[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY]

Organoboron Compounds. XI. Isomerization of 2,2'-Tolandiboronic Acid[1]

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2,2'-Dibromotolan, prepared from 2,2'-dibromobibenzyl, was converted to 2,2'-tolandiboronic acid (I) by successive reactions with *n*-butyllithium, *n*-butyl borate and water. Although stable in the presence of dilute hydrochloric acid or an acetic acid–sodium acetate buffer, Compound I isomerized to a new boronic acid, VIII, in mild alkaline solutions or in an acidic solution which contained sodium hydrogen tartrate. The net effect of the transformation was addition of a dihydroxyboryl group to the carbon–carbon triple bond. It is suggested that this isomerization involves the interaction of a complex of the boronic acid with the neighboring functional group.

2,2'-Tolandiboronic acid (I) was selected for synthesis and study since it would serve to test for possible chemical reactions involving a dihydroxyboryl group and an adjacent carbon–carbon triple bond. Aside from the intrinsic interest of investigating new functional group reactions, we wished to learn whether alkyne linkages would be sufficiently stable to be used as "spacers" in construction of polyfunctional boronic acid compounds with a prescribed geometry.[3]

The synthesis of 2,2'-tolandiboronic acid is outlined in Fig. 1.

Bromination of the known 2,2'-dibromobibenzyl[4] with *N*-bromosuccinimide yielded α,α',2,2'-tetrabromobibenzyl (II), which, in turn, afforded III on treatment with potassium hydroxide in triethylene glycol at 165°; III melted sharply at 73–73.5°, exhibited fine structure in the ultraviolet spectrum similar to that for tolan, and analyzed satisfactorily for dibromotolan. However, the presence of a band at 10.45μ in the infrared spectrum indicated that III might be a mixture of dibromotolan and dibromostilbene rather than the expected pure dibromotolan. This view was supported by a metal–halogen interchange reaction with butyllithium, which yielded, on hydrolysis, a mixture of tolan and stilbene.

Pure 2,2'-dibromotolan (V) was obtained from III by the following steps: (a) addition of bromine to form a mixture of α,α',2,2'-tetrabromostilbene (IV) and II; (b) heating the mixture of tetrabromides with potassium hydroxide in triethylene glycol to dehydrohalogenate II, thereby facilitating the separation and purification of IV; and (c) debromination of IV with zinc dust. The recovery of V from III was 65% and the over-all yield from 2,2'-dibromobibenzyl, 50%; V melted at 81° and did not absorb in the 10.4 μ region. Tolan, free of stilbene, was obtained on hydrolysis of the products of an interchange reaction with butyllithium.

Dehalogenation was not expected in the reaction of II with potassium hydroxide since *meso*-α,α'-dibromobibenzyl has been reported to give tolan under similar conditions without this complication.[5] On the other hand, debromination of stilbene dibromides by weaker bases such as pyridine[6] and potassium carbonate[6,7] is known to occur. We found that II also lost bromine when warmed with pyridine to give a high yield of 2,2'-dibromostilbene (VI),[8] identical with a sample of 2,2'-dibromostilbene prepared by the method of Stanfield and Reynolds.[9] A mixture consisting of 84% IV and 16% VI melted at 72–73° and showed the same infrared spectrum as III.

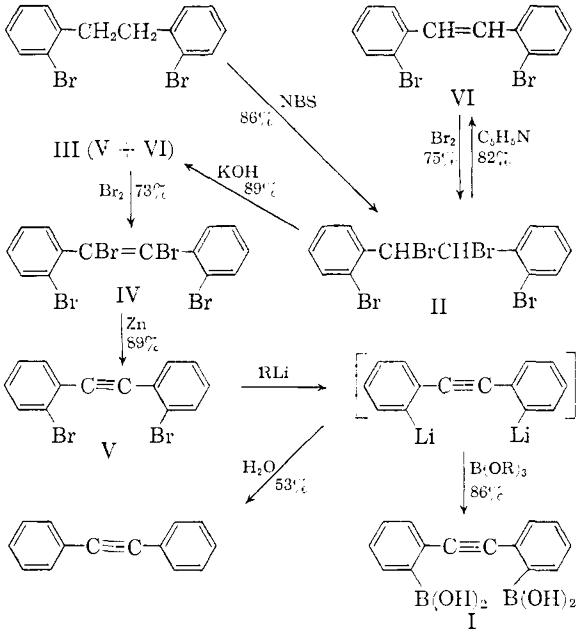

Fig. 1.—Preparation of 2,2'-tolandiboronic acid.

