TABLE II

PHYSICAL PROPERTIES OF THE ETHYLTIN CHLORIDES[a]

Formula	Density, g./ml. at 20°	Ref. index, n^{20}_D	Mole refraction Calcd.	Mole refraction Found	Melting point, °C.	Vapor pressure eqn. constants[b] A	Vapor pressure eqn. constants[b] B	Calcd. B.p., °C. at 1 atm.	Calcd. heat of vaporization, cal./mole	Trouton's const., cal./mole/degree
$C_2H_5SnCl_3$	1.965*	1.5408*	40.22	40.61*	−10	2554*	8.377*	192	11672*	25.1
$(C_2H_5)_2SnCl_2$					84	2753*	8.385*	227	12581*	25.2*
$(C_2H_5)_3SnCl$	1.429	1.5055	50.54	50.15	15	2652*	8.416*	206	12119*	25.3*

[a] For previously reported values, see E. Krause and A. V. Grosse, "Die Chemie der Metall-Organischen Verbindungen," Photolithoprint, Edwards Bros., Ann Arbor, Mich., 1943, pp. 336, 340. [b] Constants for the equation $\log P = -A/T + B$.

TABLE III

HEATS OF COMBUSTION AND HEATS OF FORMATION OF SEVERAL TIN TETRAALKYLS AT 300°K. AND 1 ATM.

Compound	$-\Delta H$comb., kcal./mole	Calcd. $-\Delta H$comb.	ΔHform, kcal./mole
$(CH_3)_4Sn$	934 ± 3 904 ± 10[a]	920	+9
$(CH_3)_3SnC_2H_5$	1034 ± 5	1077	+53
$(CH_3)_2Sn(C_2H_5)_2$	1221 ± 5	1234	+28
$CH_3Sn(C_2H_5)_3$	1358 ± 1	1391	+54
$(C_2H_5)_4Sn$	1547 ± 2 1521[b]	1548	−27 −39[b]
$(C_2H_5)_2Sn(C_4H_9)_2$	2170 ± 2	2176	−54
$(C_4H_9)_4Sn$	2816 ± 4 2773[b]	2804	−57 −111[b]
$(C_6H_{13})_4Sn$	4060 ± 3	4060	+119

[a] Data of Lippincott and Tobin.[3] [b] Data of Jones, *et al.*[4]

Table III. To obtain the values reported in the table, the following corrections were applied: (1) all weighings were reduced to weight *in vacuo;* (2) the bomb process was corrected to constant temperature (27°); (3) the combustion reaction was corrected from one at constant volume to one at a constant pressure of one atmosphere. The latter two corrections were made according to the method of Washburn.[15] The data show the expected increase in the observed heats of combustion with increased size of substituent alkyl radical. With the exception of compounds containing methyl radicals, the heats of combustion may be represented by the empirical equation

$$-\Delta H_{300} = 157n + 292$$

where n is the number of carbon atoms in the molecule.

The heats of formation given in Table III were calculated from the heats of combustion, taking the heats of formation of $H_2O(l)$, $CO_2(g)$ and $SnO_2(s)$ to be 68.317, 94.052 and 138.8 kcal. per mole, respectively.[16–18]

Comparison of the heats of combustion observed in this work with those of previous investigators[3,4] reveal that the results obtained in this investigation are consistently larger in magnitude. The principal source of error in experiments of this type, where one of the combustion products is a solid, is failure to obtain complete combustion. This would lead to low values for the observed heats of combustion. This fact, in addition to the checks between individual determinations and the agreement, within the limits of experimental error, of the observed heats of combustion with a single empirical equation, supports the higher values obtained in this investigation.

Acknowledgment.—The authors are grateful to Mr. Samuel Von Winbush and Miss Essie Shelton who performed the analyses for carbon, hydrogen, tin and chlorine. Financial help received from the Office of Naval Research is also gratefully acknowledged.

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(15) E. W. Washburn, *J. Research Natl. Bur. Standards*, **10**, 525 (1933).

(16) D. D. Wagman, J. E. Kilpatrick, W. U. Taylor, K. S. Pitzer and F. D. Rossini, *ibid.*, **34**, 143 (1945).

(17) E. J. Prosen, R. S. Jessup and F. D. Rossini, *ibid.*, **33**, 447 (1944).

(18) J. Moose and S. W. Parr, THIS JOURNAL, **46**, 2656 (1924).

