[CONTRIBUTION FROM THE DEPARTMENT OF NEUROSURGERY, MASSACHUSETTS GENERAL HOSPITAL, AND THE HARVARD MEDICAL SCHOOL, BOSTON, MASS.]

Synthesis of Aromatic Diboronic Acids[1]

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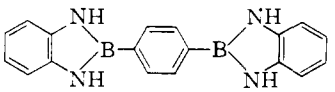
The preparations of several diboronic acids are described. The facile acylation of *o*-aminoboronic acids is observed and a possible mechanism is noted.

Introduction.—Previous studies[2-4] on the synthesis and possible utility of organoboron compounds for the therapeutic treatment of brain tumors by neutron-capture irradiation have pointed to the desirability of preparing compounds containing a higher percentage of boron. The boranes, especially the decaboranes, would meet this requirement; however, the high toxicity[5] of these substances would tend to limit their usefulness.

A second approach was to prepare the benzenediboronic acids[6-8] since the boron percentage in these is approximately 13% compared to 9% for benzeneboronic acid itself. The benzene–aqueous partition coefficient,[9] was determined for benzene-1,4-diboronic acid. It was[10] in excess of 200 compared with a value of 6 for benzeneboronic acid. Whereas benzeneboronic acid acts as a hypnotic,[11] benzene-1,4-diboronic acid was innocuous at comparable doses[10] and also gave much better tumor to brain boron ratios.[10]

On this basis it seemed desirable to prepare derivatives of benzene-1,4-diboronic acid for evaluation in tumor-bearing animals.

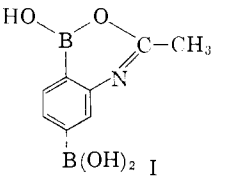
Synthesis and Discussion.—Benzene-1,4-diboronic acid was prepared[6] and its structure was verified by analysis and by reaction with two moles of *o*-phenylenediamine to form a diborimidazoline, a highly insoluble yellow-green crystalline compound with an absorption maximum at 317 mμ. This absorption is at longer wave lengths than that



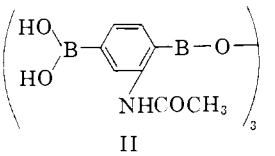
of the unsubstituted 2-phenylborimidazoline.[3] It is indicative of resonance interaction throughout the entire chain length and thus of a B–N double bond contribution to the excited state of the molecule.

The benzene-1,4-diboronic acid was readily nitrated, under the conditions used for preparing *m*-nitrobenzeneboronic acid,[12] to yield 2-nitrobenzene-1,4-diboronic acid. Nitration with a mixture of fuming nitric and concentrated sulfuric acids gave extensive decomposition. This is in contrast to the stability of the boronic acid group in *p*-carboxybenzeneboronic acid under these same conditions.[4]

The nitro compound was reduced catalytically in aqueous methanol to the 2-aminobenzene-1,4-diboronic acid. However, attempts at purification of the compound did not give a product of the expected composition. Difficulties have been encountered in the purification of other compounds containing an amino function *ortho* to the boronic acid moiety, for example 2-amino-4-carboxybenzeneboronic acid. Catalytic reduction of the 2-nitrobenzene-1,4-diboronic acid was effected in aqueous acetic acid, and on concentration of the solution a white crystalline compound was obtained which analyzed for 2-acetamidobenzene-1,4-diboronic acid monoanhydride. The existence of the acetamido function in the molecule was ascertained by deboronation of the product to yield acetanilide The structure of the compound could be either I or II.

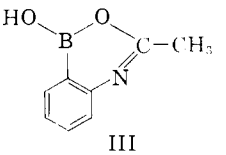


I

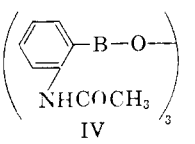


II

If the compound is an anhydride the position of the anhydride group is important. For this purpose *o*-nitrobenzeneboronic acid was reduced under the same conditions and the isolated product analyzed for 2-acetamidobenzeneboronic acid anhydride (III or IV). Thus in the case of the diboronic acid presumably the boronic acid group in



III



IV

the one position is either involved in the cyclic type of structure (I) or in formation of the anhydride (II).

Catalytic reduction of *m*-nitrobenzeneboronic acid in aqueous acetic acid yielded only *m*-aminobenzeneboronic acid. Evidently the ease of acetyl-

(1) This research was supported by U. S. Atomic Energy Commission under contract No. AT(30-1)-1093, and from the National Cancer Institute, U. S. Public Health Service Grant No. C-3174(C2) Rad.

