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A synthesis of a homologous series of aryl mono- and diboronic acids

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A SYNTHESIS OF A HOMOLOGOUS SERIES OF ARYL MONO- AND DIBORONIC ACIDS

A Thesis
Presented to
the Faculty of the School of Pharmacy
The University of the Pacific

In Partial Fulfillment
of the Requirements for the Degree
Master of Science

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by
Larry Milton Allen
July 1967

This thesis, written and submitted by

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is approved for recommendation to the

Graduate Council, University of the Pacific.

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O. H. Roscoe

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Dated July 27, 1967

ACKNOWLEDGMENT

I wish to express my sincere appreciation to Dr. Charles W. Roscoe for his guidance and assistance in directing this investigation. I am also gratefully indebted to the Gustavus and Louise Pfeiffer Research Foundation for financial assistance.

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CHAPTER I

INTRODUCTION

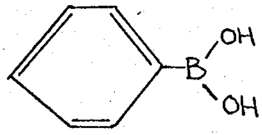
Many attempts have been made to prepare aryl boronic acids and their esters which show a preferential affinity for tumor tissue for use in radiation therapy of neoplastic disorders (1,2). The data of Soloway, as extended and refined by Hansch and his coworkers, successfully correlates the low lipid solubility and electron releasing substituents of phenyl boronic acid derivatives with increased tumor concentration (3,4,5). However, most of these organoboron compounds do not produce a sufficiently high tumor-to-normal tissue boron concentration ratio for practical use in human cancer chemotherapy by the neutron capture technique.

The knowledge that several chemical substances are preferentially taken up by tumor tissue provides the medicinal chemist the opportunity of rationally designing potential tumor inhibiting compounds linked to these carrier molecules (6,7). For the initial phase of attempts to successfully combine boronic acids or their esters with tumor concentrating material, it was deemed desirable to prepare a homologous series of aryl mono- and diboronic acids.

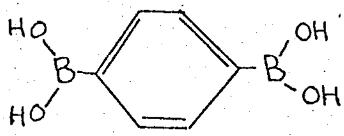
From the respective mono- or dibromo benzene, naphthalene, and anthracene derivatives (see figure 1, page 4), aryl mono- or diboronic acids were prepared by means of the Grignard reaction (see figure 2, page 5), according to the method of Nielsen and McEwen (8). The synthesis of anthracene-9,10-diboronic acid was unsuccessful although attempted by six different methods. Anthracene-9-boronic acid has been isolated previously as a side product from the synthesis of di-9-anthracylborinic acid (9), but its direct synthesis was unsuccessful in this laboratory. Naphthalene-1,4-diboronic acid, an apparently new aryl boronic acid, was successfully synthesized. For the remaining boronic acids, phenyl boronic acid is available commercially (Aldrich); benzene-1,4-diboronic acid (8) and naphthalene-1-boronic acid (10,11,12,13) have been prepared previously. The synthesis of the latter two was repeated here in order to have suitable reference compounds on hand.

The most useful derivatives for characterization of the boronic acids were the esters prepared from 2,2-dimethyl-1,3-propanediol (neopentyl glycol) and 2,2'-iminodiethanol (diethanolamine) (see figure 3, page 6; figure 4, page 7). Most ester derivatives of boronic acids seem appreciably unstable in the presence of water (30). However the diethanolamine derivative, sometimes referred to as a boroxazolidine (15), was quite stable in the presence of water and has actually been prepared in aqueous ethanol (17) and even water (14).

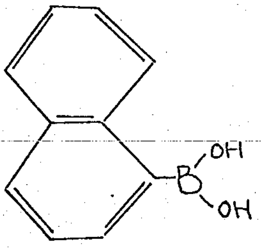
The unusual hydrolytic stability of the boroxazolidine was the foundation for formulating this boronic acid ester as a bicyclic structure with a transannular coordination bond between nitrogen and boron (19) (see figure 4, page 7). These bicyclic coordination compounds were first referred to by Weidman and Zimmerman (15,16), after an earlier suggestion of H. C. Brown (19), as diptych boroxazolidines. Examination of the infrared spectra of the boroxazolidines by many workers has produced good but not conclusive evidence for the N→B coordination (16,20, 21,22,23,24). Infrared spectral assignments for all the boroxazolidines prepared here agree quite well with those of previous workers for N→B coordination (dative bond).



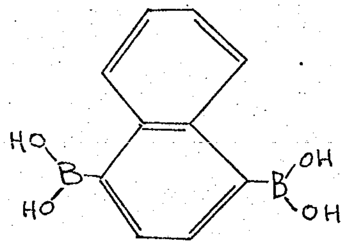
Phenylboronic Acid



Benzene-1,4-Diboronic Acid



Naphthalene-1-Boronic Acid



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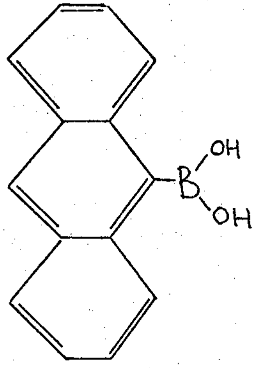
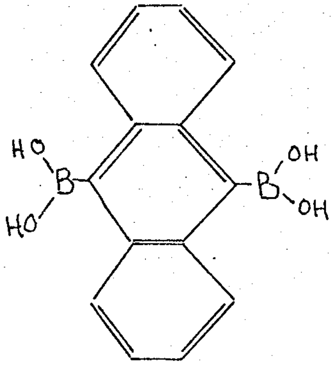


