophenylacetic acid; under the selected optimum conditions, the amino acid was separated from the reaction mass in a nearly pure state with a yield of 90%.

We have assumed that originally the ammonium salt of α-bromophenylacetic acid was formed, then formaldehyde and ammonia gave urotropine, which further reacted with the ammonium salt, followed by the cleavage of the condensation product to yield α-aminophenylacetic acid. This was confirmed by condensing α-bromophenylacetic acid with urotropine, in a molar ratio of 1:2, which gave α-aminophenylacetic acid with a yield of 78-80%.

EXPERIMENTAL

α-Aminophenylacetic Acid. Into a three-necked flask fitted with a stirrer was introduced 215 g of α-bromophenylacetic acid, 118 ml of 37% formaldehyde, and over a period of 1 h, 308.8 ml of ammonium hydroxide; the temperature in the flask was not allowed to rise above 20°. After the addition of ammonium hydroxide, the precipitate was dissolved and α-aminophenylacetic acid crystallized. The reaction mass was stirred for 3-4 h. The precipitate was separated and washed with water. The crude precipitate was dissolved in 185 ml of 20% sodium hydroxide solution, 1 g of activated carbon added, stirred, and the solution filtered. The filtrate was acidified with hydrochloric acid to pH 7.0. The α-aminophenylacetic acid precipitate was separated, washed twice with water and dried at 80-100°. Yield 136 g (90%, based on α-bromophenylacetic acid), mp 253-255°. Found %: C 63.69; H 6.01; N 9.5. $C_8H_9O_2N$. Calculated %: C 63.57; H 5.96; N 9.27.

Reaction of α-Bromophenylacetic acid with Urotropine. In a three-necked flask fitted with a stirrer, thermometer, and a dropping funnel was dissolved 13.88 g of urotropine in 30 ml of water. To this solution

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was added 10.7 g of α-bromophenylacetic acid which was gradually dissolved; the separation of α-aminophenylacetic acid began after several minutes. The reaction mass was stirred for 3-4 h, made alkaline to pH 7.0 with ammonium hydroxide, the precipitate filtered off, washed with water and dried at 80-100°. Yield 6.6 g (88%). The acid was purified as described above. Yield of α-aminophenylacetic 6 g (80%), mp 253-255°.

LITERATURE CITED

1. B. Radziszewski, Ber. Dtsch. Chem. Ges., 2, 208 (1869).
2. R. Shteiger, Synthesis of Organic Preparations, Vol. 3 [in Russian], Moscow (1952), p. 63.
3. F. Tiemann, Ber, Dtsch. Chem. Ges., 13, 383 (1880).
4. A. Ulrich, Ibid., 37, 1688 (1904).
5. I. Zelinskii and G. Stadnikov, Zh. Russk. Khim. Obsh., 38, 473 (1906).
6. A. Ingersoll and R. Adams, J. Am. Chem. Soc., 44, 2933 (1922).
7. C. Marvel and W. Noyes, Ibid., 42, 2264 (1920).
8. A. Fredga, Ark. Kemi. Mineral. Geol., 24B, No. 15, 8 (1947), Chem. Abstr., 42, No. 6343 (1948).
9. O. Stöckenius, Ber. Dtsch. Chem. Ges., 11, 2002 (1878).
10. J. Senter and S. Tucker, Chem. Soc., 113, 141 (1918).
11. Dutch Pat. 299272, Chem. Abs. 64, 3686 (1966).