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URBANA, ILLINOIS

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

# Synthesis of Aromatic Boronic Acids. Aldehydo Boronic Acids and a Boronic Acid Analog of Tyrosine[1]

BY H. R. SNYDER, ALBERT J. REEDY[2] AND WM. J. LENNARZ

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The synthesis of *o*- and *p*-bromomethylbenzeneboronic acids by the direct bromination of the tolueneboronic acids is described. *o*- and *p*-formylbenzeneboronic acids are prepared and some of their reactions with carbonyl reagents are studied. *p*-Bromomethylbenzeneboronic acid is converted to an analog of tyrosine having the boronic acid function in the place of the phenolic hydroxyl group.

Because of the numerous useful transformations to which benzyl halides and aromatic aldehydes can be submitted, it appeared probable that the substituted benzeneboronic acids carrying bromomethyl and aldehyde functions attached to the ring would be important intermediates for the synthesis of a variety of boron-containing aromatic compounds. Accordingly, a study of the synthesis and properties of *o*- and *p*-bromomethylbenzeneboronic acids and *o*- and *p*-formylbenzeneboronic acids was undertaken. Part of this work has been anticipated by Torssell,[3] who recently described the synthesis of all these compounds and the corresponding *m*-isomers. His method consisted in the introduction of one or two atoms of bromine into the methyl groups of the tolueneboronic acids, the aldehydes being obtained by hydrolysis of the dibromo derivatives. He chose the Ziegler reagent for the bromination because of the earlier report by Kuivila and Hendrickson[4] of the rapid brominolysis of aromatic boronic acids, whereby, for example, benzeneboronic acid is converted to bromobenzene. However, the experiments of Kuivila and Hendrickson[4] were conducted in 20% acetic acid, and it seemed to us by no means certain that direct bromination in anhydrous medium was excluded. It was found that in carbon tetrachloride solution and under the influence of light, *o*- and *p*-tolueneboronic acids were converted to the monobromomethyl derivatives in yields of about 90%. Torssell[3] obtained these compounds *via* the Ziegler bromination in approximately the same yield, and that method was also used in the present work.

The aldehyde synthesis contemplated consisted in the application of the Sommelet synthesis to the bromomethyl derivatives. This method proved satisfactory for the *p*-isomer, but with the *o*-bromomethyl derivative the yield was so low that it was impractical. The method developed for the *o*-aldehyde was essentially the same as that disclosed by Torssell,[3] except that we carried out the hydrolysis of the dibromomethyl derivative with alkali, whereas he employed sulfurous acid.

When *o*-bromomethylbenzeneboronic acid was extracted into aqueous 15% potassium hydroxide and the solution allowed to stand at room temperature for one hour before acidification, the product was the same as that obtained by Torssell[3] by hydrolysis with hot water and formulated as the cyclic ester I. This substance proved to be a remarkably stable boronic acid derivative. It resisted the action of dehydrating agents, being recovered unchanged even after treatment with refluxing thionyl chloride. It was also unexpectedly resistant to hydrolytic cleavage of the boronic function by acids or bases. For example, it was recovered almost quantitatively after refluxing for three hours with 10% hydrochloric acid, and even after fourteen hours the recovery was 50%. By contrast, only 10% of a sample of *p*-tolueneboronic acid was recovered after 1.5 hours, hydrolysis to toluene and boric acid having proceeded extensively. Similarly, compound I was recovered quantitatively after three hours of refluxing with 15% potassium hydroxide.

The low yield of the *o*-formylbenzeneboronic acid from the Sommelet reaction was due to the occurrence of another reaction of the primary amine which is an intermediate[5] in the Sommelet process. Under slightly different conditions from those under which the aldehydo boronic acid was obtained, there was produced a high melting substance whose analysis agreed with that calculated on the assumption of the addition of a molecule of formaldehyde and the loss of two molecules of water from the aminomethylbenzeneboronic acid. Of the structures considered (II, III, IV), only IV seems to accommodate the fact that the substance is soluble in dilute acids but insoluble in water and dilute alkali. If this is the actual structure the eight-membered ring is not highly stable, for conditions of diazotization convert the substance to the cyclic ester I.

