tained: mp 164–165.5°; ir ($CCl_4$), 1735 (carbamate C=O), and 1705 $cm^{-1}$ (conjugated ester C=O); uv max (isooctane), 209 mμ (ε 28,000), 217 sh (26,000), 232 (22,000), 277 (6400), 287 (7100), 294 (6800). An interpretable nmr using a computer of average transients could not be obtained. The compound was not further characterized.

**Registry No.**—**9,** 16916-03-3; **10,** 16916-04-4; **11,** 16916-05-5; **14,** 16960-03-5; **15,** 16916-07-7; **16,** 16916-08-8; **17,** 16916-09-9; **19,** 16916-10-2; **20,** 16916-11-3; **21,** 16916-12-4; **22,** 16916-13-5; **23,** 16916-14-6; 3-carbethoxy-9H-pyrrolo[1,2-*a*]indole, 16916-06-6.

# Displacement Reactions of Dibutyl Iodomethaneboronate and the Synthesis of Boron-Substituted Pyrimidines[1a,b]

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Dibutyl iodomethaneboronate has been synthesized by reaction of iodomethylmercuric iodide with boron tribromide followed by esterification with 1-butanol. Nucleophiles including alkoxides, amines, carbanions, and mercaptides displace iodide from dibutyl iodomethaneboronate to yield the corresponding substituted methaneboronic acid derivatives. Several boron-containing pyrimidines have been prepared by the reaction of the iodomethaneboronic ester with mercaptopyrimidines.

Reasons for studying carbon-functional boronic esters include observations of strong neighboring-group effects of boron[2-4] and the possibility of finding an effective compound for the $^{10}B$ neutron capture therapy of brain tumors.[5] Displacement of halide from an α-haloalkaneboronic ester is a potentially useful approach to a wide variety of substituted boronic esters.[3,4] However, it turned out that alkoxide ion often reacts much faster than more highly desired other nucleophiles, even mercaptides, in displacement of bromide from such compounds as dibutyl 2-bromopropane-2-boronate, owing to preliminary attack of the more basic anion on the boron atom. We thought it likely that reagents more nucleophilic toward carbon would react faster than those more basic toward boron if the transition state could be given more "SN2 character." Reduction of chain branching would accomplish this end, and a halomethaneboronic ester, $XCH_2B(OR)_2$, was therefore desired. A second advantage of such a compound would be the incorporation of a minimum of extraneous carbon along with the boron in compounds synthesized for potential biological properties.

**Synthesis of $ICH_2B(OBu)_2$.**—Our previous syntheses of α-haloalkaneboronic esters involved radical[2] or ionic[3] additions to alkeneboronic esters. An entirely new approach was therefore needed to make a halomethaneboronic ester. Chlorination of di-*t*-butyl methaneboronate with *t*-butyl hypochlorite yielded a little chloromethaneboronic ester after a lot of effort.[6] We therefore tried treating iodomethylmercuric iodide[7] with boron tribromide. After esterification of the product with 1-butanol, a low yield of dibutyl iodomethaneboronate (**1**) was obtained. Sodium iodide greatly improved the yield, evidently because it complexes with the mercury atom and makes it a better leaving electrophile.

$$ICH_2HgI + BBr_3 + NaI \longrightarrow HgI_2 + NaBr + ICH_2BBr_2 \xrightarrow{BuOH} ICH_2B(OBu)_2$$
**1**

After trying numerous variations, it was found that the best reaction conditions were about 1 day of vigorous stirring at 25°, with a large excess of boron tribromide and a moderate amount of methylene iodide, the quantity trapped in the iodomethylmercuric iodide on recrystallization (~20%) being about right. Careful vacuum drying of the $ICH_2HgI$ cut the yield in half, though increasing the amount of methylene iodide did not seem to help. It is possible that the $CH_2I_2$ functions by increasing the slight solubility of the $ICH_2HgI$ in the boron tribromide or by modifying the surface or mechanical properties of the mercury compound.

Although we are not sure that our yield (40% based on crude $ICH_2HgI$) is the best possible, it appears that instability of either the iodomethylmercury or boron compound may be a limiting factor. Heat or ultraviolet light increased the amounts of various by-products containing the $B-CH_2-B$ linkage, as shown by the appearance of several nmr peaks at τ 9.5–10. The boron tribromide treatment worked better for conversion of methylenedimercuric iodide,[7] $CH_2(HgI)_2$, into bis(dibromoboryl)methane, $CH_2(BBr_2)_2$,[1a] but this approach to methanediboronic acid has now been superseded by the much more efficient direct reaction of methylene chloride, lithium, and dimethoxyboron chloride.[8]

The crude dibutyl iodomethaneboronate (**1**) contained variable amounts of bromomethaneboronic ester, revealed by the $Br-CH_2-B$ nmr peak at τ 7.6. (For comparison, the corresponding $Cl-CH_2-B$ peak is at τ 7.2,[6] the $I-CH_2-B$ peak at τ 7.95.) The bromo compound has about the same boiling point as tributyl borate and was not isolated. Sodium iodide in acetone converted into the iodo compound (**1**).

**Displacement Reactions.**—As anticipated, dibutyl iodomethaneboronate (**1**), when treated with a wide

(1) (a) Preliminary communication: D. S. Matteson and T. C. Cheng, *J. Organomental Chem.*, **6**, 100 (1966). (b) Supported by U.S. Public Health Service Grant CA-05513 from the National Cancer Institute. (c) Alfred P. Sloan Foundation Fellow. (d) Abstracted in part from the Ph.D. Thesis of T.-C. Cheng, 1968.

(2) D. S. Matteson and R. W. H. Mah, *J. Amer. Chem. Soc.*, **85**, 2599 (1963).

(3) D. S. Matteson and G. D. Schaumberg, *J. Org. Chem.*, **31**, 726 (1966).

(4) D. S. Matteson, *Organometal. Chem. Rev.*, **1**, 1 (1966).

(5) A. H. Soloway in "Progress in Boron Chemistry," Vol. 1, H. Steinberg and A. L. McCloskey, Ed., The Macmillan Co., New York, N. Y., 1964, p 203.