The reaction of 2,2'-dibromotolan with butyllithium, followed by successive addition of butyl borate and water, yielded 2,2'-tolandiboronic acid (86%). This acid was characterized by a neutralization equivalent, the preparation of a bis-dihydrobenzoboradiazole derivative(VII)[10] and oxidation to 2,2'-dihydroxytolan by hydrogen peroxide in acetic acid. The action of water at 200° led to formation of desoxybenzoin.

Compound I proved to be much less stable in alkaline solutions than benzeneboronic acid. It

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[1] For the previous paper in this series see R. L. Letsinger and S. B. Hamilton, THIS JOURNAL, **81**, 3009 (1959).

[2] National Science Foundation Predoctoral Fellow, 1954–1958.

[3] For example, an alkyne linkage might be used to separate aromatic rings bearing -B(OH)₂ and basic N in catalysts of the type of 8-quinolineboronic acid (R. L. Letsinger and S. H. Dandegaonker, THIS JOURNAL, **80**, 498 (1958)).

[4] R. L. Letsinger and I. Skoog, *ibid.*, **77**, 5176 (1955).

[5] L. F. Fieser, *J. Chem. Ed.*, **31**, 291 (1954).

[6] P. Pfeiffer, *Ber.*, **45**, 1810 (1912).

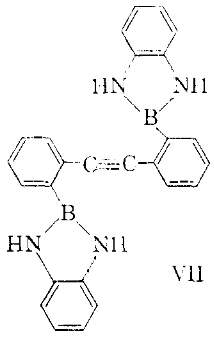
[7] P. Ruggli and R. E. Meyer, *Helv. Chim. Acta*, **5**, 49 (1922).

[8] Since with pyridine *meso*- and *d,l*-α,α'-dibromobibenzyl yield stilbene and α-bromostilbene, respectively (Pfeiffer, ref. 6), this result indicates that II is a *meso* isomer. A further analogy in support of this assignment is that bromination of bibenzyl by N-bromosuccinimide gives *meso*-α,α'-dibromobenzyl; F. D. Green, W. H. Remers and J. W. Wilson, THIS JOURNAL, **79**, 1416 (1957).

[9] J. A. Stanfield and L. B. Reynolds, *ibid.*, **74**, 2878 (1952).

[10] R. L. Letsinger and S. B. Hamilton, *ibid.*, **80**, 5411 (1958).

could be dissolved in dilute, aqueous sodium hydroxide and be recovered unchanged on acidification; however, when mild alkaline solutions of I (*p*H 9–10) were heated, a chemical change took place and a new boronic acid (VIII) was obtained on acidification. Hot, concentrated alkaline solutions converted I to a complex, oily mixture of products.


VII

Elemental analyses showed that VIII was an isomer of I ($C_{14}H_{12}O_4B_2$), and a neutralization equivalent indicated the presence of one titratable boronic acid group. Numerous differences were found in the infrared spectra of I and VIII (Fig. 3), the most significant being a new, sharp band for VIII at 6.1 μ (C=C region); VIII was converted by reaction with *o*-phenylenediamine to a bis-dihydrobenzoboradiazole (IX) which was isomeric with VII and, like VIII, exhibited a band at 6.1 μ. Oxidation of VIII with hydrogen peroxide afforded 2-(o-hydroxyphenyl)-benzofuran, and hydrolysis with water at 200° gave desoxybenzoin (see Fig. 2).

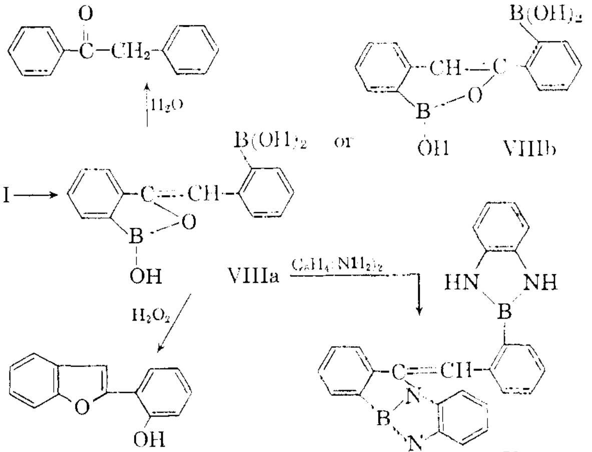
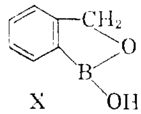


Fig. 2.—Reactions of VIII.