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

Some Studies on the Preparation of Arylboronic Acids[1]

BY HENRY GILMAN AND LEONARD O. MOORE[2]

RECEIVED JANUARY 16, 1958

The yields of boronic acids from the reaction of various organic derivatives of the Group II-B metals with tri-*n*-butyl borate are not as good as those obtained from the reaction of Grignard reagents with tri-*n*-butyl borate or from the reaction of organomercury compounds with boron trichloride. The course of the reaction of boron trichloride with organomercury compounds is dependent upon the groups substituted on the aromatic radical attached to the mercury.

An interest in boronic acids has developed recently because of the proposed use of boron-containing compounds in brain tumor therapy. The treatment involves the irradiation of carcinogenic tissue which has absorbed preferentially a compound containing boron-10.[3] Azo dyes which contain boron have been shown to be promising for this treatment,[4] but the work of several has shown

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(1) This work was supported in part by the United States Atomic Energy Commission under Contract No. AT(11-1)-59.

(2) Du Pont Teaching Fellow, 1956–1957.

(3) Naturally occurring boron contains 18.83% of this isotope. See NBS Circular No. 499, p. 7.

(4) H. Gilman, L. Santucci, D. R. Swayampati and R. O. Ranck, THIS JOURNAL, **79**, 2898 (1957).

that any boron-containing compound may be useful.[5]

The reaction of Grignard reagents with borate esters is a conventional procedure for the preparation of aromatic boronic acids[6,7]; however, many boronic acids cannot be prepared by this method because of side reactions. This study was undertaken to explore the possibility of using less reactive organometallic compounds than the Grignard reagents, which might allow the preparation of new boronic acids. Such boronic acids could conceivably be synthesized with many substituted groups which might aid the preferential absorption of the compound, or reduce undesirable secondary effects.[8]

A series of experiments was performed to compare the reactions of the organic derivatives of zinc, cadmium and mercury with tri-*n*-butyl borate. This study indicated that the order of reactivity of these three metals was: Cd > Zn > Hg. The greater reactivity of cadmium was quite unexpected since previous studies on relative reactivities with active hydrogen had indicated that zinc was more reactive than cadmium.[9] No explanation is available for the apparent reversal of the order of reactivity for these two metals in these two different reactions.

Since organomercury compounds did not react with tri-*n*-butyl borate, attempts were made to use a more reactive boron compound. The reaction of diarylmercury compounds with boron halides at elevated temperatures and pressures is known.[10–13]

The high temperature and pressure reported by others earlier are not necessary, since the reaction of boron trichloride with diphenylmercury occurs very readily at room temperature and atmospheric pressure. The reaction is not instantaneous since work-up of the reaction mixture immediately after completion of the addition of the boron trichloride gave a lower yield than did the usual procedure of allowing the mixture to stir for 30 minutes after the addition. A 100% excess of boron trichloride appears to be necessary for the best yields. The yield of benzeneboronic acid, after hydrolysis, is about the same as that which can be obtained from the reaction of tri-*n*-butyl borate with phenyllithium[14] or phenylmagnesium halide.

Before hydrolysis of the reaction mixture, the mercuric chloride which has been produced must be filtered from the solution of the arylboron dichloride. Mercury salts react with arylboronic acids to yield boric acid and the diarylmercury compound.[15,16] This reaction is so nearly complete that it has been developed into an analytical procedure for mercury.[17]

Groups attached to the aryl radical of the organomercury compound have a distinct effect upon the reaction. The hydroxy and amino groups, which aid electrophilic substitution reactions, not only seem to aid the displacement of mercury by boron, but also the displacement of boron by a proton. The reactivity in compounds containing these groups is so great that no arylboronic acid could be isolated under our experimental conditions. The three isomeric hydroxybenzeneboronic acids, which are not extremely unstable when pure, have been prepared by other means.[18] The carboxyl group has an effect opposite to that of the hydroxy and amino groups. The carboxyl group decreases the reactivity of the aryl radical so that the mercury is not displaced by boron even at elevated temperatures.

Experimental

Reaction of Tri-*n*-butyl Borate with Organic Compounds of Group II-B Metals.—To an ether solution of 0.1 equivalent of an organometallic reagent (0.1 mole of arylmetallic halides and 0.05 mole for diarylmetallic compounds) under an atmosphere of dry nitrogen in a three-necked, round-bottomed flask, was added 0.25 mole of tri-*n*-butyl borate[19] (150% excess). The reaction mixture was stirred for 6 hours and then was hydrolyzed by the addition of sufficient 10% sulfuric acid to obtain a clear aqueous layer. The layers were separated and the water layer extracted with 200 ml. of ether in three portions. The combined ether solution was then extracted with 200 ml. of 10% potassium hydroxide in three portions, and the basic solution acidified with 10% sulfuric acid to obtain the boronic acid.