(6) D. S. Matteson, *J. Org. Chem.*, **29**, 3399 (1964).

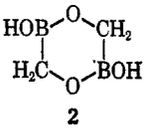
(7) E. P. Blanchard, Jr., D. C. Blomstrom, and H. E. Simmons, *J. Organometal. Chem.*, **3**, 97 (1965).

(8) R. B. Castle and D. S. Matteson, *J. Amer. Chem. Soc.*, **90**, 2194 (1968).

variety of nucleophilic reagents, gave simple displacement products. Reagents having nucleophilic sites on oxygen, nitrogen, carbon, and sulfur were tested.

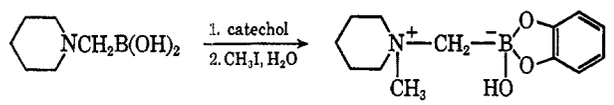
Hydroxymethaneboronic acid presented the problem of high water solubility. To avoid the need for separating it from inorganic salts and to avoid conversion of the boronic acid into a salt, an ion-exchange resin was used in the bicarbonate form as the source of base to displace iodide from the iodomethyl compound (**1**). The dimeric cyclic ester (**2**) was isolated. We have previously prepared the analogous derivative from solvolysis of 2-bromopropane-2-boronic acid,[3] and the preparation of **2** from borane carbonyl has been reported.[9]

$$ICH_2B(OBu)_2 + H_2O + HCO_3^- \longrightarrow$$



**1** **2**

Ammonia and amines react readily with **1**. We were unable to isolate aminomethaneboronic acid from inorganic salts and boric acid, a usual by-product from reactions of **1**. Dimethylaminomethaneboronic acid, $(CH_3)_2N-CH_2B(OH)_2$, was obtained in partially purified form and was characterized as the catechol ester. Piperidine yielded a much easier product to handle. Piperidinomethaneboronic acid (**3**) was converted into the catechol ester and methylated with methyl iodide to yield a quaternary ammonium derivative postulated to have the zwitterion structure (**4**). Thus, it appears



**3** **4**

that the group $N-CH_2-B$ in various forms does not hydrolyze unduly readily. Phthalimidomethaneboronic acid was also prepared very easily from **1**, but were unable to isolate any aminomethaneboronic acid after basic hydrolysis.

Schaeffer and Todd have reported the reaction of chloromethyldimethylborane, $ClCH_2B(CH_3)_2$, with sodium azide.[10] We treated our iodomethaneboronic ester with sodium azide in 1-butanol, but degradation to formaldehyde (isolated as the 2,4-dinitrophenylhydrazone) and butyl borate (isolated as boric acid after hydrolysis) occurred. The instability of the azide is probably due to a $\beta$ elimination of boron and nitrogen.

$$N_3CH_2B(OBu)_2 \xrightarrow{BuOH} N\equiv\overset{+}{N}NHCH_2\overset{-}{B}(OBu)_3 \longrightarrow N_2 + HN{=}CH_2 + B(OBu)_3$$

$$\downarrow CH_2O$$

Carbanions from active methylene compounds are readily alkylated by dibutyl iodomethaneboronate (**1**). Successful reactions have been carried out with malononitrile,[1a] methyl cyanoacetate, dimethyl malonate, and diethyl acetamidomalonate. Products were also obtained from diethyl malonate and dibutyl malonate, but these appeared to decompose partially on distillation and were not obtained pure.

$$ICH_2B(OBu)_2 + CH_2(CO_2CH_3)_2 \xrightarrow{t\text{-BuOK}} (CH_3O_2C)_2CHCH_2B(OBu)_2$$

It was hoped that the diethyl acetamidomalonate derivative (**5**) could be converted into a borono-substituted amino acid by hydrolysis. However, treatment with acid or base resulted in deboronation. The $\beta$ relationship of the boronic acid and acetamido groups probably results in an elimination reaction. Several examples of related eliminations are known.[4]

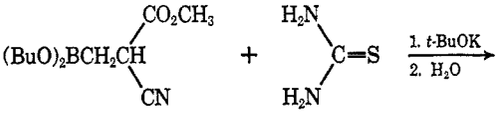
$$(EtO_2C)_2CNHAc + OH^- \longrightarrow$$

$$CH_2B(OH)_2$$

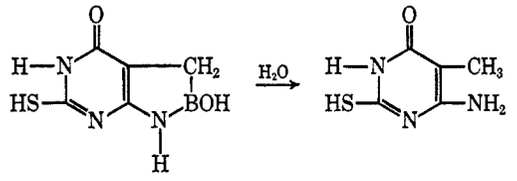
**5**

$$B(OH)_3 + AcNH_2 + (EtO_2C)_2C{=}CH_2 \longrightarrow \text{hydrolysis products}$$

Reaction of the methyl cyanoacetate derivative, methyl $\alpha$-cyano-$\beta$-dibutoxyborylpropionate (**6**), with thiourea in the presence of potassium *t*-butoxide followed by treatment with water yielded the expected 2-mercapto-4-oxy-5-oxyboromethyl-6-iminopyrimidine (**7**). However, two molecules of this compound crystallized in a tight complex with one molecule of boric acid plus the elements of water. Distillation of methanol from a suspension of **7** did not alter the elemental composition, indicating that the boric acid was tightly chelated. Several structures might be written for such a chelate. To prove that **7** contained carbon-bound boron, it was boiled in 50% methanol to cause hydrolytic deboronation. The nmr spectrum in dimethyl sulfoxide-$d_6$ showed the disappearance of the $CH_2B$ peak at $\tau$ 8.46 and its replacement by a methyl peak at $\tau$ 6.90 which was partially accomplished after 2 hr and complete after 17 hr.