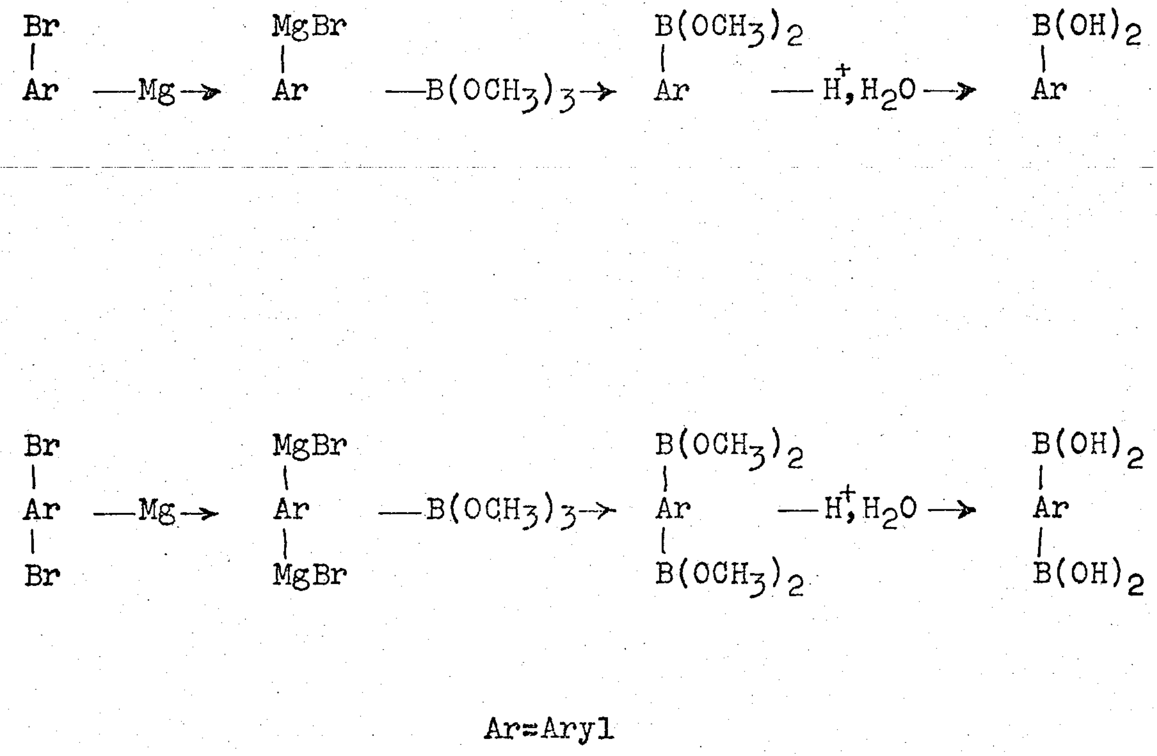
Anthracene-9-Boronic Acid



Anthracene-9,10-Diboronic Acid

FIGURE 1

HOMOLOGOUS SERIES OF ARYL MONO- AND DIBORONIC ACIDS



$$\underset{\text{Ar}}{\overset{\text{Br}}{|}} \xrightarrow{\text{Mg}} \underset{\text{Ar}}{\overset{\text{MgBr}}{|}} \xrightarrow{\text{B(OCH}_3)_3} \underset{\text{Ar}}{\overset{\text{B(OCH}_3)_2}{|}} \xrightarrow{\overset{+}{\text{H}},\text{H}_2\text{O}} \underset{\text{Ar}}{\overset{\text{B(OH)}_2}{|}}$$

$$\text{Br-Ar-Br} \xrightarrow{\text{Mg}} \text{BrMg-Ar-MgBr} \xrightarrow{\text{B(OCH}_3)_3} (\text{CH}_3\text{O})_2\text{B-Ar-B(OCH}_3)_2 \xrightarrow{\overset{+}{\text{H}},\text{H}_2\text{O}} (\text{HO})_2\text{B-Ar-B(OH)}_2$$

FIGURE 2

GRIGNARD SYNTHESIS OF ARYL MONO-
AND DIBORONIC ACIDS

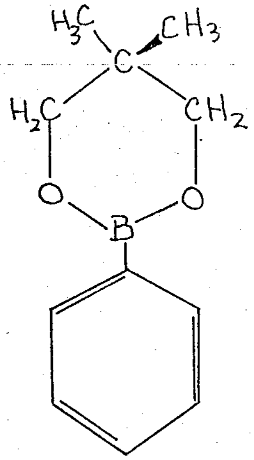


FIGURE 3

NEOPENTYL GLYCOL ESTER OF AN
ARYL BORONIC ACID

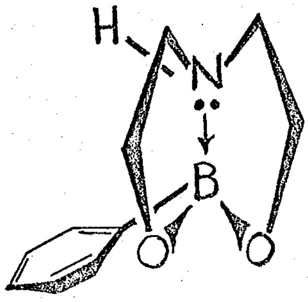


FIGURE 4

ILLUSTRATION OF THE NITROGEN-BORON
TRANSANNULAR COORDINATION IN
A DIPTYCH BOROXAZOLIDINE

CHAPTER II

REAGENTS AND MATERIALS

1. Anhydrous tetrahydrofuran was freshly prepared by distillation of commercial tetrahydrofuran previously dried with lithium aluminum hydride.
2. Unless otherwise stated, all melting points are uncorrected as determined on a Fisher Johns melting point apparatus.
3. Infrared spectra of all boronic acids and their derivatives were taken from potassium bromide pellets with a Beckman IR-5A or Perkin Elmer 337 infrared spectrophotometer.
4. All samples for elemental analysis were dried to constant weight _in vacuo_ over phosphorous pentoxide without heat.
5. Organic microanalyses were done by Galbraith Laboratories, Inc., Knoxville, Tennessee.
6. The attempted gas chromatographic analysis was performed with an Aerograph Autoprep Model A-700 gas chromatograph equipped with a 3/8" x 10' aluminum column packed with 30% silicon gum rubber (SE30) on 70/80 mesh, acid washed dimethyl-dichlorosilane (DMCS) white diatomaceous earth (Chromosorb W). The column temperature was maintained at 300°C. and the helium

flow rate at 200 ml./min.

