Anal. Calcd. for $C_{21}H_{14}O_4$: 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 = $43R$. 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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and also with 2,4-dithiouracil in a nitrogen atmosphere yielded only 6-anilinopurine and 2-mercapto-4-anilinopyrimidine, respectively. This is yet another instance of how labile the carbon–boron linkage is.

This instability is markedly altered by the introduction of a carboxyl group into phenylboronic acid. Phenylboronic acid itself can be nitrated by fuming nitric acid at a temperature of −10 to −15°,[16] but at higher temperatures extensive decomposition occurs. *p*-Carboxyphenylboronic acid, on the other hand, is readily nitrated at room temperature by a mixture of fuming nitric acid and sulfuric acids to yield a single product 2-nitro-4-carboxyphenylboronic acid. This compound had been previously prepared[17] and its stability as well as that of *p*-carboxyphenylboronic acid was observed. The attempted nitration of *m*-nitrophenylboronic acid and phenylboronic acid, itself, by this procedure resulted in the formation of *m*-dinitrobenzene as the only isolable product. In a similar manner, *m*-carboxyphenylboronic acid was nitrated to yield the known[18] 3-nitro-5-carboxyphenylboronic acid (II).

Another instance of the increased stability of the carbon–boron linkage in carboxyl-substituted phenylboronic acids was observed in attempts at chlorosulfonation of aromatic boronic acids. At 0°, *p*-tolylboronic acid reacted with chlorosulfonic acid to form *p*-toluenesulfonyl chloride. The structure of the product was verified by its conversion to *p*-toluenesulfonamide. Under identical reaction conditions, *p*-carboxyphenylboronic acid was recovered unchanged. Consequently, there would appear to be a marked difference in the stability of the carbon–boron bond in aromatic boronic acids. Both 4-dimethylamino- and 4-methoxy-α-naphthylboronic acids were easily deboronated[19] by mild acid or alkaline hydrolysis. Likewise, the brominolysis of substituted phenylboronic acids shows that those compounds with electron-releasing groups have appreciably greater rate constants.[20] The increased stability of *p*-carboxyphenylboronic acid to electrophilic displacement of the boron moiety is understandable on this basis. However, its greater stability in sulfuric–nitric acid mixtures relative to *m*-nitrophenylboronic acid requires a consideration of other factors, possibly the solvation of the carboxyl function.

A third nitrocarboxyphenylboronic acid isomer which had been described[18] was prepared by the oxidation of 3-nitro-*p*-tolylboronic acid with potassium permanganate to 3-nitro-4-carboxyphenylboronic acid (III). The permanganate oxidation of the methyl group of *p*-tolylboronic acid was a much more facile process than that with a nitro substituent *ortho* to the methyl group. The latter oxidation required longer reaction times and higher temperatures to form the corresponding aromatic carboxylic acid.

The preparation of a ureido group from the corresponding aromatic amine occurred readily without the rupture of the carbon–boron linkage. By the usual method for forming aromatic ureas,[21] 3-ureidophenylboronic acid (IV) and 3-ureido-*p*-tolylboronic acid (V) were synthesized; deboronation resulted in the formation of the corresponding ureas. The promising biological results[8] of compound IV led to the attempted preparation of a boronic acid which would contain both a carboxyl function and a ureido group. The synthetic scheme which was undertaken was the catalytic reduction of 3-nitro-4-carboxyphenylboronic acid (III) to the known[18] 3-amino-4-carboxyphenylboronic acid (VI) and its conversion to 3-ureido-4-carboxyphenylboronic acid (VII). The amino acid VI did react with potassium cyanate in an acetic acid solution to form a product. However, all attempts at the crystallization of this phenylurea were without success; only a gel could be isolated.

Preparation of an antimetabolite or any carcinostatic agent containing boron may permit this neutron-capture therapy to be applied to neoplasms other than of the central nervous system. A twofold attack on the tumor might be feasible; one, inhibition of growth; and two, incorporation of the antimetabolite[22] or carcinostatic agent into the nuclei or neoplastic cells. Such a nuclear position of a boron[10] atom by the metabolism of the tumor would allow chromosone disruption upon thermal neutron irradiation and may possibly permit lower neutron fluxes for eradication of the neoplasm.