(2) A. H. Soloway, *Science*, **128**, 1572 (1958).

(3) E. Nyilas and A. H. Soloway, THIS JOURNAL, **81**, 2681 (1959).

(4) A. H. Soloway, *ibid.*, **81**, 3017 (1959).

(5) W. H. Hill, G. H. Levinskas and J. M. Merrill, *A.M.A. Arch. Indust. Health*, **17**, 124 (1958).

(6) D. R. Nielsen and W. E. McEwen, THIS JOURNAL, **79**, 3081 (1957).

(7) W. P. Cowie, A. H. Jackson and O. C. Musgrave, *Chemistry & Industry*, 1248 (1959).

(8) O. C. Musgrave, *ibid.*, 1152 (1957).

(9) A value which has proved to be of use in determining the penetration of normal brain. Compounds with low values penetrate the brain readily and have low tumor/brain ratios.

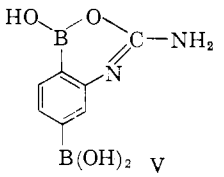
(10) A. H. Soloway, B. Whitman and J. R. Messer, *J. Pharm. and Exper. Therap.*, in press.

(11) F. Canjolle, P. Gayel, G. Roux and C. Moscarella, *Bull. Acad. Natl. Med.*, **135**, 314 (1951).

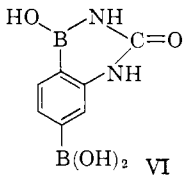
(12) W. Seaman and J. R. Johnson, THIS JOURNAL, **53**, 711 (1931).

ation is dependent upon the proximity of the amino and boronic acid. Possibly anhydride formation occurs between the boronic acid group and acetic acid when the solution is concentrated and this undergoes intramolecular acylation. The fact that *m*-aminobenzeneboronic acid exists not as the anhydride but in the free boronic acid state would be evidence against structures II and IV since *o*-substituents would not be considered to aid anhydride formation.

This acylation does not occur at room temperature in the dilute aqueous solution for the reduced product behaves as the free amine. After reduction of 2-nitrobenzene-1,4-diboronic acid, the amine was allowed to react *in situ*, without prior isolation, with potassium cyanate to form the ureido compound. As with the acetylamino derivative, the ureido compound probably exists in a cyclic structure as either V or VI. This is what would be expected from the carbon and hydrogen analysis.



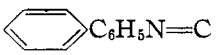
V



VI

Molecular weight determinations would differentiate between structures I and II, III and IV, and V or VI and a dimeric or trimeric anhydride but the insolubility of these compounds in nonaqueous solvent prevented the obtaining of this information.

The infrared spectra of such cyclic boron compounds have not been fully worked out so as to permit definite assignment of structure, for example, between I and II. This compound in a Nujol mull shows a series of sharp peaks at 1639, 1540 and 1494 cm.$^{-1}$ and broad bands at 2875, 1600, 1450, 1380, 1220, 1090 and 840 cm.$^{-1}$. The absorption at 1639 might be attributable to the amide I band; however, the carbonyl in anilides usually absorbs at higher frequencies. This peak could be indicative of the structure



It has been reported[13] that indolenines do show a strong band in the region of 1639–1600 cm.$^{-1}$. There is also a very strong band at 1600 cm.$^{-1}$ which could result from conjugation of the C=N with the aromatic system producing an intensification of the third aromatic band in this region. However, the peak at 1540 cm.$^{-1}$ is the position of the amide II absorption in a number of N-mono substituted amides. Nevertheless such a conjugated cyclic system as structure I cannot be considered in terms of individual bands, but it is preferable to consider the structure as a group of absorptions. The peak at 1540 cm.$^{-1}$ may be typical of such a conjugated cyclical structure. The intense broad band at 1380 cm.$^{-1}$ can be ascribed to the boronic acid moiety; such a band in the region of 1400–1300 cm.$^{-1}$ has been seen in many alkyl- and arylboronic acids. From spectral evidence it is not possible to decide definitely between structures I and II and between III and IV, but the cyclic structures certainly have not been eliminated.

The infrared spectra of 2-ureido-benzene-1,4-diboronic acid monoanhydride show sharp peaks at 2900, 1565 and 1515 cm.$^{-1}$ and broad absorption bands at 3225, 1665, 1440, 1340, 1230, 1080 and 820 cm.$^{-1}$. The broad band at 1665 cm.$^{-1}$ is very intense and does not appear in 2-acetamido-benzene-1,4-diboronic acid monoanhydride. The carbonyl absorption of a number of disubstituted ureas of the type R–NHCONHR absorb in the region of 1660 cm.$^{-1}$ and this would favor structure VI.