7. n-Butyl lithium was standardized by titrating five aliquots (0.1 ml. each) with 0.0155N HCl to the methyl orange end-point.

8. The Beilstein test and Michler's thioketone test were used to detect bromine as described by Feigl (35).

CHAPTER III

EXPERIMENTAL

I. Benzene-1,4-Diboronic Acid

The procedure was essentially that of Nielsen and McEwen (8). p-Dibromobenzene, 73.4 g. (0.3 mole), was dissolved in 500 g. of freshly distilled anhydrous tetrahydrofuran. The tetrahydrofuran solution was added dropwise over a period of one hour to 14.9 g. (0.6 mole) of magnesium turnings under nitrogen in a 2-liter, 4-neck flask equipped with condenser and stirrer. The Grignard reaction did not proceed immediately at room temperature but proceeded vigorously after the addition of a few crystals of iodine. Once the reaction subsided, the mixture was slowly warmed to 65°C. and refluxed for ten hours. After refluxing, the reaction mixture was cooled to room temperature and finally to -60°C. in a dry ice-acetone bath. Trimethyl borate, 54 g. (0.6 mole), was transferred in a dry nitrogen atmosphere to a 125-ml. dropping funnel and then added dropwise to the cold, well stirred, Grignard product over a period of one-half hour. The thick gray mixture was slowly warmed to room temperature overnight, cooled to 0°C. in an ice bath, and finally hydrolyzed with 1N HCl until the mixture gave an acidic reaction to litmus (approximately 150 ml.).

After decomposition of the excess magnesium was complete, the clear solution was extracted with 250 ml. of ether and then extracted successively with 125-ml. and 75-ml. portions of ether. The combined ether extracts were dried overnight over anhydrous magnesium sulfate.

The dry ethereal solution was filtered and the ether removed by distillation. The large white crystals were dissolved in 6 liters of hot water. The resulting solution was filtered, concentrated to 3 liters, and set aside to allow for crystallization. The cooled filtrate yielded white fluffy crystals which, after washing with 25 ml. of hot water and air-drying, weighed 20.9 g. (42% yield). Nielsen and McEwen reported a 35% yield (8). The substance had no detectable melting point below 300°C. and gave a negative test for organic bromide (see page 9). A summary of its infrared spectrum appears in Table II, page 30.

Bis (2,2-Dimethyl-1,3-Propanediol) Benzene-1,4-Diboronate

This useful ester derivative (see figure 4, page 7) was prepared by the method of Musgrave (24). Benzene-1,4-diboronic acid, 0.4765 g. (0.0029 mole), and 2,2-dimethyl-1,3-propanediol, 0.6296 g. (0.006 mole), were dissolved in 65 ml. of benzene. The water was removed as the benzene-water azeotrope and collected in a Dean-Stark type trap.

The solution was concentrated to 30 ml. and set aside in the refrigerator overnight. The crystals were collected by filtration, washed with 2 ml. of cold methanol, air dried, and stored in a desiccator overnight. This gave 0.6525 g. (72% yield) of bis (2,2-dimethyl-1,3-propanediol) benzene-1,4-diboronate with a melting point of 233°C. Musgrave (24) reported a melting point of 233-233.5°C.

Bis (2,2'-Iminodiethanol) Benzene-1,4-Diboronate

The method described above, which is essentially the same as that reported by Washburn (18), was employed for the preparation of the diethanolamine ester of benzene-1,4-diboronic acid. Bis (2,2'-iminodiethanol) benzene-1,4-diboronate was obtained in a yield of 95%. The ester did not melt below 300°C. Washburn (18) reported a yield of 99% and stated that the ester is thermally stable up to about 295°C., where it starts to slowly decompose without melting.

II. Naphthalene-1-Boronic Acid

The procedure of Nielsen and McEwen (8) was repeated starting with 1-bromonaphthalene. Naphthalene-1-boronic acid has been previously prepared by Hawthorne (10), Washburn and Albright (11), and others (12,13).

