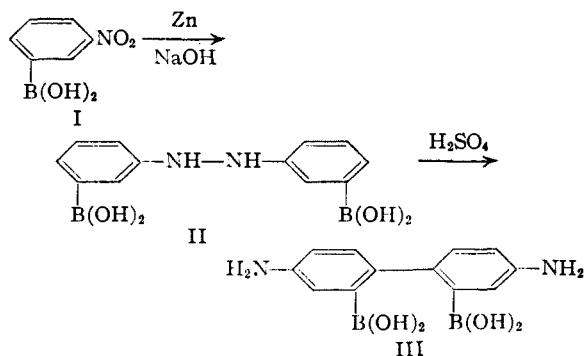


[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Synthesis of Benzidine-2,2'-diboronic Acid

BY H. R. SNYDER, CLAY WEAVER¹ AND STANLEY M. PARMETER²

Previous attempts³ to prepare a biphenyldiboronic acid by the coupling of two molecules of a diazotized aminobenzeneboronic acid in the presence of cuprous hydroxide failed because of the removal of the boronic acid function by the reducing reagent. A synthesis of 4,4'-diaminobiphenyl-2,2'-diboronic acid (III) now has been realized by the application of the benzidine rearrangement to *m*-hydrazobenzeneboronic acid (II).



The alkaline reduction of *m*-nitrobenzeneboronic acid proceeded smoothly and a good yield of the crude hydrazo compound (II) was obtained. Removal of the boronic acid groups by heating the silver salt⁴ with water gave azobenzene. Evidently the hydrazine linkage was oxidized to the azo group by the reagent (silver nitrate in the presence of ammonia). Since the reduction product (II) was nearly colorless it could not have contained an azo linkage.

The treatment of the hydrazo compound with acids, under the various conditions which have been employed to effect the benzidine rearrangement, brought about extensive decomposition of the substance. However, when the reaction was effected at temperatures of 50–60° with rather dilute hydrochloric or sulfuric acid (10–20%), the benzidine (III) was formed in sufficient quantity to permit its isolation in yields of 15–20%. The product (III) was amphoteric, and the boron content was very near the theoretical value. The substance (III) gave a good test (diazotization and coupling) for the primary aromatic amino group. When the acetyl derivative of III, prepared by treatment with acetic anhydride in water solution, was subjected to the procedure for the removal of the boronic acid group by hydrolysis of the silver salt diacetylbenzidine was formed. Similarly, treatment of the dibenzal derivative of III with

silver nitrate in the presence of ammonia gave the dibenzal derivative of benzidine.

Experimental

m-Nitrobenzeneboronic Acid.—The method of Seaman and Johnson⁴ was used on a six-fold scale without detrimental effect upon the yield (65–70%).

m-Hydrazobenzeneboronic Acid (II).—A solution of 15 g. of *m*-nitrobenzeneboronic acid, 20 g. of sodium hydroxide and 15 ml. of alcohol was heated with stirring to gentle reflux. After the solution had refluxed for twenty minutes the heating was discontinued and small portions of zinc were added at such a rate that gentle ebullition was maintained. The first portions of zinc were extremely small, as the initial reaction was quite vigorous. After 23 g. of zinc had been added the color of the solution faded to a light yellow. Near the end of the addition external heating was necessary to keep the solution refluxing. The solid material removed from the hot mixture by filtration under nitrogen was washed with 35 ml. of hot water, and the combined filtrate and washings were cooled and poured slowly with stirring into 18 ml. of cold concentrated hydrochloric acid. The resulting solution was made acid to litmus with 20% acetic acid and allowed to stand in an ice-bath for two hours. The crude *m*-hydrazobenzeneboronic acid was collected on a filter under nitrogen, and ordinarily it was used immediately in subsequent reactions without drying. The weight of the air-dried product corresponded to a yield of 91%.

The *m*-hydrazobenzeneboronic acid could be recrystallized from dilute ethanol. A sample so recrystallized and dried in the air was titrated with 0.1 *N* sodium hydroxide in a dilute ethanol solution with the aid of a pH meter. The neutralization equivalent so found was 137 (calcd., 135.9). This sample had no definite melting point; it softened at about 60° and charred at higher temperatures. A sample dried *in vacuo* over phosphorus pentoxide apparently was converted to the anhydride; it did not melt instantly on a Parr melting point bar at temperatures up to 350°, although it charred slowly at temperatures above 250°. This sample was analyzed.