On this basis, a synthetic scheme directed toward the preparation of a purine antimetabolite containing boron was undertaken.[23] The recent work of H. R. Snyder, *et al.*,[24] with the synthesis of boronophenylalanine presents a very interesting approach to this same problem. 4-Boronoanthranilic acid (VI) may also be an amino acid antagonist inhibiting utilization of tryptophan.

Other metabolic antagonists and carcinostatic agents were also considered. N-Phenylurethan has shown antimitotic action itself[25] and the urethans as a class of compounds have been employed in clinical trials[26] in the treatment of cancer. 3-Carbethoxyaminophenylboronic acid (VIII), which had been prepared,[27] was synthesized directly from *m*-aminophenylboronic acid.

In view of the incorporation of nicotinamide antagonists into neoplastic cells[22] the synthesis of such a compound containing boron was undertaken. For this purpose, *m*-aminophenylboronic acid was acylated with nicotinoyl chloride to yield 3-nicotinamidophenylboronic acid (IX). The carcinostatic activity of this compound, 4-boronoanthranilic acid and the boron-containing urethan have not been evaluated as yet.

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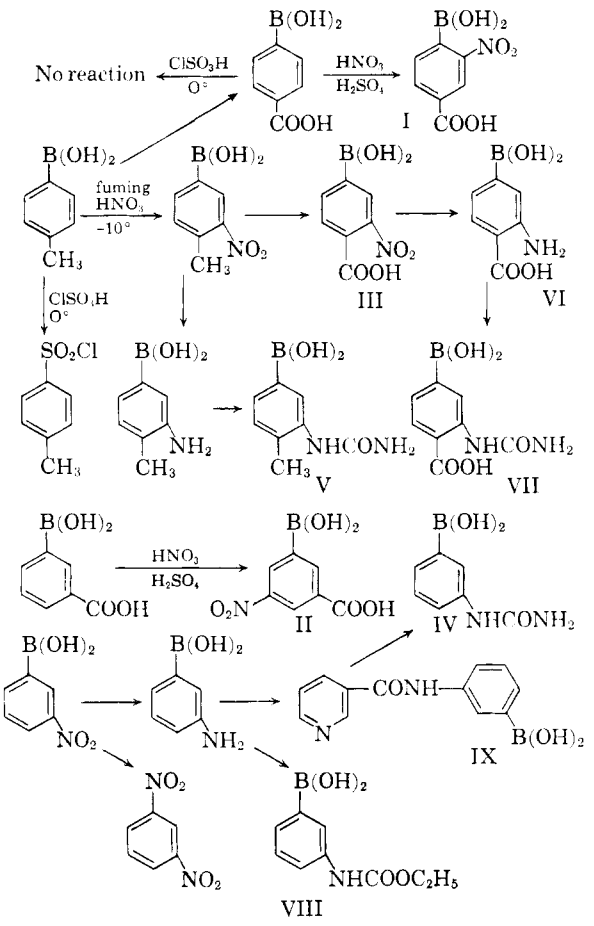

Experimental[28]

The preparation of phenylboronic acid from phenylmagnesium bromide and an alkyl borate was essentially the method of Bean and Johnson[29] with the exception that trimethyl borate was used as the ester rather than *n*-butyl borate. *p*-Tolylboronic[28] and *m*-tolylboronic[30] acids were synthesized by the same procedure. *m*-Nitro-,[31] *m*-amino,[29] 3-nitro-4-methyl[29] and 3-amino-4-methylphenylboronic acids[29] were prepared in the manner described in the literature. This also applied to formation of *p*-carboxyphenylboronic[32] and *m*-carboxyphenylboronic[33] acids.

2-Nitro-4-carboxyphenylboronic Acid (I).—To a stirred slurry of 3.0 g. of *p*-carboxyphenylboronic acid in 10 ml. of concentrated sulfuric acid was added 10 ml. of fuming nitric acid. A complete solution occurred and the mixture was allowed to stir for 30 min. before being poured onto ice. The solution was filtered, washed with a small amount of water and dried. The yield was 3.1 g., m.p. 250–255°. The solid was recrystallized from water to give 1.9 g. of pale yellow needles, m.p. 260–261°. In a similar manner 3-nitro-5-carboxyphenylboronic acid (II),[18] m.p. 227–229°, was prepared.