However monosubstituted ureas also show a band in this region as well. Broad bands in the region of 1340 and 1080 tend to obscure any confirmatory evidence for the presence of the B–N link.[3] In conclusion, no definitive statements concerning different structures can be made based on the infrared spectra.

Experimental[14]

The preparation of benzene-1,4-diboronic acid was essentially by the method of Nielsen and McEwen[6] utilizing the dimagnesium Grignard compound of *p*-dibromobenzene. *o*-Nitrobenzeneboronic acid was prepared in a manner previously described.[12]

Benzene-1,4-bis-(2′-borimidazoline).—Benzene-1,4-diboronic acid was prepared[6] and an analytical sample was obtained by successive recrystallization from water. It melted in excess of 350°.

Anal. Calcd. for $C_6H_8B_2O_4$: C, 43.47; H, 4.87. Found: C, 43.74; H, 4.83.

A solution of 1.66 g. of benzene-1,4-diboronic acid, 2.16 g. of *o*-phenylenediamine in 50 ml. of diethylene glycol dimethyl ether was refluxed for a period of one hour. As the solution began to reflux, crystalline material began to separate. At the end of the specified time, the solution was concentrated to half its volume, cooled and filtered. The yield was 2.18 g. of a yellow-green crystalline solid, m.p. >350°, which was extremely insoluble in the usual solvents. Consequently, the analysis was performed upon material which had been extracted with the diethylene glycol dimethyl ether to remove any unreacted starting material.

Anal. Calcd. for $C_{18}H_{16}B_2N_4$: N, 18.08. Found: N, 17.95.

2-Nitrobenzene-1,4-diboronic Acid.—To a solution of 15 ml. of fuming nitric acid, sp. gr. 1.50, was added a few crystals of urea. The temperature was cooled to −15° and 5 g. of powdered, dry benzene-1,4-diboronic acid was added at such a rate that the temperature did not rise above −10°. The mixture was stirred and maintained at this temperature for 10 minutes. It then was poured on ice with a small amount of water, filtered, washed with water and dried. The product was recrystallized from water and yielded 3.8 g. of light yellow solid, m.p. >350°. An analytical sample was obtained by successive recrystallizations from water.

Anal. Calcd. for $C_6H_7B_2NO_6$: C, 34.19; H, 3.35. Found: C, 34.40; H, 3.52.

2-Acetamidobenzene-1,4-diboronic Acid Monoanhydride.—Into a mixture of 40 ml. of glacial acetic acid and 20 ml. of water was suspended 4.0 g. of 2-nitrobenzene-1,4-diboronic acid and 100 mg. of platinum oxide (Adams catalyst). The solution was reduced catalytically until the uptake of hydrogen was complete. The mixture was filtered to remove the catalyst and concentrated under reduced pressure with frequent additions of water to aid in the distillation of acetic acid. The solution was cooled, filtered, washed and dried, yielding 1.6 g. of solid, m.p. >350°. Long white needles were obtained upon successive recrystallization from water.

(13) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954.

(14) Melting points are uncorrected and were obtained by capillary tube.

The product was dried at 100° for 6 hr. under vacuum and then analyzed.

Anal. Calcd. for $C_8H_9B_2NO_4$: C, 46.91; H, 4.42. Found: C, 47.23; H, 4.72.

A suspension of 210 mg. of this acetamido compound in 3 ml. of ammoniacal silver nitrate[15] was warmed on a hot-plate to effect solution. After standing for several minutes, a solid product began to crystallize, admixed with finely divided silver. The crystalline material was dissolved by warming, and the solution was treated with charcoal, filtered and cooled. The mixture was filtered, washed and dried, yielding 50 mg. of material, m.p. 110–112°. A mixed melting point of this product with acetanilide showed no depression.

2-Ureidobenzene-1,4-diboronic Acid Monoanhydride.—A suspension of 4.0 g. of 2-nitrobenzene-1,4-diboronic acid and 100 mg. of platinum oxide in a solution of 30 ml. of glacial acetic acid and 30 ml. of water was reduced catalytically. After the uptake of hydrogen was completed, the solution was filtered to remove the catalyst and the amine was converted to the urea without prior isolation of the amine. To the acetic acid solution 3.3 g. of potassium cyanate in 10 ml. of water was added. The solution was stirred, warmed to 40° and allowed to stand for 0.5 hour. The mixture was cooled, filtered, washed and dried to yield 2.1 g. of a white crystalline solid, m.p. >350°. A sample for analysis was obtained by recrystallization twice from methanol–water.

