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

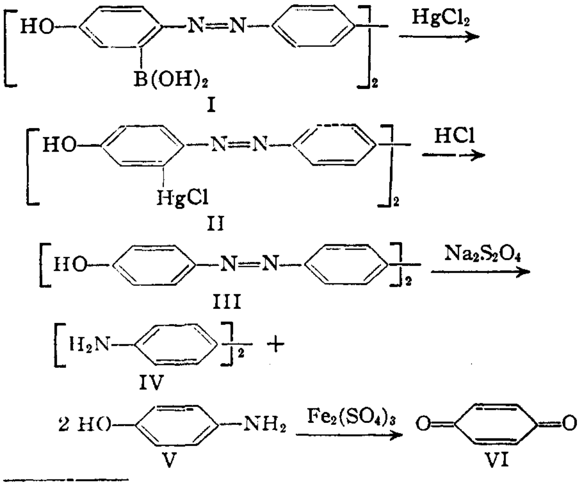
The Preparation of Some Azo Boronic Acids

BY H. R. SNYDER AND CLAY WEAVER[1,2]

In an approach to the synthesis of boron-containing azo dyes desired for use in physiological studies the reactions of diazonium compounds with some aromatic boronic acids containing dialkylamino and hydroxyl groups have been examined. *m*-Hydroxybenzeneboronic acid and *m*-diethylaminobenzeneboronic acid were selected because of their ready availability. The diazonium compounds used in the coupling reactions were those obtained from benzidine, 4,4′-diaminodiphenic acid, *p*-aminobenzoic acid and *m*-aminobenzeneboronic acid.

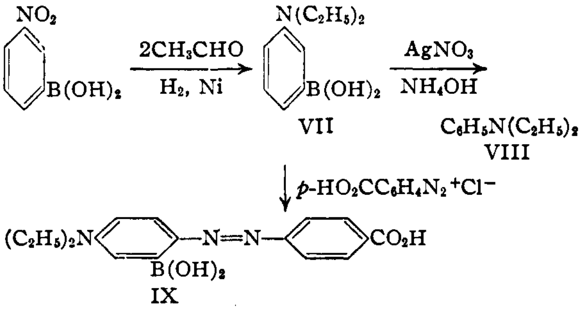
The most interesting question with regard to the proposed diazo coupling reactions concerned the stability of the aromatic boronic acids under the conditions required. *m*-Aminobenzeneboronic acid has been diazotized and the diazonium salt has been hydrolyzed to *m*-hydroxybenzeneboronic acid,[3] but the conditions employed differ greatly from those of coupling reactions. The boronic acid group is readily cleaved from the benzene ring by reagents such as copper[4] and silver[5] salts and aqueous solutions of the halogens,[4] and even by hot water,[4] so loss of the function during a diazo coupling would not be surprising.

The coupling of *m*-hydroxybenzeneboronic acid and *m*-diethylaminobenzeneboronic acid with the diazonium salts indicated was found to proceed without loss of the boronic acid function. Coupling would be expected to occur at the positions *para* to the hydroxyl and diethylamino groups. The dye from tetrazotized benzidine and *m*-hydroxybenzeneboronic acid was shown to have the expected structure (I). The structure proof was accomplished by removal of the boronic acid groups with mercuric chloride, hydrolysis of the mercury compound so formed, reduction of the resulting dye (III) to benzidine and *p*-aminophenol (V) which was identified by oxidation to *p*-benzoquinone.



m-Hydroxybenzeneboronic acid was coupled also with tetrazotized 4,4′-diaminodiphenic acid, with diazotized *p*-aminobenzoic acid and with diazotized *m*-aminobenzeneboronic acid. Evidently the boronic acid group can be present in either or both of the aromatic reagents subjected to the diazo coupling.