A solution of 1-bromonaphthalene, 51.77 g. (0.25

mole), in 400 ml. of freshly distilled anhydrous tetrahydrofuran was added dropwise over a period of one hour to 9.12 g. (0.35 mole) of magnesium turnings under nitrogen in a 2-liter, 4-neck flask equipped with condenser and stirrer. The reaction proceeded very rapidly at room temperature and required cooling with an ice bath in order to moderate the reaction. When the reaction began to subside, it was slowly warmed to 65°C. and refluxed for eighteen hours during which time the reaction mixture slowly darkened. The slurry was cooled to room temperature and then to -60°C. in a dry ice-acetone bath. To the cold, thick gray mass 30 ml. (0.25 mole) of trimethyl borate in 65 ml. of dry tetrahydrofuran was added dropwise within one-half hour. The thick slurry was slowly warmed to room temperature overnight, then cooled to 0°C. and hydrolyzed by addition of 1N HCl until the mixture gave an acidic reaction to litmus (250 ml.). The resulting clear solution was extracted successively with 250-ml., 125-ml., and 50-ml. portions of ether. The combined ether extracts were dried overnight over anhydrous magnesium sulfate. The dry ethereal solution was filtered and the ether removed by distillation. The solid brown residue was suspended in 5 liters of boiling water, and the mixture was filtered. The filtrate was concentrated to one-half its volume and set aside to allow for crystallization. The product was collected by suction filtration and air dried. The fluffy white crystals weighed 17 g. (40% yield) and melted at 213°C. Washburn and Albright (11) reported a yield of 37.5% and a melting point of 208-9°C.

2,2-Dimethyl-1,3-Propanediol Naphthalene-1-Boronate

The method of Musgrave (24) was repeated with neopentyl glycol to prepare a new ester derivative of this boronic acid. Naphthalene-1-boronic acid, 0.1720 g. (0.001 mole), and 2,2-dimethyl-1,3-propanediol, 0.1042 g. (0.001 mole), were dissolved in 30 ml. of benzene and slowly brought to reflux. After water was removed as the azeotrope, the solution was concentrated to 5 ml. and set aside in the cold overnight to effect crystallization. The white crystals were collected by filtration, washed with a few drops of cold methanol, then air dried. This gave 0.2305 g. (96% yield) of the ester melting at 68-68.5°C.

Calculated for $C_{15}H_{17}BO_2$ (M.W. 240.10): 75.03% C; 7.14% H

Found: 74.92% C; 7.16% H

2,2'-Iminodiethanol Naphthalene-1-Boronate

Naphthalene-1-boronic acid, 1.7199 g. (0.01 mole), and 2,2'-iminodiethanol, 1.051 g. (0.01 mole), were added to 600 ml. of benzene and warmed to boiling. Water was removed as the azeotrope and the benzene solution was concentrated to 300 ml. and set in the refrigerator overnight to allow for crystallization. This afforded 1.8628 g. (77.5%) of the boroxazolidine with a melting point of 236°C. When this material was recrystallized from absolute ethanol the melting point was 244°C. Letsinger and Skoog reported a yield of 88% and a melting point of 242-3°C. (17).

III. Naphthalene-1,4-Diboronic Acid

The method of Nielsen and McEwen (8) was used, starting with 1,4-dibromonaphthalene. The first attempt to isolate the diboronic acid from side products by fractional distillation of the bis (di-n-butyl) naphthalene-1,4-diboronate under reduced pressure (0.2 mm.) gave no distillate and a considerable amount of decomposition. Consequently, the Grignard reaction was repeated and the diboronic acid successfully recovered by solvent extraction.

A solution of 1,4-dibromonaphthalene, 22.9 g. (0.08 mole), in 240 ml. of freshly distilled anhydrous tetrahydrofuran was added dropwise to 4.86 g. (0.2 mole) of magnesium turnings under nitrogen in a 2-liter, 4-neck flask equipped with condenser and stirrer. No reaction occurred after addition of 40 ml. of the tetrahydrofuran solution. It was necessary to initiate the reaction by adding a few crystals of iodine and warming the solution to 45°C. After initiation the reaction continued smoothly and the remaining 200 ml. of solution was added over a period of one-half hour. The reaction was allowed to continue for another one-half hour then slowly warmed to 65°C. and allowed to reflux for twelve hours. A darkening and thickening of the reaction mixture was observed. The dark, olive-green slurry was cooled to room temperature, then to -65°C. in a dry ice-acetone bath. Trimethyl borate, 30 ml. (0.25 mole), and 75 ml. of dry tetrahydrofuran were transferred in a dry nitrogen atmosphere to a 125-ml. dropping funnel. This trimethyl borate solution was added slowly over a period of ninety minutes to the cold, well stirred, light-green mixture. The thick, now gray, slurry was allowed to warm to room temperature overnight. The mixture was then cooled to 0°C. in an ice bath, and hydrolyzed with 200 ml. of 1N HCl. The clear, light-green solution was allowed to sit overnight to allow for decomposition of the excess magnesium turnings. The dilute acidic tetrahydrofuran solution was extracted twice with 100-ml. portions of ether, then once again with 50 ml. of ether. Each ether extract was washed with 50 ml. of water, and the combined ether extracts were then dried overnight over anhydrous magnesium sulfate.

A dark brown resinous fluid was recovered after filtration of the extracts and removal of the ether by distillation. This was dissolved in 20 ml. of hot methanol, diluted with 2 liters of hot 1N HCl, and filtered twice through charcoal. The filtrate was concentrated to one-half its volume, then set aside in the refrigerator to allow for crystallization. The crystals were recovered by filtration and air dried. The dry, light-gray crystals weighed 6.481 g. (37.6% yield) and had no detectable melting point below 350°C. The solubility was determined by placing aliquots of 10 mg. in a number of 5-ml. test tubes and adding 50 microliters of various solvents and solvent combinations (see Table I).