TABLE I

BENZENEBORONIC ACID FROM TRI-*n*-BUTYL BORATE AND ORGANIC DERIVATIVE OF GROUP II-B METALS

ArM	Temp., °C.	Yield, %
$(C_6H_5)_2Zn$	25	7
$(C_6H_5)_2Zn$	−70	1
$(C_6H_5)ZnCl$	25	7
$(C_6H_5)_2Cd$	25	17
$(C_6H_5)_2Cd^a$	25	20
$(C_6H_5)_2Cd$	35	18
$(C_6H_5)_2Cd$	−12	14
$(C_6H_5)CdCl$	25	21
$(C_6H_5)_2Hg$	35	0
$(C_6H_5)_2Hg^b$	110	0

[a] Reacted for 48 hours with 0.5 mole of tri-*n*-butyl borate.
[b] Reacted for 144 hours in refluxing toluene.

Table I shows the results that were obtained from a series of reactions. The temperature is the temperature at which the tri-*n*-butyl borate was added to the organometallic re-

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(5) See ref. 4 for a bibliography on earlier work on the use of boron compounds in brain tumor therapy.

(6) M. F. Lappert, *Chem. Revs.*, **56**, 959 (1956).

(7) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, p. 1335.

(8) The reduction of undesirable biological effects of organic compounds by substituted groups is well established. The reduction of the carcinogenic activity of certain azo dyes by the presence of such groups as bromo, chloro, hydroxy, nitro and trifluoromethyl is an example. See J. P. Greenstein, "Biochemistry of Cancer," 2nd ed., Academic Press, Inc., New York, N. Y., 1954.

(9) J. F. Nelson, *Iowa State Coll. J. Sci.*, **12**, 145 (1937).

(10) A. Michaelis and P. Becker, *Ber.*, **13**, 58 (1880).

(11) A. Michaelis and P. Becker, *ibid.*, **15**, 180 (1882).

(12) A. Michaelis and M. Behrens, *ibid.*, **27**, 244 (1894).

(13) A. Michaelis, *Ann.*, **315**, 19 (1901).

(14) Yields of 70–75% of benzeneboronic acid have been obtained from phenyllithium and tri-*n*-butyl borate [H. Gilman and J. J. Goodman, unpublished studies]; 50–60% from phenyl Grignard and tri-*n*-butyl borate [F. R. Bean and J. R. Johnson, THIS JOURNAL, **54**, 4415 (1932); J. R. Johnson, private communication, Oct. 11, 1954]; and 80% from phenyl Grignard and trimethyl borate [P. A. McCusker, private communication, Feb. 23, 1955; Ruigh, Erickson, Gunderloy and Sedlak, Wright Air Development Center Technical Report 55-26, Part II, p. 59 (1955)].

(15) A. D. Ainley and F. Challenger, *J. Chem. Soc.*, 2171 (1930).

(16) H. R. Snyder and C. Weaver, THIS JOURNAL, **70**, 232 (1948).

(17) T. S. West, *Metallurgia*, **47**, 97 (1953) [*C. A.*, **47**, 4791 (1953)].

(18) H. Gilman, L. Santucci, D. R. Swayampati and R. O. Ranck, THIS JOURNAL, **79**, 3077 (1957).

(19) Part of the tri-*n*-butyl borate used in these studies was kindly provided by the Pacific Coast Borax Co.

agent and which was maintained until the mixture was hydrolyzed. The percentage yield is based upon the crude product. In all cases the purity of the crude acid seemed to be the same, since the melting points were nearly the same.

Reaction of Boron Trichloride with Organomercury Compounds.—The organomercury compound (0.05 mole) was suspended in 500 ml. of chlorobenzene in a three-necked, round-bottomed flask equipped with a stirrer, a Dry Ice–acetone condenser attached to a mercury pressure relief valve, and an inlet tube which extended below the level of the solvent. The inlet tube was connected through a mercury trap[20] to a tank of boron trichloride. Boron trichloride was bubbled into the mixture until the boron trichloride tank had decreased in weight the amount desired for the reaction. After stirring for the desired length of time, the mixture was filtered to remove the mercuric chloride and the filtrate was hydrolyzed by the slow addition of ice. The hydrolysis appeared to be catalyzed by hydrogen chloride and so once started was autocatalytic. The rate of hydrolysis could be controlled only by the amount of water added. The acid which was formed was extracted with 250 ml. of 10% potassium hydroxide in four portions. The aqueous solution was washed with 100 ml. of ether and then acidified. The cream colored solid which separated was filtered and recrystallized from water.

The results of several reactions are summarized in Table II.