**6**



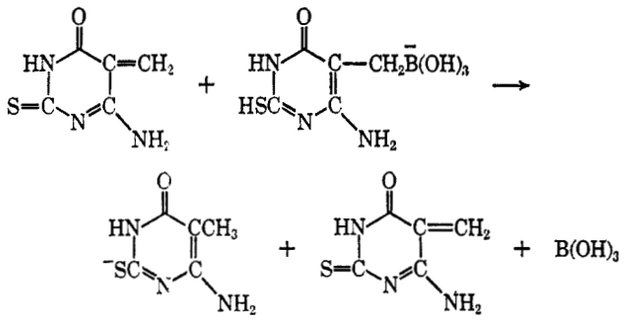
**7**

The product of the reaction of the cyanoacetic ester derivative (**6**) with guanidine was even more labile, and we were not able to obtain it except as a mixture with its deboronation product. Attempts to condense thiourea with the malononitrile derivative, $(BuO)_2BCH_2CH(CN)_2$, gave only deboronated pyrimidine.[11] Reaction of dibutyl 1-iodoethaneboronate, $(BuO)_2BCHICH_3$,[3] with malononitrile and potassium *t*-butoxide gave a rather low yield of the alkylated malononitrile, $(BuO)_2BCH(CH_3)CH(CN)_2$, and the product from reaction of this compound with thiourea appeared to be pyrimidine analogous to **7**. However, recrystallization seemed to cause either loss of boron or concentration of deboronation product, and we were unable to obtain a satisfactory analysis.[11]

The ease of deboronation of these compounds is totally unexpected. No satisfactory scheme for hydrolytic deboronation is possible, since a carbanion electron pair on the carbon from which the boron departs cannot be delocalized into the pyrimidine ring. It does no

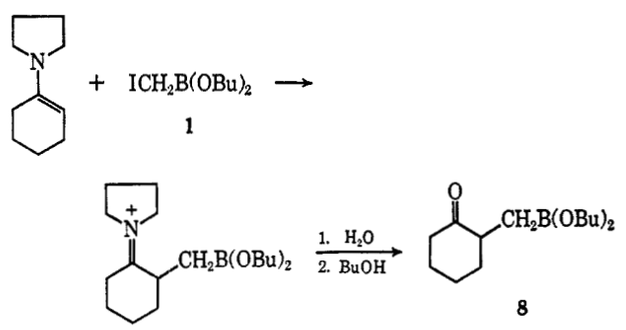
(9) L. J. Malone and M. R. Manley, *Inorg. Chem.*, **6**, 2260 (1967).
(10) R. Schaeffer and L. J. Todd, *J. Amer. Chem. Soc.*, **87**, 488 (1965).
(11) Unpublished work with J. Ebbert.

good to assume that the pyrimidine structures are wrong for this purpose, since the charge cannot be delocalized in any reasonable alternative structure. Base-catalyzed elimination of boron and cyanide from the starting cyano compounds such as $(BuO)_2BCH_2CH(CN)_2$ is conceivable and may help cause the low yields, but there is good evidence that the carbon–boron bond survives in compounds such as **7** which contain no cyano group. Some sort of oxidative cleavage to a quinoidal structure is a speculative possibility, since the quinoidal material could serve as the oxidizing agent in a chain process.



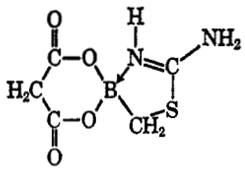
An unusual mechanism of this general type is not unreasonable in view of the highly exothermic character (perhaps 30 kcal/mol or more[4]) of deboronation.

Dibutyl iodomethaneboronate (**1**) also alkylates enamines, as shown by the conversion of 1-(1-pyrrolidinyl)cyclohexene into 2-(dibutoxyborylmethyl)cyclohexanone (**8**).



Mercaptide ions displace halide from all but the most highly branched α-haloalkaneboronic esters;[2-4] so it is hardly surprising that iodomethaneboronic ester (**1**) reacts efficiently with thiolacetate ion. Acetylthiomethaneboronic acid, $CH_3COSCH_2B(OH)_2$, has been obtained by hydrolysis of the ester. However, a number of attempts to hydrolyze the acetyl group with acid or base to obtain mercaptomethaneboronic acid, $HSCH_2B(OH)_2$, resulted in deboronation. The instability of this compound was as much unexpected as that of the pyrimidines described in a preceding paragraph. A somewhat similar mechanism, involving oxidation of $HSCH_2B(OH)_2$ to $S{=}CH_2$ with the latter serving as the oxidizing agent for the next step in a chain mechanism, is plausible. The exclusion of air from the reactions was not rigorous enough to preclude direct air oxidation, if that was unusually rapid. It is doubtful that the deboronation is purely hydrolytic, in view of the apparent stability of analogous alkylthioboron compounds.[3]

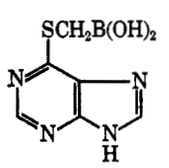
Thiourea underwent reaction with the iodomethaneboronic ester (**1**) in the usual manner.[3] The thioureidomethaneboronic acid was isolated as its catechol ester and also as the chelated anhydride with malonic acid (**9**). Similar chelates, which are surprisingly stable toward hydrolysis, have been reported previously.[12]



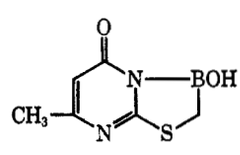
**9**

We had been totally unsuccessful in previous attempts to alkylate mercaptopyrimidines with α-haloalkaneboronic esters.[3] However, dibutyl iodomethaneboronate (**1**) underwent reaction readily with 2-thiobarbituric acid, 2-mercapto-4-oxy-6-methylpyrimidine, 2-mercapto-4-oxy-6-phenylpyrimidine, 2-mercapto-4-oxy-6-propylpyrimidine, 2-mercapto-4-oxy-6-carboxypyrimidine, and 6-mercaptopurine in refluxing acetonitrile to yield the S-boromethyl derivatives. These are not the usual conditions for alkylating mercaptopyrimidines,[13] and methyl iodide does not react with 2-mercapto-4-oxy-6-methylpyrimidine in acetonitrile. Although it is well established that S-alkylation occurs in preference to N-alkylation in alkaline solution,[13] data which support S-alkylation under neutral conditions[14] are less common. To support the structural assignments, dibutyl iodomethaneboronate (**1**) was added to an aqueous alkaline solution of 2-mercapto-4-oxy-6-methylpyrimidine and an 80% yield of the same product that resulted from reaction in acetonitrile was obtained. (Nmr spectra were weak at best owing to low solubilities and do not distinguish $S{-}CH_2{-}B$ from $N{-}CH_2{-}B$.)