Two milliliters each of benzene and glacial acetic acid were added to 400 mg. of the previously recovered crystals. The solution was warmed, rapidly filtered by suction, and the crystals were washed with cold hexane. After drying overnight and *in vacuo* at 70°C. for two hours, 70% of the white powdery product was recovered. This substance still gave no detectable melting point below 350°C. The test with Michler's thioketone for organic bromide was negative (see page 9). Gas chromatography (see page 8) of the bis (diethyl) ester, prepared by dissolving the diboronic acid in benzene and ethanol followed by removal of the benzene-ethanol-water ternary azeotrope, was unsuccessful. The ester did not pass through the column in four hours after injection of a two microliter sample.

TABLE I

RELATIVE SOLUBILITY OF NAPHTHALENE-1,4-DIBORONIC ACID*

SOLUBLE	SOLUBLE ON WARMING	INSOLUBLE
Methanol	Acetone	Pet. Ether
Ethanol	Acetone-Water	Benzene
Ether		Carbon Tetrachloride
Tetrahydrofuran		Chloroform
Dioxane		Acetone-Pet. Ether
Benzene-Ethanol (slowly)		Benzene-Ether
		Benzene-Glacial Acetic

*10 mg. to 50 µl. of solvent

Calculated for $C_{10}H_{10}B_2O_4$ (M.W. 215.81):

55.66% C; 4.67% H; 10.02% B

Found:

55.41% C; 4.77% H; 9.80% B

Bis (2,2-Dimethyl-1,3-Propanediol) Naphthalene-1,4-Diboronate

Naphthalene-1,4-diboronic acid, 0.1079 g. (0.0005 mole), and 2,2-dimethyl-1,3-propanediol, 0.1082 g. (0.00125 mole), were dissolved in 15 ml. of benzene with stirring and heating. After fifteen minutes the reactants were all dissolved and the water was removed as azeotrope. The solution was concentrated to 5 ml. and set aside overnight to allow for crystallization. It was necessary to concentrate the solution further, nearly to dryness, before the ester would crystallize in the cold. This gave 0.132 g. (75% yield) of white crystals. After recrystallization from methanol the crystals were air dried and finally stored in a desiccator overnight. This ester melted at 145.5-147.5°C. on a Kofler Micro Hot Stage.

Calculated for $C_{20}H_{26}B_2O_4$ (M.W. 352.05): 68.23% C; 7.44% H

Found: 68.49% C; 7.48% H

Bis (2,2'-Iminodiethanol) Naphthalene-1,4-Diboronate

The previous technique of using benzene to remove water as the azeotrope during the formation of the boronic acid esters was found unsuitable in this case because both the diboronic acid and its diboroxazolidine were insoluble in hot benzene. Consequently, a modification of the method of Letsinger and Skoog was used to effect esterification (17).

Naphthalene-1,4-diboronic acid, 0.1086 g. (0.0005 mole), and diethanolamine, 0.1314 g. (0.00125 mole), were dissolved in a mixture of 10 ml. absolute ethanol and 1 ml. water. The solution was concentrated to 1 ml. and set aside in the cold to allow for crystallization. Collection of the product by filtration, recrystallization from ethanol, and drying _in vacuo_ with P_2O_5 for two days gave 0.1151 g. (65% yield) of very hydroscopic white crystals. This diboroxazolidine slowly melted at 231°C. with decomposition on a Kofler Micro Hot Stage (1°C./3 min. near the melting point).

Calculated for $C_{18}H_{24}B_2O_4N_2$ (M.W. 354.03):

61.07% C; 6.84% H; 7.92% N

Found:

60.86% C; 7.04% H; 7.87% N

IV. Anthracene-9-Boronic Acid

Dodson and Fisher have reported isolating anthracene-9-boronic acid as a product of the dilute acid hydrolysis of di-9-anthracylborinic acid (9). An attempt at direct synthesis of anthracene-9-boronic acid in this laboratory has met with failure.

A solution of 9-bromoanthracene, 12.86 g. (0.05 mole), in 225 ml. of freshly distilled anhydrous tetrahydrofuran and 3.5 ml. (0.05 mole) of ethyl bromide as entrainer was added to a refluxing slurry of 3.65 g. (0.15 mole) magnesium powder (40 mesh) in 50 ml. dry tetrahydrofuran. The rate of addition throughout the reflux period was kept at one drop per three seconds so that the entrainer agent would cleanse and activate the magnesium surfaces (25,26). After approximately ten minutes the Grignard reaction slowly began, showing darkening of the reaction mixture from gold to amber to dark brown. After twenty-four hours the reaction mixture was slowly cooled to 0°C. in an ice bath, then to -65°C. in a dry ice-acetone bath. Trimethyl borate, 15 ml. (0.13 mole), in 100 ml. of dry tetrahydrofuran was added within one-half hour to the well cooled Grignard solution. When the reaction mixture had warmed overnight to room temperature it was poured onto 100 g. of ice in 100 ml. of 1N HCl. After decomposition of the excess magnesium, the aqueous solution was extracted with 100 ml. of ether, then three times more with 50-ml. portions of ether. The ether extracts were combined and washed twice with 50-ml. portions of water. The washed ether solution was dried by filtration through anhydrous sodium sulfate into a 500-ml. round bottom flask, and the ether was removed by distillation.

The sticky orange residue remaining after removal of the ether was divided into three portions. From one portion the diethyl ester was prepared by adding equal parts of absolute ethanol and benzene, followed by removal of water through azeotropic distillation. An attempt to fractionally distill this ester yielded a dull yellow sublimate that collected (at 0.15 mm., 180°C.) on the upper walls of the distillation flask. The sublimate, 0.5 g., afforded colorless crystals after two crystallizations from benzene. This was identified as anthracene from its infrared spectrum and melting point (211°C. on a Kofler Micro Hot Stage). The sublimand gave an infrared spectrum which strongly suggested the presence of some aliphatic or aryl boronic acid (see Table III, page 31). Sublimation of this material (at 0.12 mm., 150°C.) gave a light yellow sublimate which, after recrystallization from benzene, was identified as anthracene by its melting point (210°C.). No further attempts were made to process the resinous material.

