frared spectrum of this material showed the strong carbonyl band at 1750 cm.$^{-1}$, weak carboxyl carbonyl at 1725 cm.$^{-1}$, the C–O–C absorptions at 1205, 1136, 1090 and 1045 cm.$^{-1}$ and the absence of typical Si–O–Si bands. It appeared to be an impure sample of methoxyethyl propionate contaminated with propionic acid.

Anal. Calcd. for $C_6H_{12}O_3$: C, 54.5; H, 9.16. Found: C, 51.6; H, 8.75; Si < 0.5.

Cohydrolysis of Dimethyldichlorosilane and the Methyldichlorosilane–Vinyl Acetate Adduct.—A mixture of 53.7 g. of methyldichlorosilane (Dow–Corning, pure grade) and 28 g. of the methyldichlorosilane–vinyl acetate adduct (mole ratio 3:1) was added, over a 5-hr. period, to a well-stirred mixture of 250 ml. of water and 250 ml. of ether, maintained at 0–10°. The ether layer was separated and the aqueous phase was extracted with four 50-ml. portions of ether. The total ether solution was dried over magnesium sulfate and the ether was evaporated to leave a residue (49.5 g.). The residue was first distilled from a Claisen flask to give the following fractions: (1) 6.8 g., b.p. 48–57° (7 mm.), $n^{20}D$ 1.3952–1.3970; (2) 2.1 g., b.p. 56–79° (2.5 mm.), $n^{20}D$ 1.4112; (3) 11.3 g., b.p. 79–86° (2.5 mm.), $n^{20}D$ 1.4137–1.4152; (4) 3.6 g., b.p. 86–91° (2.5 mm.), $n^{20}D$ 1.4155–1.4157; (5) 8.2 g., b.p. 91–132° (2.0 mm.), $n^{20}D$ 1.4198–1.4268. A residue of 14.4 g., $n^{20}D$ 1.4291, remained. Fraction (1) was a mixture of hexamethylcyclotrisiloxane and tetramethylcyclotetrasiloxane. Fractions (3) and (4) were redistilled using a 50 × 1 cm. column packed with glass helices and gave the following fractions: (1) b.p. 75–80° (2 mm.), $n^{20}D$ 1.4122; (2) b.p. 80–81.5° (2 mm.), $n^{20}D$ 1.4141; (3) b.p. 81.5–82°, $n^{20}D$ 1.4150; (4), (5) and (6) b.p. 82.0° (2.0 mm.), $n^{20}D$ 1.4153. Fraction V, considered to be β-acetoxyethylheptamethylcyclotetrasiloxane (III), was analyzed.

Anal. Calcd. for $C_{11}H_{28}O_6Si_4$: C, 35.83; H, 7.65; Si, 30.48; mol. wt., 368.69. Found: C, 35.5, 36.1; H, 7.55, 7.86; Si, 30.85; mol. wt. (cryoscopic in benzene), 361, 353.

Nuclear Magnetic Resonance Spectra.—The samples were sealed in 5 mm. tubes and the spectra were measured by the audio side band method using the Varian Associates Model V-4300B High Resolution Spectrometer at 30 mc. and 7050 gauss.

MENLO PARK, CALIF.

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

Hydroxybenzeneboronic Acids and Anhydrides

BY HENRY GILMAN, LUDOVICO SANTUCCI, D. R. SWAYAMPATI AND R. O. RANCK

RECEIVED JANUARY 23, 1957

ortho-, *meta-* and *para*-hydroxybenzeneboronic acids and/or anhydrides were prepared by the reaction of tri-*n*-butyl borate with the corresponding organolithium compounds. The properties of the three "isomers" (boronic acid or anhydride), including anhydride formation ability, were found to vary considerably. The preparation of 2-(*m*-bromophenoxy)-tetrahydropyran and the optimum conditions for the halogen–metal interconversion of *m*-bromophenol also are reported.

In the approach to the synthesis of boron-containing azo dyestuffs,[1,2] which have been found to be of interest in the irradiation therapy of brain tumors,[3] it was thought that compounds such as *o*-hydroxybenzeneboronic acid and *m*-hydroxybenzeneboronic acid or their anhydrides would be active enough to couple with various diazonium salts. This coupling could occur either *ortho* or *para* to the hydroxy group, but primarily *para*. Perhaps the *p*-hydroxybenzeneboronic acid or its anhydride would also couple successfully with various diazonium salts. However, the possibility of losing the boronic acid group exists here more so than in the other two cases unless, of course, the coupling tends to go *ortho* to the hydroxy group. The *para* isomer was thus prepared primarily for comparison with the other members of this series.