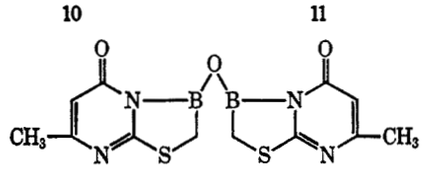
The S-boromethyl-substituted mercaptopyrimidines were obtained in varying degrees of hydration or dehydration. The boronic acid form of 6-(dihydroxyborylmethylthio)purine (**10**) crystallized with 1 mol



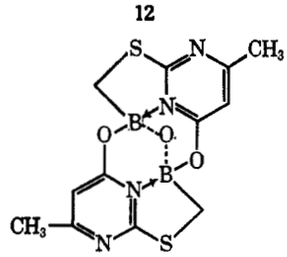
**10**



**11**



**12**



**13**

(12) D. S. Matteson and G. D. Schaumberg, *J. Organometal. Chem.*, **8**, 359 (1967).

(13) G. W. Kenner and A. Todd in "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p 283.

(14) M. Gordon, *J. Amer. Chem. Soc.*, **73**, 984 (1951).

of water. More often, the products had the composition of a boronic anhydride. For example, 2-mercapto-4-oxy-6-methylpyrimidine yielded a derivative formulated as 2-(hydroxyboromethylthio)-4-oxy-6-methylpyrimidine (**11**), and this could be dehydrated to material formulated as oxybis(2-boromethylthio-4-oxy-6-methylpyrimidine) (**12**). However, structure **12** probably does not give a complete picture of what happens, since the main changes in the infrared spectrum on dehydration include loss of the OH band near 2.9 $\mu$ together with loss of a strong band near 6.0 $\mu$, which is probably the carbonyl group. Some sort of cage structure such as **13** is a likely possibility and would account for the observed spectral changes. There is no way to measure the actual molecular weight of these exceedingly insoluble compounds, nor to decide between these and other possible arrangements of the labile B–O and B–N bonds.

Dibutyl iodomethaneboronate and 2-mercapto-6-oxypurine yielded a bis(boromethyl) derivative, postulated to be S,7-bis(dihydroxyborylmethyl)-2-mercapto-6-oxypurine since the sulfur and the 7-nitrogen are probably the most nucleophilic sites.

**Biological Tests.**—The pyrimidine compounds reported here have been submitted to Dr. A. H. Soloway, Northeastern University, to test for possible boron concentration in brain tumors in mice. The insolubility of these materials presents problems, and none has shown desirable biological properties. Other compounds tested with negative results include methanediboronic acid, iodomethaneboronic acid, hydroxymethaneboronic acid, dimethylaminomethylmethaneboronic acid, S-thioureidomethaneboronic acid, and thioacetylmethaneboronic acid.

## Experimental Section

Inert atmospheres (nitrogen or argon) were routinely used for all reactions.

**Dibutyl Iodomethaneboronate (1).**—Iodomethylmercuric iodide[7] was recrystallized once from methylene iodide, collected by suction filtration, and used directly without further drying. The methylene iodide content appeared to be about 20%; yields were much reduced if this was removed. Iodomethylmercuric iodide (100 g), dry sodium iodide (53 g), and boron tribromide (250 ml) were stirred vigorously under argon at 20–25° for 24 hr. The stirrer was a Trubore Teflon-paddle type lubricated with equal parts of Kel-F 90 chlorofluorocarbon grease and perchlorobutadiene, mixed hot, which withstood the boron bromide vapors. All liquid volatile up to ~130° (0.5 mm), as indicated by the residual mercuric iodide turning yellow, was distilled under vacuum and collected at −75°. (*CAUTION:* Methylene chloride was used for the Dry Ice bath, since this quantity of boron tribromide is extremely hazardous in case of accidental contact with most other solvents.) Most of the boron tribromide was recovered (suitable for recycling) by redistillation at atmospheric pressure through a short column, stopping the distillation as soon as it became slow to avoid overheating the residue, which consisted of bromomethylboron dibromide and iodomethylboron dibromide. These were distilled under vacuum up to about 40° (0.5 mm), then diluted with 50 ml of toluene, and stirred at −75° during the dropwise addition of 50 ml of *n*-butyl alcohol. The 1-butanol and toluene were removed under vacuum, and the residue of butyl borate, bromomethaneboronate, and iodomethaneboronate was stirred overnight with 50 ml of 1-butanol, 15 ml of acetone, and 15 g of sodium iodide. After simple vacuum distillation from the salts, the dibutyl iodomethaneboronate was isolated by careful fractionation with a spinning-band column: bp 61–63° (0.1 mm); yield 22–26 g (35–40%); nmr (neat) $\tau$ 7.95 (s, $ICH_2B$) plus $C_4H_9O$ peaks.

*Anal.* Calcd for $C_9H_{20}BIO_2$: C, 36.30; H, 6.72; B, 3.63; I, 42.61. Found: C, 36.58; H, 6.76; B, 3.71; I, 42.86.

**Iodomethaneboronic Acid.**—Exposure of 1 g of dibutyl iodomethaneboronate to the air in a thin layer until it had all been converted into solid (3 days) yielded iodomethaneboronic acid: mp 70–71°; nmr ($D_2O$) $\tau$ ~5.43 (s, OH), ~7.75 (s, $CH_2$).

*Anal.* Calcd for $CH_4BIO_2$: C, 6.46; H, 2.15; B, 5.82; I, 68.33. Found: C, 6.68; H, 2.19; B, 5.61; I, 68.48.