By the method of Torssell[18,27] 3-nitro-4-carboxyphenylboronic acid (III),[18] m.p. 218–220°, 3-amino-4-carboxyphenylboronic acid (VI),[18] m.p. >350°, and *m*-carbethoxyaminophenylboronic acid (VIII), m.p. 209–211°, were synthesized.

***m*-Ureidophenylboronic Acid (IV).**—A solution of 1.64 g. of *m*-nitrophenylboronic acid in 10 ml. of methanol and 30 ml. of water was reduced catalytically by hydrogen in the presence of 160 g. of platinum oxide. The reduction was continued for one hour in the Parr shaker, filtered through glass wool and concentrated under reduced pressure to a volume of 20 ml. To the solution was added 5 ml. of glacial acetic acid and 10 ml. of water. The mixture was again concentrated to a 20 ml. volume. Without prior isolation of the amine, it was converted to the arylurea.

To the solution of the amine, warmed to 35°, was added a mixture of 1.6 g. of potassium cyanate in 10 ml. of water. The solution was stirred and allowed to stand for one hour. It was chilled in an ice-bath, filtered, washed with a small volume of water and dried. Treatment with decolorizing charcoal followed by successive recrystallizations from small volumes of water gave 718 mg. of white crystals, m.p. >350°.

Anal. Calcd. for $C_7H_9BN_2O_3$: C, 46.71; H, 5.04. Found: C, 46.27; H, 5.05.

Solution of 29 mg. of the compound in 1 ml. of ammoniacal silver nitrate[34] resulted in the cleavage of the carbon–boron bond and the precipitation of 10 mg. of phenylurea, m.p. 144–146°. Admixture with an authentic sample showed no m.p. depression.

3-Ureido-*p*-tolylboronic Acid (V).—A solution of 1.00 g. of 3-amino-*p*-tolylboronic acid in a mixture of 5 ml. of glacial acetic acid and 10 ml. of water was warmed to 35°. To this was added with stirring a solution of 1.2 g. of potassium cyanate in 5 ml. of water. Effervescence occurred and after standing for 30 min., the precipitate which had settled out of solution was chilled, filtered, washed with water and dried. The yield was 803 mg., m.p. >350°. Successive recrystallizations from water gave white needles.

Anal. Calcd. for $C_8H_{11}BN_2O_3 \cdot H_2O$: C, 45.32; H, 6.17. Found: C, 46.03; H, 6.64.

In 2 ml. of an ammoniacal silver nitrate solution was suspended 200 mg. of 3-ureido-*p*-tolylboronic acid. The solution was warmed slightly on a steam-bath to effect solution. The mixture was allowed to remain at room temperature for 30 min., and then the precipitate was cooled, filtered, washed with a small volume of water and dried. The yield was 115 mg., m.p. 180–184°. This was recrystallized from water and 72 mg. of white crystals was obtained, m.p. 195–196°, which showed no m.p. depression on admixture of *o*-tolylurea.

3-Ureido-4-carboxyphenylboronic Acid (VII).—To a stirred suspension of 0.5 g. of the amine VI in 8 ml. of 33% acetic acid was added 0.6 g. of potassium cyanate in 3 ml. of water. The solution was warmed to 40° and then allowed to remain at room temperature for 30 min. The product was chilled, filtered, washed and dried and yielded 0.4 g., m.p. >350°. Attempts at recrystallization gave a gel.

3-Nicotinamidophenylboronic Acid (XI).—To a stirred solution containing 50 ml. of water, 3.0 g. of sodium carbonate monohydrate and 1.37 g. of *m*-aminophenylboronic acid was added 1.78 g. of nicotinoyl chloride hydrochloride. A vigorous reaction ensued and gradually over a period of 30 min. a solid separated. The solution was chilled filtered, washed and dried. The yield was 1.2 g., m.p. 185–189°. An analytical sample was prepared which melted at 205–207°.

Anal. Calcd. for $C_{12}H_{11}BN_2O_3$: C, 59.54; H, 4.58. Found: C, 59.76; H, 4.58.

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BOSTON 14, MASS.

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