These data are interpretable on the basis that VIII is the heterocyclic compound that would result from addition of a dihydroxyboryl group to the carbon–carbon triple bond. The present facts are not sufficient to differentiate between structures VIIIa and VIIIb (or IXa and a six-membered B-N-C heterocyclic system IXb), though we tend to prefer the smaller ring structures on the basis of the general proclivity of boron to form five-membered cyclic esters and complexes.

The unusual stability of the boron ester (VIII) in the presence of water finds analogy in the chemistry of compound X, which is reported to resist hydrolysis in 10% hydrochloric acid and boiling 15% potassium hydroxide.[11] The lack of acidity of the ring boron in the presence of mannitol is more surprising. We plan to prepare related, unsaturated cyclic compounds to learn more about the properties of such systems.


X

In Table I are summarized the results of a survey of the effects of various added reagents on the isomerization of 2,2′-tolandiboronic acid. The reactions were carried out in alcohol–water mixtures at reflux temperature for three hours. Two interesting conclusions may be drawn from these data. (1) The formation of VIII depends upon the hydroxide ion concentration. Thus, no isomerization could be detected for the experiments carried out in the presence of hydrochloric acid, tartaric acid, or an acetic acid–sodium acetate buffer. In solutions at *p*H 8.1–8.2 (sodium acetate or sodium hydroxide as the added reagent) the isomerization was of the order of 12–20%, and in a solution at *p*H 9.1 (sodium hydroxide added) it was about 90%. (2) The formation of VIII is markedly influenced by tartrate ion. For a reaction carried out in the presence of disodium tartrate the percentage of VIII in the recovered boronic acids was over 60% even though the *p*H of the medium was only 8.0. Even more striking, *20% isomerization of I occurred in an acidic solution (pH 4.2) which contained monosodium tartrate.* For a similar larger scale reaction that was carried out for twenty-four hours the conversion to VIII was almost quantitative.

TABLE I

CONVERSION OF I TO VIII IN ALCOHOL-WATER SOLUTIONS[a]

Added reagent	*p*H[b]	% VIII in recovd. B cpds.	Wt. % B cpds. recovd.
None	7.7	3	89
HCl[c]	1.0	0	92
NaOH[d]	8.1	12	80
NaOH[d]	8.1	20	70
NaOH[e]	9.2	90	70
NaOAc[f]-HOAc[f]	5.7	0	94
NaOAc[f]	8.2	18	79
Tartaric acid[g]	2	0	89
Na H tartrate[g]	4.2	20	77
Na H tartrate[g]	..	20	75
Na_2 tartrate[g]	8.0	63	90
Na_2 tartrate[g]	..	66	77

[a] General conditions are described in the Experimental section. [b] Measured on a Beckman *p*H meter. [c] This solution contained 0.132 g. of I, 25 ml. of 95% ethanol, 14 ml. of water and 1 ml. of concd. hydrochloric acid. [d] Solution made basic by addition of 0.2 ml. of 0.072 *N* sodium hydroxide. [e] Solution made basic by addition of 3.0 ml. of 0.072 *N* sodium hydroxide (in place of 3 ml. of water). [f] Mole ratio of added reagent to I = 14.32. [g] Mole ratio of added reagent to I = 7.16.

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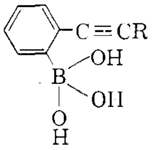
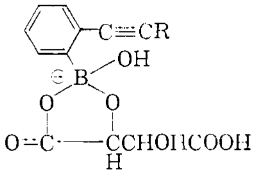
(11) H. R. Snyder, A. J. Reedy and W. J. Lennarz, THIS JOURNAL, **80**, 835 (1958); see also K. Torssell, *Arkiv Kemi*, **10**, 507 (1957).

Boric acid functions as a Lewis-type acid in aqueous solution.[12] Furthermore, boric acid[13] and benzeneboronic acid[14] form relatively stable complexes with monosodium tartrate. We therefore suggest, as the most likely of several possible mechanisms, that the isomerization of I may proceed by transfer of OH^- from a complex of the boronic acid (XIa for the base reaction, XIb for the tartrate reaction) to the neighboring alkyne linkage. According to this hypothesis the tartrate complex acts as a local source of hydroxide ion even though the bulk of the solution is acidic, a concept that raises the interesting possibility that complexing agents in general may have marked effects on rates of base-catalyzed reactions that involve functional groups in the vicinity of dihydroxyboryl groups.