**Dibutyl butoxymethaneboronate** was prepared from dibutyl iodomethaneboronate and sodium butoxide in 1-butanol as described for similar compounds:[3] bp 63–64° (0.1 mm); ir (neat) (5–16 $\mu$) 7.04 (s), 7.48 (s), 8.00 (s), 9.00 (s), 10.28 (m), 12.01 (m), 13.56 (m).

*Anal.* Calcd for $C_{13}H_{29}BO_3$: C, 64.20; H, 11.93; B, 4.10. Found: C, 64.03; H, 12.10; B, 3.93.

**B,B-Dihydroxy-2,5-dibora-1,4-dioxane (2)**, the cyclic semiester of hydroxymethaneboronic acid, was prepared by stirring 8.5 g of Dowex 1-X8 anion-exchange resin which had been converted to the bicarbonate form with 4 g of dibutyl iodomethaneboronate and 20 ml of water under argon for 3 days. The solution was filtered and concentrated under vacuum, and the solid residue was recrystallized from about 3 ml of water and 5 ml of acetone: yield 1.3 g (84%); mp 147–148°; nmr ($D_2O$) $\tau$ ~6.4 (s, $CH_2$), ~5.32 (s, OH).

*Anal.* Calcd for $C_2H_6B_2O_4$: C, 20.87; H, 5.23; B, 18.70. Found: C, 20.86; H, 5.29; B, 18.93.

**Catechol Ester of Piperidinomethaneboronic Acid (3).**—Dibutyl iodomethaneboronate (3 g) was added dropwise to 10 ml of piperidine in 20 ml of 1-butanol and stirred 10 min. The precipitated piperidine hydriodide was removed by filtration and the filtrate was concentrated. No way was found to crystallize the residue of piperidinomethanboronic acid, which was dissolved in 20 ml of acetonitrile and 5 ml of distilled water and treated with 1.08 g of catechol. The catechol derivative crystallized at once and was collected and washed repeatedly with water, ethanol, ether, and acetone. The yield was 1.2 g (50%): the product did not melt up to 250°; ir (KBr, 5–16 $\mu$) 6.72 (s), 6.86 (w), 6.95 (w), 7.3 (w), 8.02 (s), 8.16 (w), 8.7 (w), 9.11 (w), 9.92 (w), 10.13–10.23 (w), 10.59–10.68 (w), 10.92–11.0 (w), 11.26–11.4 (w), 12.3–12.5 (w), 13.70 (w).

*Anal.* Calcd for $C_{12}H_{16}BNO_2 \cdot H_2O$: C, 61.05; H, 7.72; B, 4.60; N, 5.96. Found: C, 61.36; H, 7.53; B, 4.48; N, 5.76.

**Dimethylaminomethaneboronic acid** was prepared and isolated as the **catechol ester** in the same manner as the piperidine compound, substituting dimethylamine in the procedure. In this case the catechol ester did not crystallize until the acetonitrile was evaporated and the residue was dissolved in 20 ml of water and kept in the refrigerator several days. The yield was 1.2 g (85%): mp 123–124°; nmr ($CD_3SOCD_3$) $\tau$ 7.33 (s, $CH_3$), 7.96 (s, $NCH_2B$), plus aromatic and OH peaks.

*Anal.* Calcd for $C_9H_{12}BNO_2 \cdot 2H_2O$: C, 50.74; H, 7.56; B, 5.06; N, 6.57. Found: C, 50.87; H, 7.67; B, 4.89; N, 6.74.

**The N-methyl derivative of the catechol ester of piperidinomethaneboronic acid (4)** resulted when the piperidino compound was treated with methyl iodide in dimethyl sulfoxide. The methylated compound contained hydroxide (presumably coordinated to the boron) instead of iodide and was recrystallized from dimethyl sulfoxide: it did not melt up to 250°; nmr ($CD_3SOCD_3$), $\tau$ 3.64 ($C_6H_4$), 6.2 (s, N-$CH_3$), 7.9 (s, $NCH_2B$), plus piperidino and OH absorptions.

*Anal.* Calcd for $C_{13}H_{18}BNO_3 \cdot H_2O$: C, 60.49; H, 8.20; B, 4.19; N, 5.43. Found. C, 60.73; H, 8.11; B, 4.05; N, 5.03.

**Phthalimidomethaneboronic acid** was prepared by refluxing 2.8 g of potassium phthalimide and 4 g of dibutyl iodomethaneboronate in 35 ml of 1-butanol for 8 hr, adding water, extracting into ether, and crystallizing the product from water. The yield was 2.5 g (90%), mp 134–135°.

*Anal.* Calcd for $C_9H_8BNO_4$: C, 52.73; H, 3.93; B, 5.28; N, 6.83. Found: C, 52.87; H, 3.97; B, 5.10; N, 7.03.

**Catechol Ester of S-Thioureidomethaneboronic Acid.**—Dibutyl iodomethaneboronate (3 g) and 0.74 g of thiourea were refluxed in 50 ml of acetonitrile for 3 hr, treated with 50 ml of water, and concentrated under vacuum to yield a residue of crude, hygroscopic S-thioureidomethaneboronic acid hydriodide. Treatment with catechol in water precipitated the catechol ester in 83% yield: mp 259–260° dec; nmr ($CD_3SOCD_3$) $\tau$ 3.55 (s, $C_6H_4$), 6.66 (s, NH), 7.93 (s, $SCH_2B$).[15]

(15) The infrared curve of this compound recorded on a Beckman IR-8 is reproduced in T.-C. Cheng's Ph.D. Thesis, Washington State University, 1968, available from University Microfilms, Inc., Ann Arbor, Mich.

*Anal.* Calcd for $C_8H_9BN_2O_2S$: C, 46.18; H, 4.36; B, 5.20; N, 13.47; S, 15.41. Found: C, 46.14; H, 4.34; B, 5.33; N, 13.36; S, 15.56.