*p*-Formylbenzeneboronic acid was found to undergo a number of the reactions characteristic of aromatic aldehydes, but in general only those

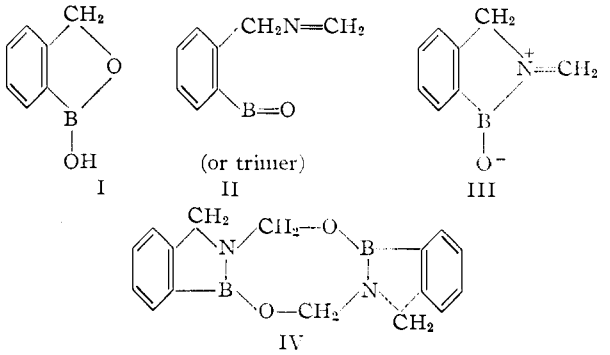
(1) Part of this work was supported by a grant [AT(11-1)-314] from the U. S. Atomic Energy Commission.

(2) Phillips Petroleum Co. Fellow, 1955–1956.

(3) K. Torssell, *Arkiv Kemi*, **10**, 507 (1957).

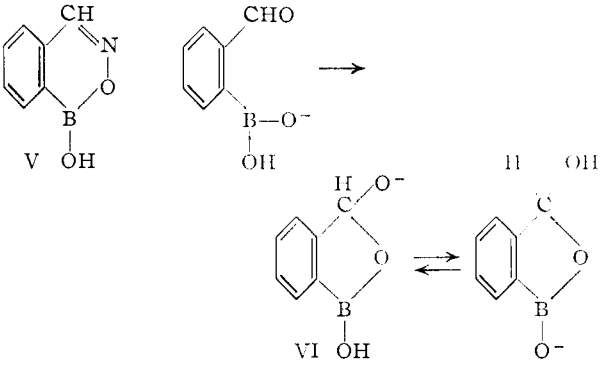
(4) H. F. Kuivila and A. R. Hendrickson, THIS JOURNAL, **74**, 5068 (1952).

(5) S. J. Angyal, "Organic Reactions," Vol. VIII, John Wiley and Sons, Inc., New York, N. Y., 1954 p. 197.

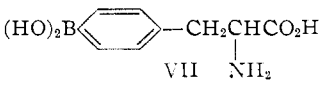


reactions which proceed under mild conditions lead to products retaining the boronic acid function. Thus, the substance condenses with nitromethane and with acetone to give the expected *p*-(β-nitrovinyl)- and *p*-(β-acetovinyl)-benzeneboronic acids. It forms a cyanohydrin and an azine, and it can be oxidized to the substituted benzoic acid and reduced to the substituted benzyl alcohol without cleavage of the boronic acid group. However, it did not undergo the benzoin condensation, of either the simple or mixed variety, and attempts to induce the Cannizzaro reaction failed.

*o*-Formylbenzeneboronic acid did not give condensation products with nitromethane or acetone. Benzoic acid was obtained from an attempted Cannizzaro reaction. 2,4-Dinitrophenylhydrazine apparently reacted normally, but difficulties in the purification of the product prevented the preparation of an analytical sample. Hydroxylamine reacted, but the product obtained contained one molecule of water less than the expected oxime. Presumably it is the cyclic derivative V. It is probable that the low reactivity of the aldehyde group in *o*-formylbenzeneboronic acid, especially in reactions catalyzed by bases, is due to the interaction of the two functions in such a way that the electron deficiency at the carbonyl carbon atom is neutralized (*e.g.*, VI).



One of the purposes of the present work was to prepare the analog of the amino acid tyrosine in which the phenolic hydroxyl group is replaced by the weakly acidic boronic acid function. *p*-Bromomethylbenzeneboronic acid was employed to alkylate acetaminomalonic ester, and the desired amino acid was obtained by hydrolysis and decarboxylation of the alkylation product in the normal sequence.[6] The substance VII strongly resembles *dl*-tyrosine in solubility, and is available for biological study, especially to determine whether it will serve to introduce boron into proteins. A selective concentration of boron in the protein of a rapidly growing neoplasm might permit the use of a therapy based on the neutron–$B^{10}$ reaction proposed by Kruger.[7]