XIa


XIb

Experimental Part

Infrared spectra were recorded with a Baird spectrophotometer, model AB-2, with the sample in potassium bromide. Ultraviolet spectra were taken with a DK-2 Beckman ratio recording instrument, with 95% ethanol as solvent. Carbon, hydrogen and nitrogen analyses were performed by Miss H. Beck.

α,α'-2,2'-Tetrabromobibenzyl (II).—A mixture of 103.5 g. (0.305 mole) of 2,2'-dibromobibenzyl,[4] 114.5 g. (0.645 mole) of N-bromosuccinimide, 1.0 g. (0.0041 mole) of benzoyl peroxide and 1.5 liters of dry carbon tetrachloride was refluxed for 19 hours. The precipitate was filtered and washed several times with hot water to give after drying 118.3 g. (78.1%) of white crystals, m.p. 241–242°. Distillation of the carbon tetrachloride and washing the residual solid with water furnished an additional 11.7 g. of product, m.p. 237.5–239°, total yield 85.6%. Subsequent recrystallizations from chloroform gave the analytical sample, m.p. 242.0–242.6°. The most prominent peaks in the infrared spectrum occurred at 6.8, 6.92, 7.83, 8.48, 8.80, 9.73, 12.17, 13.15, 13.82 and 15.20 μ.

Anal. Calcd. for $C_{14}H_{10}Br_4$: C, 33.77; H, 2.02. Found: C, 33.80; H, 1.96.

Preparation of III.—As in the preparation of tolan,[5] a mixture of 92.6 g. (0.186 mole) of tetrabromo compound II, 35.3 g. (0.628 mole) of potassium hydroxide and 800 ml. of triethylene glycol was heated with stirring for 5 minutes at 160–165°; then it was cooled and poured into a large excess of water. After standing, the precipitate was filtered, washed with water and recrystallized from ethanol; m.p. 71–73°, weight 55.8 g. (89.4%); m.p. after further recrystallization, 73.0–73.5°.

Anal. Calcd. for $C_{14}H_8Br_2$: C, 50.04; H, 2.40. Found: C, 50.2; H, 2.58.

α,α',2,2'-Tetrabromostilbene (IV).—A solution of 10 ml. (0.195 mole) of bromine in 40 ml. of carbon tetrachloride was slowly added to 49.8 g. (0.148 mole) of III dissolved in 200 ml. of carbon tetrachloride. Throughout addition the mixture was warmed on a steam-bath. Excess bromine and most of the solvent were then distilled away, leaving about 70 g. of a white, crystalline solid. This product was heated with 7.1 g. of potassium hydroxide in 500 ml. of triethylene glycol for 5 minutes at 160–170°; then the mixture was poured into water and the precipitate collected and recrystallized from chloroform. The first crop of crystals (49.1 g.) melted at 255.0–255.5°, and the second crop, (4.8 g.) at 253–254° (73.4% total yield). Strong absorption in the infrared occurred at 6.80, 6.95, 9.50, 9.76, 11.75, 13.05, 13.64 and 14.85 μ.

Anal. Calcd. for $C_{14}H_8Br_4$: C, 33.91; H, 1.63. Found: C, 33.96; H, 1.62.

2,2'-Dibromotolan (V).—A mixture of 55.5 g. (0.112 mole) of α,α',2,2'-tetrabromostilbene, 130 g. (2 g. atoms) of zinc dust and 1.5 liters of acetone was heated at reflux temperature for 3 hours and then cooled and filtered through a sintered glass funnel. Distillation of the acetone left a residue which was washed with water and recrystallized from ethanol, giving 33.3 g. (88.7%) of 2,2'-dibromotolan, m.p. 81.0–81.5°; infrared λ 6.73, 6.95, 9.55, 9.69, 13.18, 13.30, 13.92 and 14.10 μ.

Anal. Calcd. for $C_{14}H_8Br_2$: C, 50.04; H, 2.40. Found: C, 50.21; H, 2.39.

Metal-Halogen Exchange Reactions with V and III.—A solution of 1.71 g. (0.00509 mole) of V in 40 ml. of ether was added to a stirred solution of butyllithium (0.0115 mole) in 25 ml. of ether at ice temperature. A nitrogen atmosphere was maintained throughout the reaction. After 15 minutes of stirring the mixture was allowed to warm to room temperature and hydrolyzed by addition of a saturated aqueous solution of ammonium chloride. The ether layer was dried over magnesium sulfate and the low boiling organic matter removed by distillation. On recrystallization of the residue from ethanol 0.48 g. (53%) of tolan, m.p. 58–60°, was obtained.