The **malonic acid chelate of S-thioureiodomethaneboronic acid** was prepared by treatment of the crude hydriodide salt with malonic acid in water,[3] decomposing near 325° without melting: nmr ($CD_3SOCD_3$) $\tau$ 6.75 (s, $COCH_2CO$), 7.85 (s, $BCH_2S$), 1.5 (broad, NH).[15]

*Anal.* Calcd for $C_5H_7BN_2O_4S$: C, 29.73; H, 3.49; B, 5.36; N, 13.87; S, 15.87. Found: C, 29.66; H, 3.70; B, 5.23; N, 13.86; S, 15.96.

**Dibutyl Acetylthiomethaneboronate.**—A solution of 15 mmol of sodium butoxide and 1.3 g of thiolacetic acid in 25 ml of 1-butanol was stirred with 5 g of dibutyl iodomethaneboronate for 2 hr, 50 ml of water, and 50 ml of ether were added, and the organic phase was washed with saturated aqueous NaCl and dried ($MgSO_4$). The product was distilled through a spinning-band column: 3 g (70%); bp 81–82° (0.1 mm); nmr (neat), $\tau$ 7.99 (s, $COCH_3$), 8.09 (s, $BCH_2S$), plus typical $C_4H_9O$ pattern.

*Anal.* Calcd for $C_{11}H_{23}BO_3S$: C, 53.67; H, 9.42; B, 4.39; S, 13.03. Found: C, 53.93; H, 9.47; B, 4.18; S, 13.12.

**Acetylthiomethaneboronic acid** was prepared from 2 g of the butyl ester and 10 ml of water by vacuum distillation of the BuOH–$H_2O$ azeotrope and recrystallized from 2 ml of water: mp 100–101°.

*Anal.* Calcd for $C_3H_7BO_3S$: C, 26.90; H, 5.72; B, 8.08; S, 23.93. Found: C, 27.15; H, 5.15; B, 8.25; S, 23.96.

**Dimethyl (Dibutoxyborylmethyl)malonate.**—A solution of the sodium salt of dimethyl malonate was prepared from 3.55 g of the ester and an equimolar amount of sodium *t*-butoxide (from NaH) in 50 ml of *t*-butyl alcohol and 8 g of dibutyl iodomethaneboronate was added dropwise. After 3 hr, 50 ml of water and 100 ml of ether were added, the water layer was washed with 50 ml of ether and 20 ml of 1-butanol, and the combined organic phase was dried ($MgSO_4$). Distillation through a spinning-band column yielded 4.4 g (55%): bp 115–117° (0.4 mm); ir (neat) 5.8 $\mu$ (C=O).

*Anal.* Calcd for $C_{14}H_{27}BO_6$: C, 55.64; H, 9.01; B, 3.58. Found: C, 55.90; H, 9.29; B, 3.56.

**Methyl $\alpha$-cyano-$\beta$-dibutoxyborylpropionate (6)** was similarly prepared from methyl cyanoacetate: bp 100–101° (0.1 mm); ir (neat) 4.45 (C≡N), 5.72 $\mu$ (C=O).

*Anal.* Calcd for $C_{13}H_{24}BNO_4$: C, 58.01; H, 8.99; B, 4.02; N, 5.20. Found: C, 57.99; H, 9.01; B, 3.95; N, 4.99.

**Diethyl Acetamido(catechylborylmethyl)malonate.**—Reaction of diethyl acetamidomalonate gave a product which could not be distilled and did not yield a crystalline boronic acid on treatment with water. Aqueous catechol converted the boronic acid into the crystalline catechol derivative, which was recrystallized from acetone and did not melt below 200°: nmr ($CD_3SOCD_3$), $\tau$ ~3.3–3.5 ($C_6H_4$), ~8.1 (s, $CH_3CO$), ~8.4 (s, $CH_2B$), plus ethoxy pattern; ir (KBr, 5–16 $\mu$) 5.71 (s), 5.80 (m), 6.2 (s), 6.42 (s), 6.73 (s), 7.03 (w), 7.24 (w), 7.32 (m), 7.5 (w), 7.67 (m), 7.78 (m), 8.05 (s), 8.13 (s), 8.32 (m), 8.40 (m), 8.95 (m), 9.1 (m), 9.35 (w), 9.71 (m), 9.85 (w), 9.92 (w), 10.6 (w), 11.10 (m), 11.51 (w), 12.15 (w), 13.10 (w), 13.20 (w), 13.41 (m), 13.63 (s).

*Anal.* Calcd for $C_{16}H_{20}BNO_7$: C, 55.04; H, 5.77; B, 3.10; N, 4.01. Found: C, 54.88; H, 5.77; B, 3.20; N, 4.16.

**2-(Dibutoxyborylmethyl)cyclohexanone (8).**—A solution of 2.03 g of the pyrrolidine enamine from cyclohexanone[16] and 4 g of dibutyl iodomethaneboronate in 50 ml of benzene was refluxed 18 hr. Water (20 ml) was added, and the mixture was refluxed another 0.5 hr. Sulfuric acid (10%, 10 ml) was added, and the product was extracted with three portions of ether (100 ml) mixed with 1-butanol (20 ml) and then was isolated by short-path distillation at *ca.* 65° (0.1 mm): ir (neat) 3.43 (s, C–H), 5.93 (s, C=O), 7.6 $\mu$ (s, B–O).[15]

*Anal.* Calcd for $C_{15}H_{29}BO_3$: C, 67.17; H, 10.90; B, 4.03. Found: C, 67.19; H, 10.77; B, 3.96.

**2-(S-Hydroxyboromethyl)thiobarbituric Acid.**—Dibutyl iodomethaneboronate (3 g) and 1.33 g of 2-thiobarbituric acid were refluxed in 50 ml of acetonitrile for 3 hr, cooled, and treated with 40 ml of water to cause crystallization of the product, 1.6 g (87%). The analytical sample was recrystallized from a mixture of dimethylformamide, dimethyl sulfoxide, and water and decomposed without melting at 300°: ir (KBr) 2.9 (OH), 3.25 (NH or OH), 3.4, 3.5 (CH), 6.0, 6.2 $\mu$ (C=O, C=N).[15]

*Anal.* Calcd for $C_5H_5BN_2O_3S$: C, 32.46; H, 2.72; B, 5.85; N, 15.14; S, 17.33. Found: C, 33.00; H, 2.74; B, 5.65; N, 15.28; S, 17.43.