## Experimental

**Direct Bromination of *o*- and *p*-Tolueneboronic Acids.**—A 500-ml. three-necked flask was oven-dried and equipped with a dried stirrer and addition funnel. Five grams of the boronic acid, which had been air-dried, was introduced along with 100 ml. of reagent grade carbon tetrachloride. The stirrer was started, about 5 ml. of a solution of 6 g. of dry bromine in 50 ml. of reagent grade carbon tetrachloride was introduced from the funnel, and a 200-watt unfrosted tungsten lamp was placed near the flask. After an induction period varying from 5 to 15 minutes, the color of the added bromine faded, and the remainder of the bromine solution was run in in portions of about 5 ml. over a period of about 15 minutes. The *p*-bromomethylbenzeneboronic acid was the less soluble in the solvent and much of it crystallized during the bromination. The *o*-isomer remained in solution. At the end of the reaction much of the solvent was removed and the product was collected and recrystallized from chloroform. The yields of the *p*- and *o*-isomers were 7.2 g. (90%) and 7.4 g. (92%), respectively. The melting point of the *o*-isomer (139–146°) agreed reasonably well with that (142–148°) subsequently reported by Torssell,[3] but that of the *p*-isomer (138–144°) was lower (165–168°). Whereas the analysis of Torssell's[3] *o*-isomer indicated the substance to be the anhydride, analyses of both our products indicated them to be the free acids.[7a]

*Anal.* Calcd. for $C_7H_8O_2BrB$: C, 39.12; H, 3.75. Found: (*p*-isomer) C, 39.15; H, 2.98; (*o*-isomer) C, 39.03; H, 3.24.

The difficulties in reproducing melting points and analyses of boronic acids, resulting from their ready hydration and anhydride formation, are well known.[8]

***p*-Formylbenzeneboronic Acid.**—The most convenient procedure devised consisted in brominating *p*-tolueneboronic acid with N-bromosuccinimide in chloroform solution (direct bromination in chloroform failed) and treating the bromomethyl derivative *in situ* with hexamethylenetetramine. In a 500-ml. flask, a mixture of 5 g. of *p*-tolueneboronic acid, 150 ml. of dry chloroform, 650 mg. of benzoyl peroxide and 6.5 g. of N-bromosuccinimide were refluxed and illuminated with a 200-watt unfrosted tungsten lamp for 3 hours. A solution of 7 g. of hexamine in 75 ml. of dry chloroform was added in one portion and refluxing was continued for 1 hour. The hot chloroform solution was decanted and the residue in the flask was extracted with 40 ml. of hydrochloric acid of *p*H 4. The aqueous solution was freed of a few drops of chloroform and refluxed for 1 hour. The resulting hot cloudy solution was poured quickly into a beaker and treated immediately with 10 ml. of concentrated hydrochloric acid. The solution became clear and the crystallization of *p*-formylbenzeneboronic acid began immediately. It was collected from the cooled solution and recrystallized from water as colorless crystals, m.p. 240°, yield 1.5 g. (27%). Torssell's[3] sample, m.p. 230–240°, had the analysis of a hemihydrate. Our analytical sample, dried at 1 mm. at room temperature for 24 hr., had the composition of the free boronic acid.

*Anal.* Calcd. for $C_7H_7BO_3$: C, 56.07; H, 4.67. Found: C, 55.90; H, 4.52.

(6) H. R. Snyder, J. F. Shekleton and C. D. Lewis, THIS JOURNAL, **67**, 310 (1945).

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

(7a) NOTE ADDED IN PROOF.—Subsequent work by H. R. Snyder, M. S. Konecky and W. J. Lennarz, forthcoming paper, has shown these products to be mixtures of the acids and their respective anhydrides.

(8) H. R. Snyder, J. A. Kuck and J. R. Johnson, THIS JOURNAL, **60**, 105 (1938).

A sample dried at 80° at 1 mm. for 1 hr. was converted to the anhydride. *Anal.* Calcd. for $(C_7H_5BO_2)_3$: C, 63.74; H, 3.79. Found: C, 63.65; H, 3.53.