The reaction of III with butyllithium was carried out in a similar way. In this case the quantities of reagents were: 12.7 g. of III in 30 ml. of ether and 70 ml. of 1.20 *M* butyllithium. The product weighed 3.29 g. and melted at 68–72°. After two recrystallizations from ethanol the melting range was 87–95°. The infrared spectra showed that these materials were mixtures of tolan and stilbene.

2,2'-Dibromostilbene (VI).—A mixture of 1.33 g. of II and 20 ml. of pyridine was refluxed for two hours and poured into 100 ml. of 3 *M* hydrochloric acid. The precipitate on recrystallization from chloroform-hexane gave 0.74 g. (82%) of 2,2'-dibromostilbene, m.p. and mixed m.p. with a sample prepared by the method of Stanfield and Reynolds,[9] 109–110°. In our hands this provided a more convenient route to VI than the desulfuration of *o*-bromothiobenzaldehyde.[9] Infrared absorption occurred at 6.3, 6.8, 6.95, 8.2, 9.8, 10.45, 13.28, 13.9 and 15.2 μ, and the ultraviolet spectrum contained two maxima; λ 293 mμ (ε 24,000) and 232 mμ (ε 17,000). Absorption at 10.45 μ is characteristic of *trans*-stilbenes,[15] and the ultraviolet spectrum is also typical of *trans*-stilbenes. With *cis*-stilbenes the relative magnitude of the extinction coefficients of the two maxima is reversed.[15,16] These facts, supported by analogies to the chemistry of *trans*-stilbene (*trans*-stilbene is formed by dehalogenation of the *meso*-α,α'-dibromobibenzyl and yields a *meso* isomer on reaction with bromine) and by the stability of VI[9] establish with a high degree of probability that VI is a *trans* isomer, as previously suggested.[9]

A mixture of 60.6 g. (0.180 mole) of 2,2'-dibromostilbene, 40.5 g. (0.253 mole) of bromine and 350 ml. of carbon tetrachloride was refluxed for 20 hours. The precipitate was filtered, washed with carbon tetrachloride and dried, giving 67.2 g. (75%) of II, m.p. 241–242.5°.

2,2'-Tolandiboronic Acid.—A solution of 101 ml. of 0.852 *M* *n*-butyllithium (0.086 mole) was added to a stirred solution of 14.40 g. (0.0429 mole) of 2,2'-dibromotolan in 100 ml. of ether cooled in an ice-bath. The yellow mixture was stirred at 0° for 30 minutes; then it was cooled to −75° by a Dry Ice-bath. A cold solution of 20.9 g. (0.091 mole) of *n*-butyl borate in ether was rapidly added to the stirred solution (the temperature rose to −50°), after which the mixture was stirred for one hour (−75°), allowed to warm to room temperature, and poured into 3 *M* hydrochloric acid. The ether layer was separated and extracted twice with dilute sodium hydroxide solution. On acidification a white solid, m.p. 212–223°, precipitated; weight, 1.15 g. Recrystallization from ethanol–water gave 9.88 g. (86.5%) of purified 2,2'-tolandiboronic acid. The neutralization equivalent (mannitol present during the titration) of a

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[12] J. O. Edwards, C. G. Morrison, V. F. Ross and J. W. Schylz, THIS JOURNAL, **77**, 266 (1955); K. Torssell, *Arkiv Kemi*, **10**, 511 (1957).

[13] E. Darmois, *Compt. rend.*, **190**, 371 (1930); *J. chim. phys.*, **27**, 179 (1930).

[14] S. B. Hamilton, unpublished results.

[15] D. F. DeTar and L. A. Carpino, THIS JOURNAL, **78**, 475 (1956).

[16] M. Calvin and H. W. Alter, *J. Chem. Phys.*, **19**, 765 (1951); J. F. Codington and E. Mosettig, *J. Org. Chem.*, **17**, 1027 (1952).

sample melting at 233–234° was 135; that calculated for $C_{14}H_{12}B_2O_4$ is 133.

In one experiment there was isolated in addition to 2,2′-tolandiboronic acid a small amount (6% yield) of another boronic acid, m.p. 88–90°. The neutralization equivalent (298) and the analysis of the derivative with *o*-phenylenediamine (m.p. 126–127°, *Anal.* Found: N, 7.72) indicated that the substance was 2-bromo-2′-tolanboronic acid.