In addition to the purposes already discussed, these compounds, as such, should also be of interest for testing in brain tumor therapy, since the work of several[3–12] has shown that any boron compound containing some of the boron isotope 10[13] might be useful in irradiation research of this type. In addition, other pharmacological studies indicate that the hydroxyl group should increase the efficacy of such compounds.

The *m*-hydroxybenzeneboronic acid has been prepared previously[1,14,15] and was used for the preparation of azo boronic acids.[1] In these instances, the compound was prepared from *m*-aminobenzeneboronic acid by diazotization followed by hydrolysis.

The preparation of *p*-hydroxybenzeneboronic acid has been attempted in the past[14] but it never has been isolated.

The *o*-hydroxybenzeneboronic acid anhydride has not been reported as yet.

Only one other arylhydroxyboronic acid is mentioned in the literature. This is 3-hydroxy-4-methylbenzeneboronic acid[14] which was prepared from the 3-nitro-4-methylbenzeneboronic acid using catalytic reduction followed by diazotization and hydrolysis.

In the work reported here, two different approaches were tried for the preparation of each of the three isomers and a third approach was attempted for the *ortho* and *para* isomers.

The best of the three approaches involved the halogen–metal interconversion of a bromophenol isomer with *n*-butyllithium using 2 moles of the lithium reagent to 1 mole of the halogen com-

---

(1) H. R. Snyder and Clay Weaver, THIS JOURNAL, **70**, 232 (1948).

(2) H. R. Snyder and S. L. Meisel, *ibid.*, **70**, 774 (1948).

(3) P. G. Kruger, *Radiation Research*, **3**, 1 (1955).

(4) P. G. Kruger, *Proc. Nat. Acad. Sci.*, **26**, 181 (1940).

(5) P. A. Zahl, F. S. Cooper and J. R. Dunning, *ibid.*, **26**, 589 (1940).

(6) P. A. Zahl and F. S. Cooper, *Science*, **93**, 64 (1941).

(7) P. A. Zahl and L. L. Waters, *Proc. Soc. Exper. Biol. Med.*, **48**, 304 (1941).

(8) P. A. Zahl and F. S. Cooper, *Radiology*, **37**, 673 (1941).

(9) W. H. Sweet and M. Javid, *J. Neurosurg.*, **9**, 200 (1952).

(10) M. Javid, G. L. Brownell and W. H. Sweet, *J. Clin. Invest.*, **31**, 604 (1952).

(11) L. E. Farr, W. H. Sweet, J. S. Robertson, C. G. Foster, H. B. Locksley, D. L. Sutherland, M. L. Mendelsohn and E. E. Stickley, *Am. J. Roentgenol. Radium Therapy Nuclear Med.*, **71**, 279 (1954).

(12) L. E. Farr, J. S. Robertson and E. E. Stickley, *Proc. Nat. Acad. Sci.*, **40**, 1087 (1954). See, E. E. Stickley, *Am. J. Roentgenol. Radium Therapy Nuclear Med.*, **75**, 609 (1956).

(13) Naturally occurring boron compounds contain 18.83% of the boron isotope 10. See NBS Circular No. 499, p. 7.

(14) F. R. Bean and J. R. Johnson, THIS JOURNAL, **54**, 4415 (1932).

(15) M. F. Lappert, *Chem. Revs.*, **56**, 959 (1956). This is a review article on organoboron chemistry and contains most of the organoboronic acids that have been prepared up to the writing of this paper.

pound followed by reaction with tri-*n*-butyl borate, usually,[16] and subsequent hydrolysis with dilute acid. Isolation of the *meta* and *para* isomers was somewhat difficult because of their water solubility. Each was isolated successfully from an ether solution by concentration which was preceded by a series of extractions to remove a large portion of the *n*-butyl alcohol and boric acid. The *ortho* isomer could have been isolated by a similar procedure, but this was not necessary due to its limited water solubility. Isolation was effected by acidification of an alkaline extract. The yields of the three compounds prepared by this halogen–metal interconversion procedure differed greatly. The *ortho* isomer was obtained in yields as high as 65%; the *meta* isomer in much lower yields of 32%; and the *para* isomer in intermediate yields of 40%.