Anal. Calcd. for C₁₂H₁₀N₂B₂O₂: N, 11.9. Found: N, 11.5.

Removal of the Boronic Acid Groups.—Application of the procedure of Seaman and Johnson resulted in the formation of a red crystalline solid, m. p. 66–68°, which was identified as azobenzene by a mixed melting point determination.

Benzidine-2,2'-diboronic Acid.—Of a variety of procedures tested in the rearrangement of the hydrazo compound (II) the following⁴ gave the best and most consistent results. The crude, moist hydrazo compound from 15 g. of *m*-nitrobenzeneboronic acid was transferred to a flask containing 125 ml. of 10% sulfuric acid through which nitrogen had been bubbled for about an hour to remove dissolved oxygen. Without interruption of the flow of nitrogen the mixture was warmed for three hours in an ice-bath at 60°. The mixture was then filtered and the filtrate was cooled in an ice-bath while it was brought almost to the neutral point by the cautious addition of concentrated ammonium hydroxide. A brown precipitate formed during this process. If too much ammonia was added a white precipitate began to appear; when this occurred dilute sulfuric acid was added to redissolve the white material. The brown precipitate was removed by filtration and the benzidine was precipitated by the addition of ammonium hydroxide to the filtrate.

(5) The authors are indebted to Dr. Seymour L. Meisel, who carried out this preparation many times, for some of the details recorded here.

(1) du Pont Post-Doctorate Research Assistant, 1941–1942. Present address: Experimental Station, E. I. du Pont de Nemours and Co., Inc., Wilmington, Delaware.

(2) Present address: The Wm. S. Merrell Co., Cincinnati, Ohio.

(3) Snyder and Weaver, *THIS JOURNAL*, **70**, 232 (1948).

(4) Seaman and Johnson, *ibid.* **53**, 711 (1931).

For the preparation of the benzidine dihydrochloride the suspension of the benzidine was stored in a refrigerator for two days before it was collected on a filter. The solid was dried to constant weight in a vacuum desiccator and was then extracted with small portions (about 20 ml.) of boiling absolute ethanol until the amount of undissolved solid appeared to undergo no further decrease. The combined ethanol extracts were diluted with twice the volume of anhydrous ether and dry hydrogen chloride was passed into the solution until precipitation of the hydrochloride was complete. The solid was collected and the mother liquor was tested by further dilution with ether; if more solid separated it was combined with the first crop and the second mother liquor was tested in the same way. The total yield of the dihydrochloride so obtained was 3.1 g. (19.3% based on the nitro compound I). The salt had no definite melting point, but decomposed slowly at temperatures above 300°.

Anal. Calcd. for $C_{12}H_{16}O_4B_2N_2Cl_2$: N, 8.15; B, 6.28. Found: N, 8.27; B, 5.85.

For the isolation of the benzidine directly from the rearrangement mixture the crude diamine was filtered immediately after the precipitation with ammonium hydroxide and the filtrate was stored for two days in a stoppered flask. The solid collected in the filtration was extracted with 100 ml. of 30% ethanol and the extract was allowed to cool. Both the dilute ethanol extract and the ammoniacal mother liquor deposited light brown crystals; the two crops were collected and decolorized in 150 ml. of hot 30% ethanol. This solution on cooling deposited 1.6 g. (13%) of the benzidine as short flesh-colored needles melting at 232–234°. The substance was insoluble in water, aqueous ammonia and ether, but soluble in dilute sodium hydroxide dilute acids, ethanol and glacial acetic acid. A sample dried in the air had the composition of a hemihydrate.

Anal. Calcd. for $C_{12}H_{15}O_4.5N_2B_2$: C, 51.25; H, 5.38; B, 7.70. Found: C, 51.01; H, 5.64; B, 7.75.

The combustion analyses on samples dried *in vacuo* over phosphorus pentoxide were erratic with respect to carbon and the combustion residues obviously contained carbon; the hydrogen and nitrogen values on such samples indicated that they consisted of the di-anhydride.

Anal. Calcd. for $C_{12}H_{10}O_2N_2B_2$: H, 4.27; N, 11.88. Found: H, 4.45; N, 11.51.