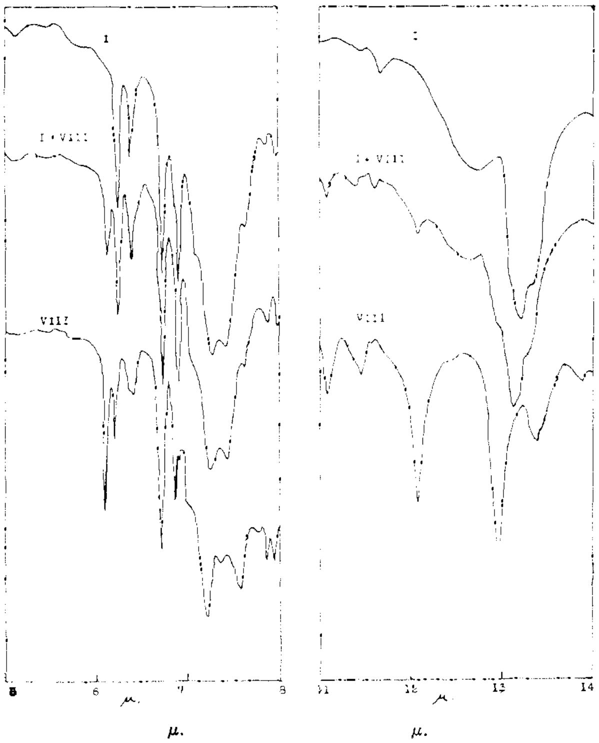

Fig. 3.—Infrared spectra of 2,2′-tolandiboronic acid (I), its isomerization product VIII, and a mixture of I and VIII.

Bis-dihydrobenzoboradiazole Derivative of 2,2′-Tolandiboronic Acid (VII).—A mixture of 0.849 g. of 2,2′-tolandiboronic acid, 0.691 g. of *p*-phenylenediamine and 20 ml. of ethanol was boiled for a few minutes on a hot-plate; then toluene was slowly added until all ethanol and water had been expelled from the boiling solution. White crystals separated from the hot solution, whereupon the mixture was allowed to cool and stand a few days at room temperature until a small volume of toluene remained. Filtration yielded 1.23 g. (94%) of the dihydrobenzoboradiazole derivative, m.p. 266–271°. An analytical sample was obtained by recrystallization from carbon tetrachloride, m.p. 274–275°; infrared 2.87, 6.74, 6.88, 7.07 (very strong), 7.32, 7.8, 13.2 and 13.7 μ.

Anal.[17] Calcd. for $C_{26}H_{20}B_2N_4$: C, 76.14; H, 4.92; B, 5.28; N, 13.66. Found: C, 75.52; H, 5.04; B, 5.21; N, 13.89.

The melting point of this derivative was sharp and reproducible. By contrast, the melting point of the boronic acid I was not a satisfactory physical constant. It depended upon the rate of heating and the manner of drying, and samples with considerably different melting points showed identical infrared spectra.

Oxidation of I with Hydrogen Peroxide.—A solution containing 0.251 g. of 2,2′-tolandiboronic acid, 10 ml. of 30% hydrogen peroxide, 10 ml. of ethanol, 10 ml. of acetic acid and 5 ml. of water was allowed to stand 10 minutes at room temperature and then poured into 150 ml. of water. On cooling and filtration, 0.114 g. (60%) of 2,2′-dihydroxytolan was obtained, m.p. 128–130°. Two recrystallizations from ethanol–water raised the melting point to 130–131°, infrared λ 2.93 μ (strong band, O–H). The product was free of boron as shown by lack of a green flame on burning and absence of boron absorption in the 7.4 μ region.

Anal. Calcd. for $C_{14}H_{10}O_2$: C, 79.88; H, 4.79. Found: C, 80.08; H, 4.79.

To confirm the structure of this phenol, which is a new compound, a sample was allowed to stand overnight with an ether solution of diazomethane. The solid remaining after evaporation of the ether was washed with potassium hydroxide solution and taken up in chloroform. This solution was filtered to remove a small amount of insoluble matter, the chloroform was evaporated, and the residue recrystallized from ethanol; m.p. 122–124°, lit. value for 2,2′-dimethoxytolan, 125°, 126°.[18] No absorption occurred in the 2.9 μ region.