**Oxybis[2-(S-boromethyl)thiobarbituric acid]** resulted when the foregoing compound was recrystallized from ethanol (1 l./g): uv max (EtOH), 275 m$\mu$ ($\epsilon$ 12,700), 256 (19,400), 230 (12,800); ir spectrum (KBr) identical with hydrated precursor.[15]

*Anal.* Calcd for $C_{10}H_8B_2N_4O_6S_2$: C, 34.12; H, 2.29; B, 6.16; N, 15.91; S, 18.22. Found: C, 34.09; H, 2.43; B, 5.96; N, 15.90; S, 18.08.

**2-Hydroxyboromethylthio-4-oxy-6-methylpyrimidine (11)** was prepared in the same manner as the thiobarbituric acid analog, substituting 2-mercapto-4-oxy-6-methylpyrimidine in the ingredients. The first fraction which crystallized, mp ~260°, gave an analysis which was not quite correct for $C_6H_7BN_2O_2S$ (C 2% low). After 2 days storage at 5°, a second crop was collected from the aqueous acetonitrile mother liquor, 1 g (45%), mp 326–334° dec, correct analysis for the dihydrate (or monohydrate of the boronic acid having the ring opened). The infrared spectra (KBr) of the two forms were the same: 2.90, 2.98, 3.10 (OH, NH), 6.02 (C=O), 6.20, 6.27, 6.37, 6.48, 6.58 $\mu$ (pyrimidine).[15]

*Anal.* Calcd for $C_6H_7BN_2O_2S \cdot 2H_2O$: C, 33.05; H, 5.09; B, 4.96; N, 12.85; S, 14.71. Found: C, 33.00; H, 5.10; B, 5.01; N, 13.03; S, 14.47.

**Oxybis(2-boromethylthio-4-oxy-6-methylpyrimidine) (12 or 13)** was prepared by heating either of the two hydrates described in the preceding paragraph to ~100° under vacuum (0.1 mm) for 2–4 hr. The analytical sample was recrystallized from a large volume of ethanol: uv max (EtOH) 274 m$\mu$ ($\epsilon$ 22,900), 237 (66,500); ir (KBr) 2.9 (weak, residual OH), 6.0 (weak, residual C=O), 6.2–6.3, 6.50, 6.70 $\mu$ (pyrimidine), numerous other differences from hydrated form.[15]

*Anal.* Calcd for $C_{12}H_{12}B_2N_4O_3S_2$: C, 41.65; H, 3.50; B, 6.25; N, 16.17; S, 18.53. Found: C, 41.84; H, 3.51; B, 6.08; N, 15.95; S, 18.25.

The **catechol ester of 2-hydroxyboromethylthio-4-oxy-6-methylpyrimidine** was prepared by stirring a suspension of 0.5 g of the pyrimidine in 25 ml of water with 0.3 g of catechol for 1.5 hr at 25°. The crystalline product (0.7 g) was washed repeatedly with water, and acetone: mp 265–270°.

*Anal.* Calcd for $C_{12}H_{13}BN_2O_4S$: C, 49.33; H, 4.48; B, 3.70; N, 9.59; S, 10.97. Found: C, 49.69; H, 4.57; B, 3.57; N, 9.75; S, 11.02.

**Oxybis(2-boromethylthio-4-oxy-6-phenylpyrimidine)** was prepared by the same method described for the thiobarbituric acid analog, substituting 2-mercapto-4-oxy-6-phenylpyrimidine in the ingredients: mp 328–331° dec.[15]

*Anal.* Calcd for $C_{22}H_{16}B_2N_4O_3S_2$: C, 56.20; H, 3.41; B, 4.60; N, 11.92; S, 13.64. Found: C, 56.09; H, 3.40; B, 4.57; N, 11.94; S, 13.51.

**Oxybis(2-boromethylthio-4-oxy-6-propylpyrimidine)** was similarly prepared from 2-mercapto-4-oxy-6-propylpyrimidine and did not melt below 250°.[15]

*Anal.* Calcd for $C_{16}H_{20}B_2N_4O_3S_2$: C, 47.79; H, 5.01; B, 5.38; N, 13.93; S, 15.95. Found: C, 47.61; H, 4.88; B, 5.15; N, 14.13; S, 15.70.

**6-(Dihydroxyborylmethylthio)purine** was similarly prepared from 6-mercaptopurine and recrystallized by dissolving in 50 ml of water and precipitating with 100 ml of acetone: mp 235–244° dec; ir (KBr) 2.9 (s), 6.27 (s), 6.79 (m), 6.90 (m), 7.15 (m), 7.50 (m), 7.65 (w), 7.95 (m), 8.20 (w), 8.74–9.30 (m), 9.8 (m), 10.6 (w), 11.30 (m), 12.0–12.5 (m), 12.7 (w), 14.5 (w), 15.50 $\mu$ (m).

*Anal.* Calcd for $C_6H_7BN_4O_2S \cdot H_2O$: C, 31.60; H, 3.97; B, 4.74; N, 24.56; S, 14.06. Found: C, 31.46; H, 4.04; B, 4.97; N, 24.13; S, 13.63.

**S,7-Bis(dihydroxyborylmethyl)-2-mercapto-6-oxypurine** was similarly prepared from 2-mercapto-6-oxypurine and recrystallized from ethanol–water and decomposed at 330° without melting.[15]

*Anal.* Calcd for $C_7H_{10}B_2N_4O_5S \cdot H_2O$: C, 27.85; H, 4.01; B, 7.16; N, 18.56; S, 10.62. Found: C, 28.14; H, 3.35; B, 7.18; N, 18.94; S, 10.61.