The remaining two portions of the ether extracts were dissolved in 3 liters hot water and hot dilute sodium hydroxide, respectively. After concentration to 500 ml., these solutions yielded the sticky resinous material once again.

V. Anthracene-9,10-Diboronic Acid

In a 2-liter, 4-neck flask equipped with stirrer, condenser, thermometer, and side flask for transferring solids, 25.2 g. (0.075 mole) of 9,10-dibromoanthracene was dissolved in 500 ml. of dry tetrahydrofuran under nitrogen. When this slurry was cooled to 20°C., a few (two) magnesium turnings were added from the 125-ml. erlenmeyer side flask. As no reaction was observed after ten minutes, the tetrahydrofuran solution was then warmed to 40°C. and a few more magnesium turnings were added. All the dihalide dissolved after one-half hour and it appeared that the Grignard reaction had started. The remaining magnesium turnings, 3.89 g. (0.15 mole), were slowly added within twenty hours to the vigorously refluxing mixture. This solution was cooled to room temperature, then to -60°C. in a dry ice-acetone bath. Trimethyl borate, 16.6 g. (0.16 mole), dissolved in 50 ml. of dry tetrahydrofuran was added dropwise over a period of one hour to the well cooled Grignard solution. After another hour the reaction mixture was allowed to warm to room temperature. This solution was hydrolyzed by addition of 125 ml. of ice cold 1N HCl. The solution was extracted three times with 50-ml. portions of ether. The combined ether extracts were washed three times with 50-ml. portions of water and dried over anhydrous magnesium sulfate. Distillation of the ether left a bright yellow residue. This was recrystallized twice from benzene and identified as 9,10-dibromoanthracene, 21.7 g. (86% yield), by its infrared spectrum and melting point (223-4°C.).

This experiment was repeated with the same quantities of material but with a reversed order of addition. The magnesium turnings were added to the dry tetrahydrofuran solution before the 9,10-dibromoanthracene was added from the side flask. After a thirty-six hour reflux period, addition of trimethyl borate, subsequent hydrolysis, and ether extraction in the usual manner, the Grignard reaction gave 22 g. (87% yield) of 9,10-dibromoanthracene.

The Grignard reaction was attempted a third time using the entrainer technique and pulverized magnesium turnings (25,26,27). Ethyl bromide as entrainer, 10 ml. (0.13 mole), and iodine (1 mg.) were dissolved in 85 ml. dry tetrahydrofuran. This solution was added slowly (1 drop/5 sec.) from a dropping funnel to a vigorously refluxing solution of 20.16 g. (0.06 mole) 9,10-dibromoanthracene, 6.56 g. (0.27 mole) magnesium powder, and 500 ml. dry tetrahydrofuran under a nitrogen atmosphere. The reaction began very vigorously after ninety minutes. External heating was stopped momentarily until the reaction subsided. After two hours the external heating was reapplied to maintain reflux for another twenty-two hours. The slow rate of addition of entrainer was maintained throughout this twenty-four hour period to insure constantly clean and active magnesium surfaces. At the end of the reflux period the now dark brown Grignard solution was cooled to -70°C. in a dry ice-acetone bath. Trimethyl borate, 26 g. (0.25 mole), was transferred to a 125-ml. dropping funnel in a nitrogen atmosphere, then added dropwise over a period of one-half hour to the well cooled Grignard solution. This solution was warmed to room temperature overnight, gently refluxed one hour, and finally cooled to 10°C. The brown slurry was poured onto 100 g. of ice in 150 ml. of 1N HCl. After decomposition of the excess magnesium the solution was extracted twice with 50-ml. portions of ether. The combined ether extracts were washed twice with 100-ml. portions of water and dried over anhydrous magnesium sulfate. This ether solution was concentrated to one-half its volume and divided into two equal portions.

One portion was extracted five times with 100-ml. portions of 2N NaOH. No precipitate was observed when the alkaline extract was made acidic with 1N HCl. From the other portion a dark brown syrup was recovered after complete removal of the ether. This sticky syrup was extracted with 3 liters of hot water, filtered twice through charcoal, and finally filtered once again without charcoal. This dilute aqueous solution did not give any precipitate until concentrated to 100 ml. The precipitate was collected by filtration and air dried. The white crystals, 5 g., were recrystallized from hexane. These crystals had no detectable melting point below 300°C. and had positive Beilstein and Michler's thioketone tests for bromine. The infrared spectrum suggested a phenolic compound (see Table IVa., page 32). The ferric chloride and ferric ammonium sulfate tests were negative, but the diazotized sulfanilic acid test was positive. This material was assumed to be 9-bromo-10-hydroxyanthracene.