Another approach which was used is somewhat the same as that which has just been described except that the hydroxy group of the bromophenol isomers was etherified by the use of dihydropyran.[17,18] Both the 2-(*o*-bromophenoxy)-tetrahydropyran[18] and the 2-(*p*-bromophenoxy)-tetrahydropyran[17] have been reported previously, but the 2-(*m*-bromophenoxy)-tetrahydropyran is new and is reported here. The procedure was the same as in the preparation of the *ortho* and *para* isomers.

In each of these cases, the 2-(bromophenoxy)-tetrahydropyranyl isomer was treated with an equimolar amount of *n*-butyllithium followed by reaction with tri-*n*-butyl borate at a low temperature and subsequent hydrolysis. A 55% yield of the *o*-hydroxybenzeneboronic acid anhydride, which was isolated by acidification of an alkaline extract, was obtained. This is quite comparable to that which was obtained when the unprotected *o*-bromophenol was used as the starting material. The main advantage of using the acetal is the smaller *n*-butyllithium requirement in this case, only half as much being necessary as when *o*-bromophenol is used as the starting material.

The attempt to prepare *m*-hydroxybenzeneboronic acid using 2-(*m*-bromophenoxy)-tetrahydropyran as the starting material was unsuccessful. A solid material which defied purification was isolated but never identified.

When the 2-(*p*-bromophenoxy)-tetrahydropyran was treated with *n*-butyllithium and tri-*n*-butyl borate, followed by acid hydrolysis, 2-hydroxy-5-bromobenzeneboronic acid was isolated instead of *p*-hydroxybenzeneboronic acid.[19]

The third approach to the synthesis of *ortho*- and *para*-hydroxybenzeneboronic acid or anhydride involved the reaction of *o*- and *p*-chloromercuriphenol with boron trichloride in chlorobenzene followed by hydrolysis. This work was unsuccessful. Both benzeneboronic acid[20] and *o*-methoxybenzeneboronic acid[21] have been prepared by similar methods. However, the conversion of *o*-chloromercuriphenol and acetoxymercuribenzene to the corresponding boronic acids with tri-*n*-butyl borate, made by Snyder and Weaver,[1] was not successful.

Purification of the *ortho* and *meta* isomers was best accomplished by recrystallization of the crude material from ethylene chloride.[22] Usually two or three recrystallizations were required to get material of the maximum melting point, both compounds crystallizing as the anhydride. The *para* isomer was purified by recrystallization from acetone containing a small amount of water; recrystallization of this purified acid from ethylene chloride seemed to produce a mixture of anhydride and acid.

In the course of the investigation numerous solvents for the recrystallization of the *ortho* and *meta* isomers were investigated. It was found that the *ortho* isomer could be purified successfully from many solvents including benzene, toluene, water, acetone–water and acetone–benzene. It is interesting to note that regardless of the solvent used, the material always separated as the anhydride. In contrast to this, no solvent other than ethylene chloride seemed to be suitable for recrystallization of the *meta* isomer. No extensive solvent study was made on the *para* isomer.

From these results, it is seen that the ease of anhydride formation of the three isomers varies considerably. The anhydride seems to be the stable form of the *ortho* isomer. Exposure of the *o*-hydroxybenzeneboronic acid anhydride to a moist atmosphere for 6 months failed to convert it to the acid.

Although Bean and Johnson[14] reported a possible acid–anhydride mixture for the *meta* isomer recrystallized from ethylene chloride containing a small amount of acetone (based on the carbon and hydrogen analyses), the material prepared in this current work seems to be definitely the anhydride (based on the neutralization equivalent and boron analysis) which may possibly be the more stable form, although this was not definitely established.

The stable form of the *para* isomer seems to be the acid. This is based on the difficulty of conversion to the anhydride either by heating in the vacuum oven for 70 hr. at 90° or recrystallization from ethylene chloride. In both cases, material having a neutralization equivalent intermediate between the acid and anhydride was obtained.

There was a wide variation in melting point of the *ortho* isomer depending on which solvent was used for recrystallization. For example, material recrystallized from toluene generally melted over the range of 170–175° while material recrystallized from ethylene chloride had a melting point as high as 193–194°, although this was not obtained consistently. What was believed to be an analytically pure sample, obtained by recrystallization from an acetone–water system, melted over the range of 180–183°. Despite these differences in melting points, all of these specimens had the

---

[16] In some experiments, trimethyl borate was used.