Removal of the Boronic Acid Groups from Derivatives of the Benzidine (III). (a) *Diacetylbenzidine*.—A solution of 1.36 g. of the diamine in 25 ml. of water containing 0.83 ml. of concentrated hydrochloric acid was treated with 1.16 ml. of acetic anhydride and then warmed to 50°. A solution of 0.82 g. of sodium acetate in 5 ml. of water was

added, and the mixture was cooled in an ice-bath. A solid weighing 1.13 g. was collected which was soluble in dilute sodium hydroxide but insoluble in water and acids. A portion of the material was recrystallized from a large volume of 50% ethanol. The analytical data indicated that part of the material had lost boronic acid groups during the reaction.

Anal. Calcd. for $C_{16}H_{18}N_2O_6B_2$: C, 54.0; H, 5.1; B, 6.1. Found: C, 57.4; H, 5.4; B, 4.5.

A sample of about 0.5 g. of the crude acetyl derivative was suspended in 30 ml. of 50% ethanol and treated with 10 ml. of 10% aqueous silver nitrate and 6 drops of concentrated aqueous ammonia. The resulting mixture, which contained a brown precipitate, was refluxed for fifteen minutes and filtered hot. The filtrate deposited a white powder which melted at 329–331°, alone or mixed with authentic diacetylbenzidine.

(b) *Dibenzalbenzidine*.—To a warm solution of 0.5 g. of the benzidine in 70 ml. of 95% ethanol was added 1 ml. of benzaldehyde. The solution soon began to deposit fine crystals, which were collected after four hours. The yellow product melted at 141–143° and weighed 0.8 g. (97%). The substance could be recrystallized from benzene, but the product so obtained had no definite melting point; the material probably suffered the loss of water from the boronic acid groups during the heating with benzene. About 0.2 g. of the freshly prepared benzal derivative was suspended in 50 ml. of water and treated with six drops of aqueous ammonia; dilute aqueous silver nitrate was added until no further precipitation occurred and the brown solid was separated. The solid was added to 25 ml. of water and the mixture was boiled gently for fifteen minutes. The cooled mixture was filtered and the solid was extracted with 20 ml. of hot benzene. The yellow plates which separated when the benzene solution was cooled melted at 232–234°; the substance did not contain boron, and the melting point was not changed by mixture with authentic dibenzalbenzidine.

Summary

m-Hydrazobenzeneboronic acid can be prepared in good yield by the reduction of *m*-nitrobenzeneboronic acid with zinc in the presence of alkali. Rearrangement of the hydrazo compound by acids leads to complex mixtures, but under certain conditions benzidine-2,2'-diboronic acid is produced and can be isolated in yields of about 20%.

URBANA, ILLINOIS

RECEIVED AUGUST 18, 1947

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Synthesis of Azo Boronic Acids. II. Dyes from Tetratozized Benzidine-2,2'-diboronic Acid

BY H. R. SNYDER AND SEYMOUR L. MEISEL¹

The speculations of Kruger² and Zahl and others^{3–5} on the possible development of an irradiation therapy based on the nuclear disintegration process (equation 1) occurring when the boron isotope of atomic weight 10 captures a slow neutron have provoked an interest in the synthesis of

(1) Present address: Socony-Vacuum Oil Co., Inc., Paulsboro, N. J.

(2) Kruger, *Proc. Nat. Acad. Sci.*, **26**, 181 (1940).

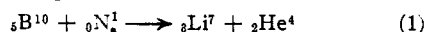
(3) Zahl, Cooper and Dunning, *ibid.*, **26**, 589 (1940).

(4) Zahl and Cooper, *Science*, **93**, 64 (1941).

(5) Zahl and Waters, *Proc. Soc. Exper. Biol. Med.*, **48**, 304 (1941).

(6) Zahl and Cooper, *Radiology*, **37**, 673 (1941).

boron-containing dyes having structures similar to those of Trypan Blue and Evans Blue. Such substances might be expected to concentrate in certain tissues, which might then be irradiated with slow neutrons with the result that the energetic nuclear disintegration would be localized. Re-



cent studies⁷ on the localization of derivatives of Trypan Blue and Evans Blue containing radioactive bromine indicate that the relative concentra-

(7) Moore, Tobin and Aub, *J. Clin. Invest.*, **22**, 161 (1943).