After the disappointing results of the previous three attempts to synthesize anthracene-9,10-diboronic acid via the Grignard reagent, it was apparent that a more successful method must be found. In hopes that the more reactive n-butyl lithium might lead to the desired product, the suggestions of previous workers for the preparation of anthracene-9,10-dicarboxylic acid (28,29) were employed.

n-Butyl lithium in hexane, 92 ml. (0.15 mole), was transferred by pipette to a 125-ml. dropping funnel in a dry nitrogen atmosphere. This solution was added dropwise within one-half hour to 500 ml. of dry tetrahydrofuran in a 2-liter, 4-neck reaction flask under nitrogen. The 9,10-dibromoanthracene, 16.8 g. (0.05 mole), was simultaneously added from a 125-ml. erlenmeyer flask to the tetrahydrofuran. The reaction mixture developed a bright orange color that turned to a dark brown as the tetrahydrofuran was brought to reflux. The solution was refluxed for one-half hour then cooled to -65°C. in a dry ice-acetone bath before trimethyl borate, 26 g. (0.25 mole), was added within one hour from a 125-ml. dropping funnel. The reaction mixture was warmed to room temperature overnight, cooled to 10°C., and finally hydrolyzed by addition of 150 ml. ice cold 1N HCl. After the aqueous-tetrahydrofuran solution was extracted twice with 75-ml. portions of ether, the combined ether extracts were washed twice with 50-ml. portions of water, then dried over anhydrous magnesium sulfate. The dry ether solution was filtered and the ether removed by distillation. A portion of the resulting dark brown residue was extracted with 500 ml. of hot aqueous methanol (50%). The solution was filtered twice to remove the insoluble material, concentrated to one-half its volume, and allowed to stand overnight in the cold to allow for crystallization. One gram of white crystals was collected by filtration and air dried. The infrared spectrum was identical to that of the material recovered from the concentrated aqueous extract in the previous experiment (see Table IVa., page 32).

Soxhlet extraction with benzene and dilute sodium hydroxide of the remaining portion of the dark brown residue yielded only an amorphous material.

The organo-lithium method used above was repeated but the reflux period was increased to twelve hours. Following the usual process 9,10-dibromoanthracene (85%) was recovered and identified by its melting point (222°C.) and infrared spectrum. No other product was identified.

The organo-lithium method was attempted one further time but with only a four hour reflux period. The infrared spectrum of the resulting syrupy brown material indicated aliphatic and aromatic boronic acids (see Table IVb., page 32). The Beilstein test for bromine was positive. This evidence suggested n-butyl boronic acid, n-butyl bromide, anthracene-9-bromo-10-boronic acid, and/or anthracene-9,10-diboronic acid. After removal of any n-butyl bromide (b.p. 101.6°C.) the Beilstein test and infrared spectrum remained unchanged. The syrupy residue was dissolved in 500 ml. of hot benzene, concentrated to one-half its volume, and then allowed to stand for two days in the cold to effect crystallization. The long colorless crystals which collected after the solvent was removed by filtration were washed with cold benzene and air dried. This substance was found to be very soluble in water and acetone but only slightly soluble in hexane, benzene, and carbon tetrachloride. Recrystallization from 300 ml. of carbon tetrachloride afforded 1.5 g. of white crystals.

This product had a melting point of 90-2°C. It was identified as n-butylboronic acid (m.p. 92-4°C.) by its infrared spectrum.

A brown resinous substance was recovered after complete removal of benzene from the mother liquor. The infrared spectrum of the product revealed only aromatic and aliphatic materials. Furthermore, the Beilstein and Michler's thioketone tests for bromine were positive. This material was tentatively identified as a crude mixture of 9-bromo-10-n-butylanthracene and 9,10-di-n-butylanthracene. No further attempt was made to process this resinous substance.

TABLE II

INFRARED FREQUENCY CORRELATION CHART FOR ARYL BORONIC ACIDS AND THEIR DERIVATIVES

COMPOUND	FREQUENCY ASSIGNMENTS*						
	C-H	N-H	B-C	asym. B-O	N→B	C-O	N→B
			stretching				bend
Benzene-1,4-Diboronic Acid	3300 s,bd		1410 s,sh	1360 s,sh			
bis (neopentyl glycol) ester			1418 s,sh	1342 m,bd		1095 w,bd	
bis (diethanolamine) ester		3110 m,sh	weak	1360 w,sh	1222 s,sh	1070 s,bd	926 s,sh
Naphthalene-1-Boronic Acid	3250 m,bd		1400 m,bd	1340 s,sh			
neopentyl glycol ester			1405 s,sh	1320 m,sh		1088 m,sh	
diethanolamine ester		3150 m,bd	weak	1340 w,sh	1222 s,sh	1072 s,bd	915 m,bd
Naphthalene-1,4-Diboronic Acid	3300 s,bd		1399 s,sh	1340 s,sh			
bis (neopentyl glycol) ester			1410 s,sh	1320 m,sh		1075 w,sh	
bis (diethanolamine) ester		3110 m,sh	weak	1340 w,sh	1230 s,sh	1072 s,bd	921 s,sh

*All Assignments in cm^{-1}

s=strong, m=moderate, w=weak; sh=sharp, bd=broad

TABLE III

SUMMARY OF THE INFRARED SPECTRAL DATA FOR CRUDE SUBLIMAND RECOVERED AFTER AN ATTEMPT TO ISOLATE ANTHRACENE-9-BORONIC ACID

FREQUENCY (cm^{-1})	ASSIGNMENT
3450 (s)*	O-H stretch
3050 (s)	Olefinic C-H
2950 (s)	Aliphatic C-H
1320 (s,bd)	Aryl B-O stretch
1050 (s,bd)	-OH bending
880 (s)	Isolated H of Aromatic
740 (s)	Adjacent 4H