**o-Formylbenzeneboronic Acid.**—The best procedure was similar to Torssell's,[3] except that the dibromo compound was not isolated and was hydrolyzed with alkali rather than dilute sulfurous acid.

In a 100-ml. flask a mixture of 1 g. of *o*-tolueneboronic acid, 40 ml. of dry carbon tetrachloride, 2.6 g. of N-bromosuccinimide and 260 mg. of fresh benzoyl peroxide was refluxed and illuminated by a 200-watt unfrosted tungsten lamp for 2.5 hr. The solution was filtered from succinimide and extracted with two 15-ml. portions of 15% potassium hydroxide. After 15 minutes the alkaline extract was acidified, allowed to stand 2 hr., and extracted with two 25-ml. portions of ether. The residue from the removal of the ether was recrystallized from water to give 370 mg. (36%) of *o*-formylbenzeneboronic acid, m.p. 118–120° (lit.[3] 115–123°). Analysis indicated the sample, like Torssell's,[3] to have the composition of the free boronic acid.

This product was obtained from *o*-toluneboronic acid in only 10% yield when the method described above for the *p*-isomer was employed.

***p*-(β-Nitrovinyl)-benzeneboronic Acid.**—A solution of 500 mg. of *p*-formylbenzeneboronic acid, 200 mg. of nitromethane and 4 ml. of ethanol was cooled to 5°, and a solution of 274 mg. of sodium hydroxide in 4 ml. of water slowly was added while the temperature was kept below 10°. The mixture was stirred at 10° for 15 min., and enough sodium hydroxide was added to clarify the solution. The solution was cooled to 5° and added to a cold (0°) solution of 2 ml. of concentrated hydrochloric acid in 3 ml. of water. The yellow solid which separated was collected and recrystallized from 33% ethanol; yield 455 mg. (70%) of light yellow solid, m.p. 289–290° dec.

*Anal.* Calcd. for $C_8H_8NBO_4$: C, 49.78; H, 4.18; N, 7.26. Found: C, 49.60; H, 4.34; N, 7.00.

*o*-Formylbenzeneboronic acid was recovered when treated with nitromethane under these conditions.

***p*-(β-Acetovinyl)-benzeneboronic Acid.**—A solution prepared from 1 g. of *p*-formylbenzeneboronic acid, 15 ml. of acetone, 5 ml. of water and 5 ml. of 10% sodium hydroxide was kept at a temperature below 30° by cooling under tap water. The flask then was stoppered and allowed to stand at room temperature. After about 1 hr., crystals began to separate from the yellow solution; after four hours they were collected and the filtrate was acidified. The precipitate formed was recrystallized from aqueous ethanol to give 700 mg. of product of m.p. 205–212°. The crystals (400 mg.) separated from the alkaline solution gave a flame test for sodium. They were dissolved in 10 ml. of water; acidification of this solution produced 350 mg. of the free acid of m.p. 205–212°. The total yield was 1.05 g. (80%).

*Anal.* Calcd. for $C_{10}H_{11}BO_3$: C, 63.22; H, 5.80. Found: C, 63.12; H, 6.00.

*o*-Formylbenzeneboronic acid was recovered when treated with acetone under these conditions.

**Cyanohydrin of *p*-Formylbenzeneboronic Acid.**—To an aqueous solution of 3.5 g. of potassium cyanide, 7 ml. of water and 1 g. of *p*-formylbenzeneboronic acid kept at 10° was added slowly a cold solution of 0.57 ml. of concentrated sulfuric acid in 1.73 ml. of water. The mixture was filtered and the filtrate was acidified with 10% hydrochloric acid and allowed to stand at 10° for 10 min. It was then extracted with ether; the ether extract was dried over magnesium sulfate and concentrated on the steam-bath. The residual oil crystallized on standing. The solid so formed softened at about 65° and appeared to undergo several changes before completely melting at 104°. A solvent for recrystallization was not found. A sample dried at room temperature t 1 mm. for 24 hr. was analyzed.

*Anal.* Calcd. for $C_8H_8NBO_3$: C, 54.30; H, 4.52. Found: C, 54.22; H, 4.40.