The *m*-diethylaminobenzeneboronic acid (VII) used was not isolated in the pure state. It was prepared from *m*-nitrobenzeneboronic acid by reduction in the presence of acetaldehyde.[6] No satisfactory solvent or solvent mixture for its recrystallization was found. Removal of the boronic acid group by treatment with ammoniacal silver nitrate converted it to diethylaniline (VIII), identified as the chloroplatinate, and the dye (IX) formed by coupling the crude *m*-diethylaminobenzeneboronic acid with diazotized *p*-aminobenzoic acid had the expected composition.



A projected approach to the synthesis of a biphenyldiboronic acid consisted in the coupling of two molecules of a diazotized aminobenzeneboronic acid in the presence of cuprous hydroxide, in analogy to the preparation of diphenic acid from diazotized anthranilic acid.[7] To determine whether the boronic acid group would survive the required treatment, benzeneboronic acid was subjected to the conditions of the diphenic acid preparation. The odor of benzene was evident immediately. The hydrocarbon was recovered by steam distillation and identified as the dinitro derivative. It appears unlikely that the so-called symmetrical coupling can be applied to diazotized aminoboronic acids.

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(3) Bean and Johnson, THIS JOURNAL, **54**, 4415 (1932).

(4) Ainley and Challenger, *J. Chem. Soc.*, 2171 (1930).

(5) Seaman and Johnson, THIS JOURNAL, **53**, 711 (1931).

(6) Emerson and Uraneck, *ibid.*, **63**, 749 (1941), describe the general method used.

(7) Atkinson and Lawler, "Org. Syn.," 2nd ed., Coll. Vol. I, 222 (1941).

One of the earliest methods of preparing aromatic boronic acids made use of the reaction between a diaryl mercury and boron chloride.[8] Apparently the use of more readily available mercurials, such as $ArHgOCOCH_3$ and ArHgCl, in similar reactions with esters of boric acid has not been attempted. Accordingly *o*-chloromercuriphenol and acetoxymercuribenzene were heated with *n*-butyl borate, but there was no evidence of the desired reactions when the reagents were heated in benzene or in the absence of solvents at temperatures as high as 150°.

Experimental

A. Azo Dyes from *m*-Hydroxybenzeneboronic Acid. (1) 2-(*p*-Carboxybenzeneazo)-5-hydroxybenzene-1-boronic Acid.—A suspension of 0.9 g. of *p*-aminobenzoic acid in 10 ml. of 3 *N* hydrochloric acid was diazotized with 0.48 g. of sodium nitrite in 5 ml. of water. The cold diazonium salt solution was added dropwise to a cold solution of 0.9 g. of *m*-hydroxybenzeneboronic[3] acid in 10 ml. of 20% aqueous sodium hydroxide. The deep red mixture was allowed to stand for one hour, with occasional stirring, and then was added slowly to 10 ml. of cold 6 *N* hydrochloric acid. The gelatinous precipitate was coagulated by the addition of 50 ml. of ethanol and heating; after cooling the mixture was filtered through hardened filter paper. The orange solid was dissolved in 50 ml. of warm ethanol and caused to crystallize by dilution with an equal volume of warm water and cooling. After a second recrystallization it weighed 1.6 g. (88%) and melted at 254–256°. The boron content was determined by ignition of the residue from the combustion and weighing of the boric oxide so formed. Because of occlusion of carbonaceous material in the residue before final ignition, the carbon analyses of organoboron compounds often are low.

Anal. Calcd. for $C_{13}H_{11}BN_2O_5$: C, 54.6; H, 3.9; N, 9.8; B, 3.8. Found: C, 52.8; H, 4.3; N, 9.7; B, 4.2.