Preparation of VIII from I in the Presence of Tartrate.—A mixture of 2.40 g. (9 mmoles) of 2,2′-tolandiboronic acid, 2.89 g. (19.2 mmoles) of *d*-tartaric acid, 8.8 ml. of 2.18 *M* sodium hydroxide solution (19 mmoles) 67 ml. of water and 75 ml. of ethanol was refluxed for 24 hours. After cooling and acidification with 3 ml. of concd. hydrochloric acid the solution was reduced to half its volume by distillation *in vacuo*. The resulting precipitate was collected, washed thoroughly with sodium bicarbonate solution and water, and dried at 55° overnight. The product, 2.15 g. (89.5%), m.p. 170–200°, on recrystallization from acetic acid gave needles, m.p. 201–202°.

Anal. Calcd. for $C_{14}H_{12}O_4B_2$: C, 63.24; H, 4.55; B, 8.14; neut. equiv., 266 (on assumption of one titratable boronic acid group per molecule). Found: C, 63.15[19]; H, 4.57[19]; B, 8.81[17]; neut. equiv. (titration with mannitol present), 268.

In another experiment the conversion I → VIII was carried out in the presence of disodium tartrate. The quantities of reagents were 1.47 g. of I, 5.86 g. (0.039 mole) of *d*-tartaric acid, 30.5 ml. of 2.56 *M* sodium hydroxide solution (0.78 mole), 85 ml. of ethanol and 55 ml. of water. The solution was refluxed for 6.25 hours and worked up as in the previous case. The product, 1.16 g. (79%), was the same as obtained from the monosodium tartrate reaction.

Derivative of VIII with *o*-Phenylenediamine (IX).—By the procedure used for preparation of VI, 0.838 g. (65.9%) of a dihydrobenzoboradiazole type derivative IX was obtained from 0.824 g. (3.1 mmoles) of VIII and 0.670 g. (6.2 mmoles) of *o*-phenylenediamine. After two recrystallizations from carbon tetrachloride it melted at 227.5–228°. Some of the major differences in the infrared spectra of IX and VI resembled the differences for the spectra of VIII and I in that VIII showed strong absorption bands which were absent for I at 6.15, 12.0 and 12.93 μ.

Anal. Calcd. for $C_{26}H_{20}B_2N_4$: C, 76.14; H, 4.92; B, 5.28; N, 13.66. Found: C,[17] 75.52; H,[17] 4.97; B,[17] 5.33; N, 13.37.

Oxidation of VIII with Hydrogen Peroxide.—A solution of 4.8 g. of 30% hydrogen peroxide was added to a mixture of 1.02 g. of VIII in a solution of 5 ml. of acetic acid, 5 ml. of ethanol and 5 ml. of water. After 10 minutes the mixture was poured into water and worked up as in the oxidation of I. There was obtained 0.497 g. (62%) of 2-(*o*-hydroxyphenyl)-benzofuran, m.p. 90–94°. After two recrystallizations from methanol–water it melted at 97.5–98°, lit.[20] 94–98°. A flame test for boron was negative. Ferric chloride reagent gave a dark solution. The infrared spectrum showed a medium band at 3.0 μ (O-H) but no carbonyl band and no band at 6.1 μ.

Anal. Calcd. for $C_{14}H_{10}O_2$: C, 79.98; H, 4.79. Found: C, 79.50; H, 4.75.

As added evidence for the structure of the oxidation product, a benzoate ester was prepared by shaking an alkaline solution of the hydroxyphenylbenzofuran with benzoyl chloride until the excess benzoyl chloride had dissolved. The ester, separated by an ether extraction, melted after recrystallization from ethanol-water at 108–108.5°. The infrared spectrum showed a band at 5.77 μ (C=O) but no bands at 3.0 or 6.1 μ.

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(17) Carbon, hydrogen and boron analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

(18) G. H. Coleman, W. H. Holst and R. D. Maxwell, This Journal, **58**, 2310 (1936); C. Weygand and T. Siebenmark, *Ber.*, **73**, 765 (1940).

(19) Analysis performed by the Microtech Laboratories, Skokie, Ill.

(20) F. B. LaForge, This Journal, **55**, 3040 (1933).

Anal. Calcd. for $C_{21}H_{14}O_3$: C, 80.24; H, 4.49. Found: C, 79.80; H, 4.49.