[17] W. E. Parham and E. L. Anderson, This Journal, **70**, 4187 (1948).

[18] B. F. Hofferth, Doctoral Dissertation, Iowa State College, 1950.

[19] Ludovico Santucci, unpublished studies.

[20] L. O. Moore, unpublished studies. See A. Michaelis, *Ann.*, **315**, 19 (1901), for the preparation of benzeneboronic acid from diphenylmercury and boron trichloride.

[21] A. Michaelis and M. Behrens, *Ber.*, **27**, 244 (1894).

[22] Eastman Kodak white label 1,2-dichloroethane distilled over phosphorus pentoxide was used.

same neutralization equivalent. We believe that the neutralization equivalent is more of a criterion of purity than the melting point. The large differences in melting point as well as the relatively large melting point range possibly can be explained by the ratio of monomer, dimer and perhaps even trimer in the purified material. The fact that these forms may exist is based on a molecular weight determination on material recrystallized from water and having a melting point of 194–195°. This was found to be approximately 200. The molecular weight for the monomer is 120.

Both the melting points and water solubilities of these boronic acids and/or anhydrides follow the general pattern established by their carboxylic acid analogs, although there is a much more pronounced difference between the solubilities of the *o*-hydroxybenzeneboronic acid anhydride and the *meta* and *para* isomers than exists in the carboxylic acid series. There does not seem to be any logical explanation for the good water solubilities of the *meta*-anhydride and the *para*-acid in the boron series. The poor water solubility of the *o*-hydroxybenzeneboronic acid anhydride with respect to the other two isomers might be explained partially by its polymer formation. However, it is not known whether the *meta* and *para* isomers prepared in this work tend to dimerize or not. Table I shows the melting point and solubility correlation of the two series.

TABLE I

CORRELATION OF MELTING POINT AND WATER SOLUBILITIES OF HYDROXYBORONIC ACID ISOMERS WITH THEIR CORRESPONDING CARBOXY ANALOGS

	Hydroxyboronic acid		Hydroxycarboxylic acid	
Isomer	M.p., °C.	H_2O sol. (qual.)[c]	M.p., °C.	H_2O sol. (g./100 cc.)
ortho	193–194[a,b]	Poor[c]	159	0.18[20]
meta	225[b]	Very good[c]	201.3	.92[18]
para	238	Very good[c]	213	.79[15]

[a] This is the highest melting point that was obtained for this isomer. Other material of this type with a suitable neutralization equivalent had a melting point range as low as 170–175° depending upon the solvent which was used for recrystallization. [b] The anhydride. [c] Only qualitative solubility information is available.

Since no halogen–metal interconversion study had ever been carried out on the *m*-bromophenol as has been done on the *ortho* and *para* isomers,[23,24] the optimal conditions for this were determined. The amount of halogen–metal interconversion, as determined by carbonation to form the carboxylic acid, increased up through a 4-hour reaction period at 20°. Longer reaction times at this temperature did not show any higher yields. There was some indication that the yield decreased slightly with the longer reaction times (up to 24 hr.), although this was not appreciable. For this reason no reaction temperature higher than 20° was studied. Lower temperatures were not investigated.

A 34% yield of pure *m*-hydroxybenzoic acid was obtained when the halogen–metal interconversion was carried out for 4 hr. at 20° followed by carbonation and hydrolysis. In previous studies,[23,24] a 67% yield of the *ortho* isomer and a 41% yield of the *para* isomer were obtained.

Experimental[25]