(2) **a. Preparation of 4,4′-bis-(2-Borono-4-hydroxybenzeneazo)-biphenyl.**[9]—The tetrazonium salt solution prepared from 6.7 g. of benzidine in 40 ml. of 7 *N* hydrochloric acid and 5 g. of sodium nitrite in 20 ml. of water was added to a cold (10°) solution of 10 g. of *m*-hydroxybenzeneboronic acid in a mixture of 20 g. of sodium carbonate in 80 ml. of water and 40 ml. of 10% aqueous sodium hydroxide. Stirring at 10° was continued for one hour. The deep purple mixture was poured into 50 ml. of cold concentrated hydrochloric acid and the solid was collected on a filter and washed free of chlorides with distilled water. The dry product weighed 12 g. It was recrystallized by dissolving it in the minimum quantity of hot ethanol, diluting with hot water and cooling. The deep red solid decomposed slowly at temperatures above 300°, but no definite melting or decomposition point could be discerned.

Anal. Calcd. for $C_{24}H_{20}B_2O_6N_4$: C, 59.8; H, 4.2; N, 11.6. Found: C, 61.6; H, 4.3; N, 11.4.

b. Structure Proof.—A solution of 12 g. of the dye in 200 ml. of hot ethanol was treated with an excess of mercuric chloride dissolved in 50% ethanol. The mixture was boiled under reflux for three hours, and the insoluble red mercury compound was collected and dried. A mixture of the red-brown powder (wt. 21 g.) and 100 ml. of 6 *N* hydrochloric acid was heated under reflux for two hours. The nearly black solid was collected by filtration and washed with water. After drying it weighed 11 g. It was mixed with 200 ml. of 10% sodium hydroxide at 60° and 25 g. of sodium hydrosulfite was added. After fifteen minutes, during which the temperature rose to 65°, a second 25-g. portion of sodium hydrosulfite was added. The mixture was heated on the steam-bath until no further fading of the color occurred. The solution was allowed to stand overnight and then neutralized to a *p*H of about 8 (Alk-Acid paper) with carbon dioxide. The tan precipitate was collected and digested twice with 50-ml. portions of warm 10% aqueous sodium hydroxide to separate the aminophenol from the benzidine. The combined extracts were acidified with 25% sulfuric acid and mixed with 100 g. of ferric sulfate and steam-distilled until 50 ml. of distillate had collected. On cooling, this distillate deposited 1.6 g. of *p*-benzoquinone, m. p. 113–115° (not depressed by admixture of authentic *p*-benzoquinone). The crude benzidine remaining from the alkaline extraction was heated with 100 ml. of water and the solution was decolorized. Cooling caused the separation of about 1 g. of pure benzidine, identified by melting point and mixed melting point.

(3) **4,4′-bis-(2-Borono-4-hydroxybenzeneazo)-diphenic Acid.**—A filtered solution of 2 g. of 4,4′-diaminodiphenic acid in 10 ml. of water and 5 ml. of concentrated hydrochloric acid was tetrazotized at 0° with 1 g. of sodium nitrite in 10 ml. of water. The resulting solution was added slowly to a cold solution of 2 g. of *m*-hydroxybenzeneboronic acid in 40 ml. of 5% aqueous sodium hydroxide containing 5 g. of sodium carbonate. The deep purple mixture was stirred for two hours, then heated to 75° and treated with a little charcoal. The filtered solution was added slowly with stirring to 20 cc. of cold concentrated hydrochloric acid. The resulting red colloidal suspension was heated to promote coagulation and filtered through a hardened filter paper. The solid was washed with water and dried (wt., 3.8 g.). It was redissolved in aqueous sodium hydroxide, treated with charcoal, filtered and acidified as before to yield a brick-red powder. This was dissolved in 50 ml. of ethanol, and the hot solution was filtered and diluted to incipient precipitation with hot water and cooled. The fine, red powder weighed 1.2 g.; an additional quantity of 1.9 g. was obtained by further dilution of the mother liquor. The solid had no definite melting point, but slowly decomposed at temperatures above 300°.

Anal. Calcd. for $C_{26}H_{20}B_2N_4O_{10}$: C, 54.8; H, 3.5; N, 9.8; B, 3.8. Found: C, 55.8; H, 3.9; N, 10.2; B, 3.2.