Hydrolytic Cleavage of I and VIII.—2,2′-Tolandiboronic acid (0.507 g.) and 0.4 ml. of water were sealed in a Pyrex tube and heated for 29 hours at 200° in an autoclave. Compound VIII (0.331 g.) and 0.4 ml. of water were treated similarly. Both reactions yielded yellow oils which were ether soluble and a white solid (boric acid) which was insoluble in ether. The ether solutions were washed with sodium hydroxide solution and evaporated. The product from VIII solidified (m.p. 25–45°), and the infrared spectrum was essentially the same as that of an authentic sample of desoxybenzoin. The residue from the reaction of I failed to crystallize. Both the product from VIII and I, however, yielded a 2,4-dinitrophenylhydrazone derivative which melted at 201–202°. Desoxybenzoin 2,4-dinitrophenylhydrazone melted at 200–202° and the melting point was not depressed on admixture with the dinitrophenylhydrazone derivatives of the products of I and VIII.

Test Series of Conversion of I to VIII.—Unless otherwise noted, the solutions contained in each case approximately 0.3 g. (accurately weighed) of 2,2′-tolandiboronic acid, 15 ml. of water, 15 ml. of 95% ethanol and the added reagents (sodium hydroxide, tartaric acid, etc.) as indicated in Table I. They were heated at reflux for 3 hours and then cooled, acidified with hydrochloric acid and stripped of most of the solvent *in vacuo*. The resulting precipitates were collected, washed with sodium bicarbonate and with water and dried at 55°. Infrared spectra were taken in potassium bromide pellets which were 2% sample by weight. The significant features of the spectra of I, VIII, and one of the mixtures of I and VIII (from the sodium acetate reaction) are shown in Fig. 3. Increasing percentages of VIII were marked by increasing intensities of the bands at 6.1, 11.1, 12.1 and 12.9 μ and decreasing intensities of the bands at 6.25, 9.55 and 13.2 μ. (I and VIII absorbed strongly in the B–O region, 7.25 μ, and the O–H region, 2.95 μ for I and 2.90 μ for VIII. Neither absorbed in the region for anhydrides of boronic acids, 14–15 μ.[21]) It was found from known sample mixtures of I and VIII (possessing 0, 18, 50, 64 and 100% of VIII) that the ratio of the intensities of the bands at 6.1 and 6.25 μ (designated as R) was proportional to the percentage of VIII in the boronic acid mixture up to 64% VIII. The % VIII values listed in Table I were obtained from the empirical relationship: % VIII = 43*R*. The accuracy of these analyses was particularly good for low percentages of VIII. Since *R* was not very sensitive to minor fluctuations in thickness of the pellet or the concentration of the sample in the pellet even the poorer values in the range of 60% VIII should be within several per cent. of the true value. At high percentages of VIII the shape of the spectrum in the 12.8–13.4 μ region was a more reliable index of the composition than the bands at 6.1 and 6.25 μ.

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Stability and Synthesis of Phenylboronic Acids[1]

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The preparation of several substituted carboxyphenylboronic acids is described. The marked stability of the carbon–boron bond in such compounds is noted. Three boron-containing compounds with potential carcinostatic properties have been synthesized.

Introduction.—In an investigation designed to prepare organoboron compounds for possible utilization in the treatment of brain tumors by neutron-capture irradiation[2–7] several monosubstituted phenylboronic acids were screened[8] in C_3H mice with subcutaneous gliomas. The purpose of that study was to determine the structure and position of the substituted groups on the boronic acid which, in animal tests, resulted in a high tumor to brain differential boron concentration. An increased concentration in the neoplasm relative to the brain would permit selective destruction of tumor cells adjacent to normal nervous tissue upon thermal neutron irradiation. The feasibility of this procedure depends upon a difference in permeability between normal and neoplastic cells. In the case of brain and brain tumor, such a difference exists because of an alteration in the blood-brain barrier in the neoplasm.[9,10] Of the compounds tested,[8] those with a carboxyl group in the *m*- or *p*-position or a *meta*-ureido function offered the most promise with regard to toxicity and tumor to brain boron ratio. Consequently, the synthesis of other carboxyphenylboronic acids was undertaken.

Synthesis and Discussion.—The introduction of substituents into the nucleus or side chain of an aromatic boronic acid and the reactions which such compounds can undergo are very limited. The cleavage of the carbon–boron bond by a variety of agents such as acid, base, water at elevated temperatures, hydrogen peroxide, halogens, salts of the B subgroup elements and organometallic compounds is a facile process and has been observed by many investigators.[11–15] Attempts to prepare a boron-containing purine or pyrimidine by the interaction at elevated temperatures of *m*-aminophenylboronic acid with 6-methylmercaptopurine

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