***o*-Hydroxybenzeneboronic Acid Anhydride. (a) From *o*-Bromophenol.**—To 91 g. (0.525 mole) of *o*-bromophenol dissolved in 200 ml. of anhydrous ether, cooled in an ice-bath, was added 1.08 moles of *n*-butyllithium[26] in 800 ml. of anhydrous ether. This addition was made over a period of 75 minutes, and agitation was continued for 3 hr. at 20–25° following completion of the addition at which time Color Test II[27] was negative. This halogen–metal interconversion has been reported previously.[23,24] This ether solution of lithium *o*-lithiophenoxide was then added over a period of 1 hr. to a solution composed of 248 g. (1.08 moles) of tri-*n*-butyl borate and 200 ml. of anhydrous ether cooled to −70° by means of a Dry Ice–acetone bath. Color Test I[28] was negative immediately upon completion of the addition. The reaction was permitted to warm to 0° and was hydrolyzed by the addition of 360 ml. (1.045 moles) of 10% hydrochloric acid. The aqueous layer was separated from the ether layer and was washed twice with 200-ml. portions of ether which were combined with the main ether solution. This combined ether solution was then extracted with 800 ml. of 10% sodium hydroxide in three portions. The extract was washed once with 200 ml. of ether. This alkaline solution was heated on the steam plate to expel any residual ether, after which it was acidified by the addition of 10% hydrochloric acid. The solid which precipitated weighed 76 g. after drying and had a melting point range of 130–150°. This crude material was recrystallized twice from toluene to give 35 g. (55.5%) of material melting over the range of 170–175°. This yield includes the additional material obtained by concentration of the recrystallizing liquors.

Other experiments were conducted in which variations were made in the finishing procedure. Using the same procedure as described above for the preparation of the compound, isolation was accomplished after the acid hydrolysis by evaporating the ether layer to dryness. From 98.5 g. (0.57 mole) of *o*-bromophenol, 91 g. of crude product having a melting point range of 130–148° was obtained. This was washed thoroughly with 400 ml. of water leaving 47 g. of insoluble material having a melting point range of 165–170°. This represents a 69% yield of reasonably satisfactory material. Recrystallization of this material from approximately 1 liter of dry ethylene chloride gave 37 g. of material having a melting point range of 175–180°. This represents a 55% yield of nearly pure material.

When using this second finishing procedure, it was thought that trimethyl borate would be more adaptable than tri-*n*-butyl borate since it would then involve the evaporation of methyl alcohol along with the other volatile material instead of *n*-butyl alcohol. An experiment which employed 94 g. (0.545 mole) of *o*-bromophenol with 117 g. (1.12 moles) of trimethyl borate and using the technique just discussed gave 37 g. of washed semi-pure product having a melting point range of 170–175°. This represents a yield of 56.5%. Recrystallization of the product from ethylene chloride gave 30 g. (47%) of material melting over the range of 180–185°.

The analytical sample was recrystallized from an acetone–water system to give material melting over the range of 180–183°. The optimum amounts of material were found to be 5 g. of solute for 300 ml. of water and 60 ml. of acetone. The infrared spectrum supported the structure.

---

(23) H. Gilman, C. E. Arntzen and F. J. Webb, *J. Org. Chem.*, **10**, 374 (1945).

(24) H. Gilman and C. E. Arntzen, THIS JOURNAL, **69**, 1537 (1947).

(25) All melting points are uncorrected and were measured using a previously unheated oil-bath. The neutralization equivalents were obtained by dissolving 50 to 100 mg. of the compound in 50 ml. of 50% ethanol or in 50 ml. of water if its solubility permitted, adding 20 times the sample weight of D-mannitol and then titrating with standard sodium hydroxide using phenolphthalein as the indicator. In the case of *p*-hydroxybenzeneboronic acid, darkening of the solution during the titration necessitated the use of a Beckman Model G *p*H meter to detect the end-point.

(26) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn and L. S. Miller, THIS JOURNAL, **71**, 1499 (1949).

(27) H. Gilman and J. Swiss, *ibid.*, **62**, 1847 (1940).

(28) H. Gilman and F. Schulze, *ibid.*, **47**, 2002 (1925).

Anal. Calcd. for $C_6H_5BO_2$: C, 60.09; H, 4.20; B, 9.02; neut. equiv., 119.94. Found: C, 60.24, 60.30; H, 4.12, 4.18; B, 9.12, 9.21; neut. equiv., 120.0.

(b) **From 2-(*o*-Bromophenoxy)-tetrahydropyran.**—To a stirred solution of 25.7 g. (0.1 mole) of 2-(*o*-bromophenoxy)-tetrahydropyran[18] and 100 ml. of anhydrous ether, cooled in an ice-bath, was added 0.1 mole of *n*-butyllithium[26] in 88 ml. of ether over a period of 15 minutes. Agitation was continued for 1 hr. at room temperature following completion of the addition. Color Test II[27] was negative at this time. The reaction mass consisted of a solid suspended in ether.