Anal. Calcd. for $C_7H_8B_2N_2O_4$: C, 40.85; H, 3.91. Found: C, 40.99; H, 4.16.

A solution of 300 mg. of the ureido compound in 5 ml. of ammoniacal silver nitrate[15] was prepared by warming the mixture on a hot-plate. The solution was heated for 10 min., treated with charcoal, filtered and cooled. A precipitate of 77 mg. was obtained which showed no melting point depression with phenylurea.

2-Acetamidobenzeneboronic Acid Anhydride.—A suspension of 5 g. of *o*-nitrobenzeneboronic acid in 50 ml. of 50% acetic acid was reduced catalytically in the presence of 200 mg. of platinum oxide. After the absorption of hydrogen was complete, the solution was filtered and concentrated under reduced pressure with frequent additions of water in order to remove the acetic acid. The concentrated aqueous solution upon cooling yielded 2.5 g. of a white crystalline solid, m.p. 298–300°. A sample for analysis was successively recrystallized from methanol–water; m.p. 300–301°.

Anal. Calcd. for $C_8H_8BNO_2$: C, 59.68; H, 5.01. Found: C, 59.14; H, 5.48.

A suspension of 200 mg. of *o*-acetamidobenzeneboronic acid anhydride in 3 ml. of 10% ammoniacal silver nitrate[15] was warmed until the solid completely dissolved. The solution was filtered while hot to remove any finely divided silver. Upon crystallization, 77 mg. of acetanilide was obtained.

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(15) One gram of silver nitrate was dissolved in 8 ml. of water and this was diluted to 10 ml. with 28% aqueous ammonia.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

The Formation of Trianisylmethylcarbonium Ion by the Interaction of Tetraanisylethylene with Electron Acceptors[1]

BY ROBERT E. BUCKLES, RONALD E. ERICKSON,[2] JOHN D. SNYDER[3] AND WILLIS B. PERSON

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When tetraanisylethylene (I) interacted with various electron acceptors, a characteristic blue (λ_{max} around 575 mμ) solution was usually observed. On standing, dilute solutions (10^{-3} *M* or less) of this blue complex gradually turned yellow (λ_{max} around 490 mμ). The yellow absorbing species in these solutions has been identified as trianisylmethylcarbonium ion (II) on the basis of its visible absorption spectrum. When a relatively large volume of a solution (5×10^{-3} *M*) of I in ethylene chloride was allowed to react with an equimolar amount of chlorine for two days a 22% yield of 4′-methoxy-2,2,2-trianisylacetophenone (III) could be isolated. This pinacolone on interaction with electron acceptors also gave solutions of II. These solutions could be prepared with higher concentrations than those possible starting with I. With these more concentrated solutions identification of II by means of infrared absorption spectroscopy was possible. The relative intensities of ten absorption bands in the infrared spectra of various model compounds and in the infrared spectra of the solutions under investigation were compared in order to establish the identification.

An earlier report[4] described in detail the changes in the ultraviolet and visible absorption spectrum observed when tetraanisylethylene (tetrakis-(*p*-methoxyphenyl)-ethylene) (I) interacted with bromine in ethylene chloride. In the present investigation the same general behavior was observed when Compound I interacted with a number of other electron acceptors. First a blue solution with a broad absorption peak around 575 mμ was observed. On standing, this blue solution slowly turned yellow if the concentration of I was of the order of 10^{-3} *M* or less. This yellow solution was characterized by an absorption peak around 490 mμ. In more concentrated solutions either the change to the yellow solution was incomplete or side reactions such as halogenation became important so that the yellow absorbing species was still formed only in relatively low concentrations.

Representative electron acceptors which were observed to give this interaction with I are listed in Table I along with the wave length characteristic of the absorption peak of the final yellow solution. In each case except for that of iodine in ethylene chloride the electron acceptor interacted with I to give a blue solution (λ_{max} around 575 mμ), which slowly turned yellow on standing. The molar absorbancy index (molar extinction coefficient) of the peak near 490 mμ, based on the initial concentration of I, was found to be as high as 5×10^4 in some experiments involving iodine chloride,

(1) This investigation was sponsored in part by the Office of Ordnance Research, U. S. Army. The determination of infrared data was aided by a grant from the National Science Foundation.

(2) Monsanto Predoctoral Fellow, 1957–1958.

(3) Du Pont Predoctoral Fellow, 1957–1958.

(4) R. E. Buckles and W. D. Womer, THIS JOURNAL, **80**, 5055 (1958).