**Other Derivatives of *p*-Formylbenzeneboronic Acid.—The azine**, prepared by reaction with undiluted hydrazine monohydrate and recrystallized from aqueous dimethylformamide, melted at 295°. The sample analyzed was dried at 80° at 1 mm. for 3 days.

*Anal.* Calcd. for $C_{14}H_{14}N_2B_2O_4$: C, 56.80; H, 4.74. Found: C, 56.48; H, 5.12.

Oxidation with potassium permanganate at room temperature converted *p*-formylbenzeneboronic acid to *p*-carboxybenzeneboronic acid in 86% yield, m.p. 219–220° (lit.[9] 225°).

Hydrogenation in ethanol over platinum oxide converted *p*-formylbenzeneboronic acid to a material obtained as a gelatinous solid which resisted attempts at purification. Apparently the same product resulted from alkaline hydrolysis of *p*-bromomethylbenzeneboronic acid. Torssell[3] found the product of hydrolysis by water to be intractable.

**Attempts to Effect Cannizzaro and Benzoin Reactions.**—*p*-Formylbenzeneboronic acid was recovered from experiments in which it was treated with aqueous sodium hydroxide of 10 or 20% concentration at temperatures varying from room temperature to the reflux temperature and over periods varying from 45 min. to 12 hr. In some of the experiments the odor of benzaldehyde was detected. *p*-Formylbenzeneboronic acid was recovered when subjected to the conditions of the benzoin condensation[10] for periods ranging from 40 min. to 90 min. Attempts to obtain a mixed benzoin by condensation with benzaldehyde, *p*-dimethylaminobenzaldehyde and *p*-nitrobenzaldehyde were also unsuccessful.

When 600 mg. of *o*-formylbenzeneboronic acid was refluxed for 2 hr. with 5 ml. of deoxygenated 20% sodium hydroxide under an atmosphere of nitrogen, 300 mg. of benzoic acid (m.p. and mixed m.p. 120–122°) was obtained.

**Reaction of *o*-Formylbenzeneboronic Acid with Hydroxylamine.**—The *p*H of a solution of 500 mg. of *o*-formylbenzeneboronic acid and 360 mg. of hydroxylamine hydrochloride in 20 ml. of hot water was adjusted to 7 by the addition of sodium hydroxide. After 15 min. at reflux the solution was cooled and made strongly acid with concentrated hydrochloric acid. After two days in the refrigerator the fine precipitate had assumed a crystalline appearance and was collected and recrystallized from water. It weighed 420 mg. (85%) and melted at 150–155°. The analytical sample was dried at room temperature at 1 mm. for 15 hr.

*Anal.* Calcd. for $C_7H_6NBO_2$: C, 57.14; H, 4.08. Found: C, 57.24; H, 4.27.

**Alkaline Hydrolysis of *o*-Bromomethylbenzeneboronic Acid.**—The carbon tetrachloride solution in which 5 g. of *o*-toluneboronic acid had been treated with 6 g. of bromine, as described above, was extracted with two 40-ml. portions of 15% potassium hydroxide. After standing at room temperature for 1 hr. the alkaline solution was acidified with 15% hydrochloric acid and the solid was collected. The filtrate was concentrated to 50 ml. and extracted with ether; the material so obtained was combined with the solid obtained by the filtration. Recrystallization from water gave 3.5 g. (70%) of the cyclic ester I, m.p. 96–98° (lit. 97–98°).

**Reaction of *o*-Bromomethylbenzeneboronic Acid with Hexamethylenetetramine to Produce IV.**—A solution of 25 g. of *o*-toluneboronic acid, 32.5 g. of N-bromosuccinimide, 3.25 g. of benzoyl peroxide and 350 ml. of dry chloroform was refluxed for 3 hr. A solution of 30 g. of hexamine in 200 ml. of chloroform was added and refluxing was continued for 15 min. The hot chloroform solution was decanted and the residue was dissolved in 100 ml. of aqueous hydrochloric acid of *p*H 4. The aqueous solution, after separation from a little chloroform, was refluxed for 1 hr., during which time a solid separated. The solid was collected and recrystallized from dimethylformamide; yield 5.2 g. (20%), m.p. 308–309°. The substance is soluble in dilute hydrochloric acid, and insoluble in water and dilute base.