**2-(Dihydroxyborylmethylthio)-4-carboxyuracil** was similarly prepared from thioorotic acid, was not recrystallized, but was washed with water, acetone, and then boiling 1,2-dimethoxyethane, and decomposed at 250° without melting (up to 350°).[15]

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*Anal.* Calcd for $C_6H_7BN_2O_5S$: C, 31.33; H, 3.07; B, 4.70; N, 12.18; S, 13.94. Found: C, 31.07; H, 2.69; B, 4.74; N, 11.89; S, 13.95.

**2-Mercapto-4-oxy-5-(oxyboromethyl)-6-iminopyrimidine (7).**—A solution of 0.85 g of thiourea, an equimolar quantity of potassium *t*-butoxide, and 3 g of methyl α-cyano-β-dibutoxyborylpropionate in 40 ml of *t*-butyl alcohol was kept at 70° for 2 hr, then neutralized (to pH paper, pH about 7) with glacial acetic acid, and diluted with 40 ml of water. The product crystallized together with some boric acid, evidently tightly held in a chelate since attempted removal as the methyl borate azeotrope did not change the composition: yield 0.57 g (21%), recrystallized from methanol–water; nmr ($CD_3SOCD_3$) τ 8.46 (s, $CCH_2B$), 6.16 (s, NH, SH); decomposed at 250° without melting up to 350°; ir (KBr) 3.0 (NH), 6.1–6.5 μ (pyrimidine).[15]

*Anal.* Calcd for $C_{10}H_{13}B_3N_6O_6S_2$: C, 29.30; H, 3.20; B, 7.92; N, 20.50; S, 15.65. Found: C, 29.29, 29.27; H, 3.79, 3.74; B, 7.95 7.75; N, 19.97, 20.27; S, 15.80, 15.68.

A sample of the pyrimidine **7** without chelated boric acid was obtained on one occasion, but we were unable to purify it to the usual analytical standard. The reaction mixture was treated with acetic acid and then water, as described in the preceding paragraph, and was then extracted with a mixture of 1-butanol and ether. The aqueous phase was concentrated, and the oily residue was treated with acetone and allowed to stand for 1 month in the refrigerator to crystallize it.

**Registry No.**—**1,** 13251-29-1; iodomethaneboronic acid, 16876-23-6; dibutyl butoxymethaneboronate, 16876-24-7; **2,** 13536-41-9; catechol ester of **3,** 13251-31-5; dimethylaminomethaneboronic acid catechol ester, 16876-27-0; **4,** 16973-90-3; phthalimidomethaneboronic acid, 16876-28-1; catechol ester of S-thioureidomethaneboronic acid, 16876-29-2; dibutyl acetylthiomethaneboronate, 16876-30-5; acetylthiomethaneboronic acid, 16876-31-6; dimethyl (dibutoxyborylmethyl)-malonate, 16876-32-7; **6,** 16876-33-8; diethyl acetamido(catechylborylmethyl)malonate, 16876-34-9; **8,** 16876-35-0; **9,** 16876-36-1; 2-(S-hydroxyboromethyl)thiobarbituric acid, 16876-37-2; oxybis[2-(S-boromethyl)thiobarbituric acid], 16876-38-3; **10,** 16876-39-4; **11,** 16876-40-7; catechol ester of **11,** 16915-93-8; **12,** 16876-41-8; **13,** 16876-42-9; oxybis(2-boromethylthio-4-oxy-6-phenylpyrimidine), 16876-43-0; oxybis(2-boromethylthio-4-oxy-6-propylpyrimidine), 16876-44-1; S-7-bis(dihydroxyborylmethyl)-2-mercapto-6-oxypurine, 16876-45-2; 2-(dihydroxyborylmethylthio)-4-carboxyluracil, 16876-46-3.

# The Mechanism of the Prins Reaction. VI. The Solvolysis of Optically Active *trans*-2-Hydroxymethylcyclohexyl Brosylate and Related Arenesulfonates[1]

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The solvolysis of optically active *trans*-2-hydroxymethylcyclohexyl brosylate yields *trans*-2-hydroxymethylcyclohexanol with complete retention of optical activity. This result may be attributed to the intervention of a four-membered oxonium ion intermediate or reaction of the carbonium ion with solvent before any conformational change. The solvolyses of *trans*-2-hydroxymethylcyclopentyl β-naphthalenesulfonate and *threo*-1-hydroxy-2-methyl-3-butyl β-naphthalenesulfonate proceed with elimination, rearrangement, and complete inversion of configuration which indicates that these compounds are not suitable for generating the intermediate responsible for *trans* addition in the Prins reaction. The solvolysis of *cis*-2-hydroxycyclohexylcarbinyl brosylate yields no *trans*-2-hydroxymethylcyclohexanol, a compound which would be expected if four-membered-ring oxonium-ion intermediates were important in these reactions.

One of the most interesting features of the Prins reaction is the highly stereoselective *trans* addition found with simple alicyclic and acylic olefins. The Prins reaction of cyclohexene has been studied most extensively and the major products of the reaction are derivatives of *trans*-2-hydroxymethylcyclohexanol with only traces of the *cis* isomers.[3-5] Similarly, the Prins reactions of *cis*- and *trans*-2-butene appear to yield mainly the products of *trans* addition[6] and we find only a trace of the *cis* addition product in the Prins reaction of *trans*-2-butene.

A case of nonstereospecific addition has been reported by LeBel, Liesemer, and Mehemedbasich who find that the Prins reactions of *cis*- and *trans*-4-octene yield products of both *cis* and *trans* addition.[7] Moreover, the two olefins give different ratios of *trans* to *cis* addition. However, this lack of stereoselectivity may be the result of working in dioxane solution since dioxane is known to alter the stereochemistry of solvolysis reactions.[8] This possibility is also supported by the observation that the Prins reaction with cyclohexene in dioxane solution affords a 20% yield of the *cis* addition product.[9]

Several mechanisms have been proposed to account for the stereoselectivity of the Prins reaction with simple olefins. The mechanism which has been mentioned most frequently involves an intermediate four-membered-ring oxonium ion.[3,7,10,11] The second mechanism involves a three-membered bridged ion similar to the intermediates suggested for other examples of electrophilic additions to double bonds.[5,12,13] It is fair to say that no data have been presented which un-

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