The 2-(*o*-lithiophenoxy)-tetrahydropyran suspension was then added over a period of 20 minutes to a stirred solution of 34.5 g. (0.15 mole) of tri-*n*-butyl borate in 100 ml. of anhydrous ether previously cooled to −70° by means of a Dry Ice–acetone bath. The temperature was maintained below −65° during the addition and for 2 hr. following completion of the addition at which time Color Test I[28] was negative. After warming to 0°, the reaction mass was hydrolyzed by the addition of 10% hydrochloric acid. The aqueous layer was separated from the ether and washed twice with fresh ether. The combined ether solutions were then extracted with two 50-ml. portions of 10% sodium hydroxide. The alkaline solution was washed with a 100-ml. portion of ether, warmed on the steam-bath to expel any residual ether, treated with Norit-A, filtered, cooled and acidified with 10% hydrochloric acid. The gray product which separated was filtered, washed with water and dried to give 10.0 g. (83%) of crude product melting over the range of 170–175°. Recrystallization of this material from a benzene–acetone system gave 6.6 g. (55%) of product melting at 180–181°. An admixture of this with authentic 2-hydroxybenzeneboronic acid anhydride melted undepressed.

***m*-Hydroxybenzeneboronic Acid Anhydride.**—Thirty-four and six-tenths grams (0.2 mole) of *m*-bromophenol was dissolved in 90 ml. of anhydrous ether in a nitrogen atmosphere. To this stirred solution was added 0.44 mole of *n*-butyllithium[26] in 332 ml. of anhydrous ether over a period of 50 minutes, the temperature being maintained at 20° by means of a water-bath. Agitation was continued for 4 hr. at 20° at which time Color Test II[27] was negative. This ether solution of lithium *m*-lithiophenoxide then was added over a 30-minute period to a stirred solution of 140 g. (0.6 mole) of tri-*n*-butyl borate in 220 ml. of anhydrous ether previously cooled to −70° by means of a Dry Ice–acetone bath. During this time the reaction mixture became extremely viscous. Upon completion of the addition, the mixture was permitted to warm to 0°. Color Test I[28] was negative. The reaction mixture was hydrolyzed with 250 ml. of a saturated ammonium chloride solution followed by 150 ml. of 10% hydrochloric acid to get the *p*H below 7 and 100 ml. of water to dissolve some still remaining solid. The aqueous layer was separated from the ether and was washed twice with 100-ml. portions of ether which were combined with the main portion. The ether solution was extracted ten times with 60-ml. portions of 10% sodium carbonate which were poured into a stirred mixture of 400 ml. of ether and 500 ml. of a saturated ammonium chloride solution. Four hundred milliliters of 10% hydrochloric acid also was added to get the *p*H to 6. The aqueous layer was separated from the ether and was extracted several times with additional ether which was combined with the main portion. Evaporation of the ether layer to dryness left a solid material which upon crystallization from ethylene chloride gave 6 g. (25%) of material having a melting point of 208–212°. The initial ether layer was evaporated to about one-fourth its original volume and the same process was repeated. This gave an additional 1.1 g. (4.5%) of material melting at 208–212°. The two final acid aqueous layers were combined and evaporated to one-fourth volume. This was extracted several times with ether to give 0.9 g. (3.8%) of material melting at 215–230°. All of the crude material was combined and recrystallized from ethylene chloride to give 7.3 g. (30.4%) of material melting at 215–225° dec. The analytical sample was recrystallized an additional time from ethylene chloride.

The infrared spectrum supported the structure.

Anal. Calcd. for $C_6H_5BO_2$: B, 9.02; neut. equiv., 119.94. Found: B, 9.11; neut. equiv., 117, 122.4.

***p*-Hydroxybenzeneboronic Acid.**—The halogen–metal interconversion carried out was essentially that which has been described previously,[23] although a larger excess of *n*-butyllithium was used.