*Anal.* Calcd. for $C_{16}H_{16}N_2B_2O_2$: C, 66.29; H, 5.52; N, 9.66. Found: C, 65.99; H, 5.71; N, 9.65.

When this substance was dissolved in 10% hydrochloric acid and treated with sodium nitrite, effervescence occurred and a precipitate formed. The solid proved to be identical with the cyclic ester I.

***p*-(2,2-Dicarbethoxy-2-acetaminoethyl)-benzeneboronic Acid (VIII).**—A solution of sodium ethoxide was prepared from 3.16 g. of sodium and 300 ml. of absolute ethanol in an oven-dried flask fitted with a stirrer and a condenser protected by a drying tube, and 28.8 g. of diethyl acetaminomalonate was added. To the yellow solution 19.7 g. of *p*-

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

(10) W. S. Ide and J. S. Buck, "Organic Reactions," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 269.

bromomethylbenzeneboronic acid (dried 2 hr. in a desiccator) was added, and the mixture was stirred under gentle reflux for 11 hr. It was cooled to room temperature, treated with 12 ml. of 3 *N* hydrochloric acid and filtered from the precipitated inorganic salt. The filtrate was concentrated to a yellow semi-solid and this was crystallized from about 600 ml. of 33% ethanol to give 21.7 g. (67.7%) of white crystals, m.p. 220–223°. The analytical sample was twice recrystallized from water and dried at about 2 mm. at room temperature for 36 hr.

*Anal.* Calcd. for $C_{18}H_{22}BNO_7$: C, 54.71; H, 6.31; N, 3.98. Found: C, 54.62; H, 6.43; N, 3.85.

*p*-(**2-Carboxy-2-acetaminoethyl**)-**benzeneboronic Acid** (**IX**).—A mixture of 21.7 g. of VIII and 180 ml. of 5% aqueous sodium hydroxide was stirred under reflux for 3.75 hr. To the cooled solution 90 ml. of 3 *N* hydrochloric acid was added slowly, and the resulting mixture was heated under reflux for 1 hr. The residue from concentration *in vacuo* of the mixture was crystallized from the minimum amount of water to give 13.5 g. (87%) of white crystalline IX, m.p. 168–170°.

*Anal.* Calcd. for $C_{11}H_{14}BNO_6$: C, 52.60; H, 5.62; N, 5.57. Found: C, 52.30; H, 5.78; N, 5.43.

*p*-(**2-Carboxy-2-aminoethyl**)-**benzeneboronic Acid** (**4-Boronophenylalanine**) **VII**.—A mixture of 13.5 g. of IX and a solution of 16 g. of sodium hydroxide in 250 ml. of water was stirred under reflux for 9 hr. The solution was acidified by the careful addition of 25 ml. of concentrated hydrochloric acid, which caused the separation of a white solid. The *p*H of the mixture was adjusted to 6.2 with ammonium hydroxide, and the mixture was concentrated to 100 ml. *in vacuo*. (In subsequent preparations it was found that a purer product resulted when the final volume was 175 ml.) After storage overnight in the refrigerator the solid was separated and washed with water. The yield of VII was 8.3 g. (74%), m.p. 285–290° dec.

*Anal.* Calcd. for $C_9H_{12}BNO_4$: C, 51.69; H, 5.79; N, 6.70. Found: C, 51.74; H, 6.00; N, 6.66.

**Properties of 4-Boronophenylalanine (VII)**.—4-Boronophenylalanine readily formed a hydrochloride by treating a small amount (0.1–0.2 g.) of it with 3 ml. of 1 *N* HCl and then slowly evaporating to dryness. The white crystals thus obtained had m.p. 200–203° and were very soluble in water. The infrared spectrum (Nujol) of the hydrochloride showed the presence of an un-ionized carboxyl group by the strong band present at 1740 cm.$^{-1}$, in contrast to the free amino acid, which has an ionized carboxyl group (strong absorption at 1640 cm.$^{-1}$).