(4) **2-(3-Boronobenzeneazo)-5-hydroxybenzeneboronic Acid.**—*m*-Nitrobenzeneboronic acid was reduced catalytically in aqueous methanol and after displacement of the methanol by water the aminoboronic acid was diazotized without isolation. The diazonium solution prepared from 5.6 g. of the nitro compound was added slowly to a cold solution of 4.2 g. of *m*-hydroxybenzeneboronic acid in 100 ml. of 10% aqueous sodium hydroxide. The deep red solution was allowed to stand overnight and then poured into an excess of 25% sulfuric acid. The red colloidal suspension was decanted from a brown gum and the gum was extracted with hot water. The extract was combined with the suspension and the mixture was cooled and filtered. The brick-red solid (wt. 2 g.) was recrystallized from a mixture of 100 ml. of water and 10 ml. of ethanol. The product decomposed at temperatures above 350°. A solution of about 0.1 g. of the dye in 40 ml. of 50% ethanol containing 5 g. of mannitol was titrated against 0.05 *N* sodium hydroxide by means of a Hellige *p*H meter.

Anal. Calcd. for $C_{12}H_{12}B_2N_2O_5$: C, 50.4; H, 4.2; N, 9.8; B, 7.6; neut. equiv., 143. Found: C, 50.4; H, 4.4; N, 9.8; B, 7.7; neut. equiv., 142.

B. 2-(*p*-Carboxybenzeneazo)-5-diethylaminobenzeneboronic Acid. (1) Preparation of *m*-Diethylaminobenzeneboronic Acid.—A solution of 3.4 g. of *m*-nitrobenzeneboronic acid and 3 ml. of glacial acetic acid in 30 ml. of ethanol was shaken with about 1 ml. of Raney nickel catalyst and filtered into a reduction bottle. After the addition of 3.4 ml. of freshly distilled acetaldehyde and about 0.05 g. of platinum oxide catalyst the mixture was shaken under hydrogen at 2–3 atmospheres pressure for thirty-six hours. The solution was filtered into a Claisen

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(8) Michaelis and Becker, *Ber.*, **13**, 58 (1880); **15**, 180 (1882).

(9) The prefix "borono" is used to designate the boronic acid $[-B(OH)_2]$ group.

flask and concentrated under diminished pressure at room temperature. The residual oil was dissolved in 30 ml. of 10% sulfuric acid, treated with Darco and added slowly to 100 ml. of 15% aqueous sodium bicarbonate. The pink precipitate was dissolved in 5% aqueous sodium hydroxide and treated with Norite. The solution was acidified with 10% sulfuric acid and added to a bicarbonate solution. The nearly white product, after drying *in vacuo* over phosphorus pentoxide, melted at 142–144°. No satisfactory solvent for recrystallization was found. About 0.5 g. of the solid was treated with ammoniacal silver nitrate,[6] and the diethylaniline formed was recovered by steam distillation and identified as the picrate and the chloroplatinate by melting points and mixed melting points.

(2) **Coupling Reaction.**—The diazonium salt solution prepared from 1.8 g. of *p*-aminobenzoic acid in 20 ml. of 3 *N* hydrochloric acid and 0.9 g. of sodium nitrite in 5 ml. of water was added slowly at 0° to 2.5 g. of the diethylaminobenzeneboronic acid in 10 ml. of 3 *N* hydrochloric acid. The resulting mixture was poured with stirring into 15 ml. of 6 *N* sodium hydroxide solution. The precipitate which formed in the deep violet solution was collected and dissolved in 50 ml. of glacial acetic acid. The filtered solution was diluted with 100 ml. of water and the red-brown solid which precipitated was recrystallized from 50% ethanol, yielding 2.9 g. (65%) of the pure substance, m. p. 248–250°.

Anal. Calcd. for $C_{17}H_{20}BN_3O_4$: C, 59.8; H, 5.9; B, 3.2. Found: C, 59.7; H, 5.7; B, 3.3.