To a stirred solution of 33.7 g. (0.2 mole) of *p*-bromophenol dissolved in 80 ml. of anhydrous ether, 415 ml. of 1.45 *N* *n*-butyllithium (0.6 mole) was added at room temperature over a 45-minute period. Following completion of the addition, the reaction mixture was refluxed for 2 hr. After cooling with an ice-bath, the lithium *p*-lithiophenoxide suspension was added over a period of 50 minutes to a stirred solution of 140 g. (0.6 mole) of tri-*n*-butyl borate in 200 ml. of anhydrous ether previously cooled to −70° by means of a Dry Ice–acetone bath. After agitating for 2 hr. at this temperature following completion of the addition, Color Test I[28] was negative. The mixture was permitted to warm to 0° and was hydrolyzed by the addition of a saturated solution of ammonium chloride. A small amount of 10% hydrochloric acid also was added to lower the *p*H to 6. The two layers which resulted were separated, the aqueous layer being washed with fresh ether which was combined with the main ether portion. This ether extract was concentrated and was shaken with 600 ml. of 10% sodium carbonate in nine portions. Each alkaline extract was poured into a flask containing a stirred excess of saturated ammonium chloride solution and ether. This ether layer was separated from the aqueous layer, the latter being extracted with fresh ether which was combined with this second main ether portion. The ether extract was concentrated under vacuum without applying heat. About 4 g. (14.5%) of product melting at 238° crystallized from the concentrated ether solution. Recrystallization of this material from acetone containing a few drops of water did not alter the melting point.

Evaporation of the ether solution to dryness left a semicrystalline residue which, after drying on a porous plate, weighed 9.2 g. and melted at 187–191°. Recrystallization of this material from acetone containing a few drops of water and employing a Norit-A treatment gave 4.75 g. (17.4%) of crystals melting at 230.5–231°.

In other experiments, an extraction with 8% sodium bicarbonate preceding the one with sodium carbonate and an extraction with 5% sodium hydroxide following the sodium carbonate extraction, each yielded about 0.4 g. of crude material. A final extraction with 20% sodium hydroxide gave only 0.2 g. more of very impure product.

Other experiments carried out under a variety of conditions were inferior to the procedure described above.

The analytical sample was recrystallized two more times from acetone containing a small amount of water. This material melted at 238° and gave a violet-blue color with ferric chloride. The infrared analysis confirmed the expected structure.

Anal. Calcd. for $C_6H_7BO_3$: B, 7.85; neut. equiv., 137.93. Found: B, 7.82; neut. equiv., 138.4, 136.6, 137.0.

When recrystallizing the material from acetone–water a definite crystal structure first formed, but as the material dried it disintegrated into a powder. It was thought that the anhydride might be forming but the neutralization equivalent does not support this. The powdery product was recrystallized from ethylene chloride to give material having a neutralization equivalent of 130. Heating the acid in a vacuum oven for 70 hr. at 90° gave material having a neutralization equivalent of 125.

2-(*m*-Bromophenoxy)-tetrahydropyran.—To a stirred mixture of 33.6 g. (0.4 mole) of freshly distilled dihydropyran and 4 drops of concentrated hydrochloric acid previously heated to 60° was added 34.6 g. (0.2 mole) of *m*-bromophenol over a period of 30 minutes. The rate was such as to keep the temperature below 70°. Agitation was continued for 2 hr. following completion of the addition, the temperature being permitted to drop to that of the room. Eighty milliliters of ether was added to the reaction mass which was then extracted with three 20-ml. portions of 10% sodium hydroxide. These basic aqueous layers were combined and extracted with three 50-ml. portions of ether. An additional 100 ml. of water was put in to dissolve an orange-colored solid which separated during this operation. The ether extracts were combined and were dried with anhydrous sodium sulfate. The ether and excess dihydropyran were removed by distillation at atmospheric pressure after which the remaining material was subjected to vacuum distillation. The material boiled over the range of 98–105° at 2 mm. pressure. This material was distilled a second time, two fractions being collected. The first fraction weighed 5 g. and distilled at 119–120° (1 mm.), while the second fraction distilled at 115° (0.4 mm.), n^{20}_D 1.5504, d^{20}_{20} 1.3952, and weighed 38.5 g. This second fraction represents a 75% yield of 2-(*m*-bromophenoxy)-tetrahydropyran. The method used to prepare this compound follows closely that for the *o*-bromo[18] and *p*-bromo[17] isomers.

Anal. Calcd. for $C_{11}H_{13}BrO_2$: Br, 31.08; *MR*D, 58.12. Found: Br, 30.60, 30.55; *MR*D, 58.75.

m-**Hydroxybenzoic Acid.**—Eight and sixty-five hundredths gram of *m*-bromophenol was treated with 0.11 mole of *n*-butyllithium for 4 hr. at 20°. The reaction was terminated by pouring it jet-wise into a stirred slurry of Dry Ice and ether. After the mixture had warmed to room temperature, it was hydrolyzed by the addition of 50 ml. of 10% hydrochloric acid. The aqueous layer was separated and was washed twice with 50-ml. portions of ether which were combined with the main portion. The ether solution was extracted with three 25-ml. portions of 10% sodium hydroxide which were combined and acidified with concentrated hydrochloric acid. The solid which precipitated was dried and sublimed under vacuum twice to give 2.3 g. (33.3%) of material melting at 196–198° (lit. value, 201°).