Treatment of a boronic acid with sodium hydroxide is known to effect deboronation[11] and should, in this case, produce phenylalanine. A solution of 0.5 g. of 4-boronophenylalanine in 20 ml. of 5% sodium hydroxide, contained in a copper flask, was refluxed for 48 hr. The solution was then filtered through a sintered funnel while still hot, neutralized to *p*H 3 with hydrochloric acid, and then adjusted to *p*H 5.7 with ammonium hydroxide. The white inorganic material which precipitated at this point was filtered off, and the filtrate evaporated almost to dryness *in vacuo*. The resulting white residue was taken up in 10 ml. of water and warmed to dissolve any soluble inorganic material. Next the remaining white solid was filtered off. It had m.p. 235–240°. This low m.p. suggested the possibility of a mixture of 4-boronophenylalanine and phenylalanine. This was verified by descending paper chromotography, using a butanol–acetic acid–water solvent system (40:10:50). Samples of 4-boronophenylalanine, phenylalanine, 50% 4-boronophenylananine–50% phenylalanine mixture, and the sample obtained by the sodium hydroxide treatment were spotted on the paper and migration allowed to proceed at 35° for 7 hours. The paper was then dried at room temperature overnight, sprayed with a 0.4% solution of ninhydrin in water-saturated butanol, and developed by heating to 50–60° for 30 minutes. The $R_f$ values obtained are as follows: 4-boronophenylalanine, 0.46; phenylalanine, 0.69; 50% 4-boronophenylalanine–50% phenylalanine, 0.69, 0.46; product of sodium hydroxide treatment, 0.69, 0.46. Further evidence for the presence of phenylalanine as the deboronation product lies in the fact that the infrared spectrum of this product is similar to that of phenylalanine, and differs only in the presence of several additional absorption bands which are probably due to impurities.

4-Boronophenylalanine may be titrated and gives a titration curve similar in shape to that of a normal amino acid. The sample was dissolved in excess sodium hydroxide and titrated with 0.1 *N* HCl, the *p*H being measured by means of a Beckman *p*H meter equipped with a glass–calomel electrode system. That the boronic acid function has a $pK_a'$ of the same magnitude as the ammonium ion was demonstrated by the fact that on the basic side of the titration curve two equivalents of acid were required for neutralization of 4-boronophenylalanine, while phenylalanine required only one equivalent.

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

URBANA, ILLINOIS

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF VANDERBILT UNIVERSITY]

# Organic Disulfides and Related Substances. I. Oxidation of Thiols to Disulfides with Lead Tetraacetate[1]

BY LAMAR FIELD AND JOHN E. LAWSON[2]

RECEIVED AUGUST 19, 1957

Lead tetraacetate was used for oxidizing thiols to disulfides typifying various classes, including alkyl, benzyl, aryl, substituted aryl, heterocyclic and acyl. One mole of the tetraacetate oxidized two of thiol. The tetraacetate did not cleave 2-mercaptoethanol but instead oxidized it smoothly to the disulfide. An amount sufficient for reaction only with benzenethiol or pinacol in a mixture of both effected oxidation of the thiol and little or no cleavage of the glycol.

The selectivity of lead tetraacetate has made it a valuable oxidant for synthesis and determination of structure.[3] There seemed a good likelihood that its use could be extended profitably to organic disulfides either for conventional reactions[3] not involving sulfur or for reactions of the sulfur atoms such as oxidation or cleavage. Comment on lead tetraacetate in relation to disulfides seems to have been made only by Bourne and co-workers[4] who, in a study of sugar mercaptals, mentioned its oxidation of α-toluenethiol but not the yield or quality of the disulfide formed.

(1) Presented at the Southeastern Regional Meeting of the American Chemical Society at Durham, N. C., Nov. 14–16, 1957. Abstracted from a portion of the Ph.D. dissertation of J.E.L., August, 1957. The authors are indebted to the Office of Ordnance Research, U. S. Army, for support of this work. Helpful suggestions were contributed by Paul E. Drummond.

(2) Du Pont Postgraduate Teaching Fellow, 1955–1957.

(3) For reviews, see (a) W. A. Waters in "Organic Chemistry, An Advanced Treatise," H. Gilman, Ed., Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 1185; (b) R. Criegee in "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1948, p. 1.

(4) E. J. Bourne, W. M. Corbett, M. Stacey and R. Stephens, *Chemistry & Industry*, 106 (1954).