C. **Conversion of Benzeneboronic Acid to Benzene by the Action of Cuprous Hydroxide.**—The reducing solution prepared from ammoniacal cupric sulfate[7] and hydroxylamine was mixed with benzeneboronic acid under the conditions of the diphenic acid preparation.[7] The odor of benzene was evident immediately. The hydrocarbon produced from 1 g. of the boronic acid was recovered by steam distillation and treated with nitric and sulfuric acids. The *m*-dinitrobenzene so formed, m. p. 87–89°, was identified by melting point and mixed melting point.

D. **Attempts to Use Mercuriphenyl Derivatives in the Boronic Acid Synthesis.**—No evidence of reaction was observed when a mixture of 8.5 g. of acetoxymercuribenzene and 23 g. of *n*-butyl borate was heated on the steam-bath for one hour. The mixture was heated at 140–150° for three hours and poured into excess 3 *N* hydrochloric acid. Evaporation of ether extracts of the aqueous solution yielded no benzeneboronic acid. Similar results were obtained in experiments in which benzene was used as solvent for the reagents.

A mixture of 8.2 g. of *o*-chloromercuriphenol, 16 g. of *n*-butyl borate and 50 ml. of benzene was heated under reflux for fourteen hours and then poured into excess 6 *N* hydrochloric acid. The organic liquid was removed by distillation and the hot aqueous solution was filtered and cooled. The recovery of *o*-chloromercuribenzene, m. p. 150°, was almost quantitative.

Summary

Several azo dyes containing the boronic acid group have been prepared by the action of diazonium salts on *m*-hydroxybenzeneboronic and *m*-diethylaminobenzeneboronic acids. One such dye has been prepared by coupling diazotized *m*-aminobenzeneboronic acid with *m*-hydroxybenzeneboronic acid. There is no indication of the loss of the boronic acid function during these couplings.

The cuprous hydroxide solution prepared from ammoniacal cupric sulfate and hydroxylamine is an effective reagent for the removal of the boronic acid group from the benzene nucleus.

Attempts to effect reaction between *n*-butyl borate and *o*-chloromercuriphenol or acetoxymercuribenzene have been unsuccessful.

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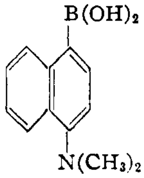
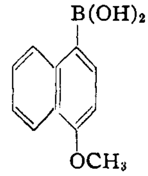
[Contribution from the Noyes Chemical Laboratory, University of Illinois]

Synthesis and Reactions of Some Substituted Naphthaleneboronic Acids

By H. R. Snyder and F. W. Wyman[1]

It has been shown[2] that azoboronic acids can be obtained by coupling of diazonium compounds with *m*-hydroxybenzeneboronic acid and with *m*-diethylaminobenzeneboronic acid. There is no indication of displacement of the boronic acid function in such coupling reactions. In connection with a projected synthesis of boron-containing azo dyes of possible use in physiological studies, it became desirable to determine whether the boronic acid group attached to an aminonaphthyl or alkoxynaphthyl radical might be expected to withstand the conditions of the coupling reaction and other substitutions. It would appear that the most drastic tests of the stability of the boronic acid group in such substances could be made on compounds having the 1,4-orientation. Accordingly, 4-dimethylamino-1-naphthaleneboronic acid (I) and 4-methoxy-1-naphthaleneboronic acid (II) have been prepared for study.


I


II

The boronic acids (I and II) were prepared by the usual method from the Grignard reagents and butyl borate. Each substance melted with decomposition over a range which varied with the rate of heating and with the previous history of the sample. This behavior is characteristic of boronic acids and is to be ascribed to the dehydration of the substances (and their hydrates) to the boron oxides. Satisfactory combustion analyses of the compounds I and II were not attained, because of the varying degree of hydration of the analytical samples and the entrapment of particles of carbon in the glass-like residue of boric oxide

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[2] Snyder and Weaver, This Journal, 69, 232 (1947).