Acknowledgments.—We wish to thank Mr. Robert McCord and Mr. E. Miller Layton, Jr., of the Ames Laboratory of the Atomic Energy Commission for the infrared spectra.

We also wish to acknowledge the financial support of the Division of Biology and Medicine of the United States Atomic Energy Commmission which has made this work possible. The results of the biological testing of these compounds will be reported by Dr. Otho D. Easterday of the Brookhaven National Laboratory.

AMES, IOWA

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF KANSAS]

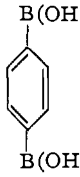
Benzenediboronic Acids

BY DONALD R. NIELSEN AND WILLIAM E. MCEWEN

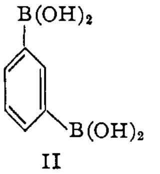
RECEIVED JANUARY 31, 1957

Benzene-1,4-diboronic acid (I) and benzene-1,3-diboronic acid (II) have been synthesized and characterized by conversion to the respective tetra-*n*-butyl esters and bis-(dichloroboryl)-benzenes.

Although more than 70 aliphatic and aromatic monoboronic acids have been described in the literature, there is no report of the synthesis of diboronic acids.[1] As part of a broad investigation of the physical and chemical properties of bifunctional organoboron compounds, syntheses of benzene-1,4-diboronic acid (I) and benzene-1,3-diboronic acid (II) have now been devised.

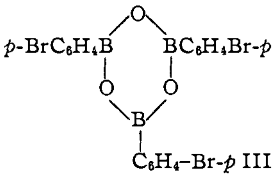


I

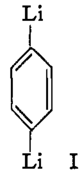


II

Benzene-1,4-diboronic acid (I) has been prepared in low yield by four different methods. When a mixture of *p*-bromophenylboronic anhydride (III), dispersed sodium and methyl borate in hexane was heated for two hours, then hydrolyzed, benzene-1,4-diboronic acid (I) was obtained in 4% yield. Reaction of di-*n*-butyl *p*-bromophenylboronate, magnesium and methyl borate in refluxing 1,2-dimethoxyethane for 30 hours gave, after hydrolysis of the reaction mixture, a 10% yield of I. The yield of benzene-1,4-diboronic acid (I) amounted to 26% in a reaction in which methyl borate, which had been frozen and pulverized, was added to a suspension of *p*-dilithiobenzene (IV) in petroleum ether at −30°, followed by hydrolysis of the reaction mixture. The dilithio compound IV was prepared by metal–halogen exchange between *n*-butyllithium and *p*-dibromobenzene according to the procedure of Gilman, Langham and Moore.[2] It is noteworthy that the yield of I is considerably below that of terephthalic acid, which may be obtained in 66–89% yield by an analogous carbonation reaction of the exchange mixture.



III



IV

The best yield of I was obtained by use of the Grignard reaction. A mixture of *p*-dibromobenzene and two equivalents of magnesium in tetrahydrofuran was refluxed for a period of seven hours, then methyl borate was added to the reaction mixture maintained at about −30°. After hydrolysis of the reaction products, the resulting acids were esterified with *n*-butyl alcohol and the esters fractionated. There was obtained tetra-*n*-butyl benzene-1,4-diboronate (V) in 35% yield, together with di-*n*-butyl *p*-bromophenylboronate (5%) and di-*n*-butyl phenylboronate (19%). Hydrolysis of the butyl esters gave quantitative yields of the respective arylboronic acids. The prolonged period of heating is evidently necessary for the formation of the dimagnesium Grignard compound in moderately satisfactory yield, since the yield of benzene-1,4-diboronic acid (I) dropped to 10% when the mixture of *p*-dibromobenzene and magnesium was heated for only 2.5 hours prior to the reaction with methyl borate. Extended refluxing of a solution of *p*-dibromobenzene in ethyl ether

---

[1] M. F. Lappert, *Chem. Revs.*, **56**, 959 (1956).

[2] H. Gilman, W. Langham and F. W. Moore, THIS JOURNAL, **62**, 2327 (1940).