*s-strong
bd-broad

TABLE IV

SUMMARY OF THE INFRARED SPECTRAL DATA FOR CRUDE PRODUCTS RECOVERED AFTER ATTEMPTS TO SYNTHESIZE ANTHRACENE-9,10-DIBORONIC ACID

a. From the Grignard Reaction

FREQUENCY (cm^{-1})	ASSIGNMENT
3250 (s)*	O-H
1200 (s)	Phenolic -OH
770 (m)	Adjacent 4H of aromatic
645 (m)	Aryl C-Br deformation

b. From n-Butyl Lithium Reaction

FREQUENCY (cm^{-1})	ASSIGNMENT
3500 (m)	O-H
3050 (w)	Aryl =C-H
2900,2710 (s)	C-H
1400-1300 (w)	B-O ?
750 (s)	Adjacent 4H of aromatic
727 (s)	$-(CH_2)_4-$

*s-strong
m-medium
w-weak

CHAPTER IV

DISCUSSION

The order of relative ease toward formation of the Grignard reagent from aryl halide was observed to be: 1-bromonaphthalene $>$ p-dibromobenzene $\gg$ 1,4-dibromonaphthalene $\gg$ 9-bromoanthracene $>$ 9,10-dibromoanthracene. This sequence is consistent with the well known deactivating influence of halogens, decreasing ring aromaticity, and increasing steric hindrance near the C-Br bond.

The relatively low reactivities of the bromoanthracenes in the Grignard reaction, if in fact they do react at all, suggests that their activation energies are high. Consequently, the Grignard reagent would be less discriminate in its attack on trimethyl borate. Thus, after the addition of trimethyl borate the Grignard reaction might yield anthracene boronic acid, dianthracylborinic acid, or trianthracyl boron. In the future it may be wise to add the well cooled Grignard to the cold trimethyl borate (31,32). This method would favor formation of the desired boronic acid because there always would be a high ratio of trimethyl borate to Grignard reagent.

Failure here to successfully synthesize anthracene-9,10-diboronic acid via its dilithio derivative only confirms observations by Gilman and coworkers on other aryl boronic acids (33,34). These investigators found that even at low temperatures cleavage of boronic acids was facile with a strong base such as n-butyl lithium, and that naphthalene-1-boronic acid was less stable than benzene boronic acid.

The infrared frequency correlation chart (see Table II, page 30) depicts pertinent infrared spectral assignments for the arylboronic acids and their ester derivatives.

The strong broad band at 1340 ± 20 cm^{-1} for these arylboronic acids is consistent with assignments made by others for the B-O asymmetric stretching frequency (36). Werner and O'Brien suggested the intensity and stability of this band reflects some double bond character due to $\pi-\pi^*$ bonding via back coordination from oxygen to boron (36). If an amine is complexed to an oxyborane, the amine's lone pair of electrons can complete the boron octet and reduce back-coordination between oxygen and boron to a minimum (23). Infrared absorption for the asymmetric B-O stretch in these oxyborane-amine complexes is weak or absent reflecting the reduced B-O bond strength (23).

Greenwood and Wade (20) have assigned the infrared frequency range 1099-1250 cm^{-1}, although Letsinger and Hamilton (23) indicated a narrower range (1136-1250 cm^{-1}), for a stretching mode of the coordinated boron-nitrogen bond (dative bond). Zimmerman and coworkers have assigned to the stretching and bending modes for the N→B dative bond in a series of boroxazolidines the infrared frequencies 1200 and 920 cm^{-1}, respectively (16). However, Zimmerman claimed that subsequent studies failed to confirm his assignments, at least in a simple way, and no confidence to date (1963) could be placed in infrared spectral data as direct proof of N→B dative bonding (38). Prominent and stable infrared bands were found near 1225 and 921 cm^{-1} for the three aryl diptych boroxazolidines prepared in this laboratory. These bands did not appear for components of the diptych boroxazolidines.

Many conflicting infrared spectral assignments have been made for the B-Aryl bond. Bellamy and coworkers (22) assigned a strong sharp absorption band to the B-Aryl bond between 1430-40 cm^{-1}. Gerrard (37) assigned the strong absorption between 1250-80 cm^{-1} to the B-Aryl bond and Santucci and Gilman (33) assigned a strong band between 1086-95 cm^{-1} to this bond. However, the 1430-40 cm^{-1} and 1250-80 cm^{-1} bands, which also appear for aryl bromides, probably represent aromatic C=C stretching and C-H in-plane bending modes, respectively (39,40). The band at 1086-95 cm^{-1}, which invariably appears in boronic acid esters, probably represents a -C-O-B-O-C- or aromatic in-plane deformation mode (39,40). Infrared spectral analysis of three aryl boronic acids and their neopentyl glycol ester derivatives (see Table II, page 30) revealed a strong sharp band at 1408 ± 10 cm^{-1} which did not appear for p-dibromobenzene, 1-bromonaphthalene, or 1,4-dibromonaphthalene. Furthermore, upon boron-amine coordination in diptych boroxazolidines, this band was observed to decrease in intensity in the same manner as the B-O asymmetric stretching band.

Hammett para substituent constants (-0.01σ; $-0.179\sigma^+$) indicate for the phenyl nucleus a weak tendency toward electron donation (41). Should there exist some partial double bond character in the B-C bond due to π-π bonding via back-coordination from carbon to boron, then upon boron-amine coordination one might expect the B-C bond to be weakened; likewise the infrared absorption would decrease.

This author concurs with H. K. Zimmerman (38) that correlation of infrared spectral data is not a simple task, especially for the boroxazolidines, and more detailed infrared investigations are most certainly needed.

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