TABLE II

REACTION OF BORON TRICHLORIDE WITH ORGANOMERCURY COMPOUNDS

ArM	Excess BCl_3, %	Reacn. time, hr.[a]	Yield, %[b]
$(C_6H_5)_2Hg$	100	0.5	70.5
$(C_6H_5)_2Hg$	100	0	55.0
$(C_6H_5)_2Hg$	50	2.5	52.0
$(C_6H_5)_2Hg$	50	3	57.0
$(C_6H_5)_2Hg$	200	6	70.0
p-$ClHgC_6H_4OH$[c]	100	10	0.0[d]
p-$CH_3COOHgC_6H_4NH_2$	100	10	0.0[e]
p-$ClHgC_6H_4COOH$	100	4	0.0[f]
p-$ClHgC_6H_4COOH$[g]	1000	12	0.0[f]

[a] This represents the time after the addition of the boron trichloride was complete. [b] The yield is based upon the recrystallized boronic acid. [c] Used 0.2 mole of organomercury compound. [d] There was separated 54% of phenol and 92% of mercuric chloride. [e] Isolated nearly 100% of mercuric chloride. [f] Recovered the starting mercury compound quantitatively. [g] This reaction was run at 120°.

AMES, IOWA

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[20] (20) This trap served to remove any chlorine which was present in the boron trichloride as well as to allow the rate of addition to be observed carefully.

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

Aryl Boronic Acids. II. Aryl Boronic Anhydrides and their Amine Complexes[1]

BY H. R. SNYDER, MILTON S. KONECKY[2] AND W. J. LENNARZ

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The change of an arylboronic acid to its anhydride, which sometimes occurs when the acid is simply warmed in an anhydrous solvent, can be detected by examination of the infrared absorption spectrum of the sample. As a result of the change, the hydroxyl absorption band of the acid disappears and a new absorption near 700 cm.$^{-1}$, characteristic of the anhydride, appears. The bromination of p-tolueneboronic acid in carbon tetrachloride is found to produce a mixture of p-bromomethylbenzeneboronic acid and its anhydride. The yield in the bromination is increased by prior conversion of p-tolueneboronic acid to its anhydride. The formation of complexes between arylboronic anhydrides and amines is studied further, and the use of the complexes in the purification of the boronic acids is suggested.

The syntheses of boronic acid analogs of azo dyes,[3a,b,4] diaminoacridine dyes[5] and certain amino acids[6] are of interest because the substances may be of use in the boron-disintegration therapy of brain tumors proposed by Kruger.[7] In this therapy, tumor cells are destroyed by the dissipation of the high energy of products resulting from the neutron-induced disintegration of the boron isotope 10 which has been localized within the neoplasm in the form of some suitable organic derivative.

In the course of recent studies in this Laboratory devoted to the synthesis of these boronic acid analogs, the ease with which aryl boronic acids form the corresponding anhydrides, a phenomenon noted by Gilman, *et al.*,[8] for o-hydroxybenzeneboronic acid, has been observed. With the objective of developing a criterion for distinguishing a boronic acid and its anhydride from each other and from mixtures of both, the infrared spectra of several aryl boronic acids and the corresponding anhydrides were studied.

As a result of this study a region of absorption, invariably strong and sharp, between 680 and 705 cm.$^{-1}$ has been empirically assigned to the aryl boronic anhydride structure. This absorption is absent from the spectrum of a pure aryl boronic acid, while the infrared absorption attributed to the hydroxyl group of a boronic acid is not detected in the spectrum of a pure anhydride. The infrared spectrum of a mixture of an acid and anhydride exhibits both of these absorption bands in diminished intensity. Table I shows the region of absorption in the infrared for the hydroxyl group of the boronic acid together with the position of the anhydride band for the corresponding anhydride. The absorption band which invariably occurs near 1350 cm.$^{-1}$ with both aryl boronic acids

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[1] (1) Part of this work was supported by a grant [AT(11-1)-314] from the Atomic Energy Commission.

[2] (2) Texas Co. Fellow, 1956–1957.

[3] (3) (a) H. R. Snyder and C. Weaver, THIS JOURNAL, **70**, 232 (1948); (b) H. R. Snyder and S. L. Meisel, *ibid.*, **70**, 774 (1948).

[4] (4) H. Gilman, L. Santucci, D. Swayampati and R. Ranck, *ibid.*, **79**, 2898 (1957).

[5] (5) M. S. Konecky, Thesis, Doctor of Philosophy, University of Illinois, 1958.

[6] (6) H. R. Snyder, A. J. Reedy and W. J. Lennarz, THIS JOURNAL, **80**, 835 (1958).

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

[8] (8) H. Gilman, L. Santucci, D. Swayampati and R. Ranck, THIS JOURNAL, **79**, 3077 (1957).