Reactions of α-Haloalkaneboronic Esters[1a]

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Received September 15, 1965

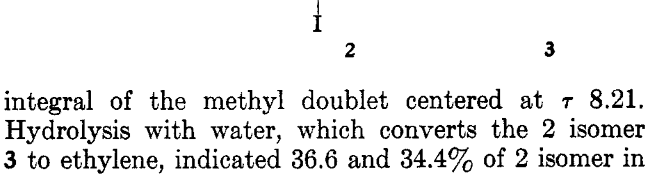
New α-haloalkaneboronic esters have been synthesized and mechanisms and synthetic utility of their reactions with nucleophiles have been investigated. Radical addition of bromomalononitrile to dibutyl vinylboronate has yielded dibutyl 1-bromo-3,3-dicyanopropane-1-boronate, which cyclizes to dibutyl 2,2-dicyanocyclopropaneboronate on treatment with bases. Polar additions of hydrogen halides to dialkyl vinylboronates have yielded 1-bromo- and 1-iodoethaneboronic esters. Sodium thiophenolate in butanol with dibutyl 1-iodoethaneboronate yields dibutyl 1-phenylthioethaneboronate, but with dibutyl 2-bromopropane-2-boronate yields dibutyl 2-butoxypropane-2-boronate. Thiourea reacts with either type of α-haloalkaneboronic ester, leading to S-boronoalkylthiouronium salts. Displacement of bromide from these α-bromoalkaneboronic esters by iodide is rapid, though not so remarkably accelerated as in the trichloromethyl-substituted series reported earlier. Solvolysis of dibutyl 2-bromopropane-2-boronate in aqueous ethanol yields 2-hydroxypropane-2-boronic acid. Kinetic study indicates a process with a high degree of carbonium ion character, with significant acceleration by the boron atom.

α-Haloalkaneboronic esters are potentially useful intermediates for the synthesis of a wide variety of water-soluble boronic acids, which are of interest as possible agents for therapy of brain tumors by B^{10} neutron capture.[2] The reactivity of the halogen as a leaving group in nucleophilic displacements is known to be greatly enhanced by the neighboring boron atom.[3]

Two useful synthetic routes to α-haloalkaneboronic esters are known. Radical addition of bromotrichloromethane and related polyhalomethanes to α,β-unsaturated boronic esters has yielded γ-substituted α-haloalkaneboronic esters.[4] More recently, reaction of liquid hydrogen bromide with α-methyl-α,β-unsaturated boronic esters has been found to yield α-haloalkaneboronic esters.[5] In the present investigation we have extended both synthetic routes to new types of α-haloalkaneboronic esters. Reactions of these compounds have been explored both for synthetic utility and mechanistic information.

Results

Haloalkaneboronic Esters.—In previous work,[5] dibutyl vinylboronate (1) was found to be inert to liquid hydrogen bromide at −70°. We have now found that in refluxing hydrogen iodide a mixture of dibutyl 1-iodoethaneboronate (2) and 2-iodoethaneboronate (3) is formed in about 60% yield. The proportion of 1 isomer 2 was found to be 62% by nmr, based on the integral of the methyl doublet centered at τ 8.21. Hydrolysis with water, which converts the 2 isomer 3 to ethylene, indicated 36.6 and 34.4% of 2 isomer in duplicate determinations, which should be corrected to ~40% to allow for the nonquantitative recovery of ethylene.



$$\underset{\mathbf{1}}{CH_2{=}CH{-}B(OBu)_2} + HI \longrightarrow \underset{\mathbf{2}}{CH_3\underset{I}{C}HB(OBu)_2} + \underset{\mathbf{3}}{ICH_2CH_2B(OBu)_2}$$

Pure dibutyl 1-iodoethaneboronate (2) was readily obtained by the preferential destruction of the 2 isomer in aqueous ethanol. However, recovery was only fair and the compound proved light sensitive and unstable on storage. Decomposition products included iodine and butyl borate.

We then tried the reaction of dibutyl vinylboronate (1) with liquid hydrogen bromide under pressure at 20–25°. The desired reaction occurred, but the boiling point of dibutyl 1-bromoethaneboronate was too close to that of butyl borate, an inevitable by-product, to permit separation. However, dipropyl vinylboronate yielded 16% of dipropyl 1-bromoethaneboronate (4), $CH_3CHBrB(OPr)_2$. Solvolysis in aqueous propanol removed the 2 isomer and the subsequent extraction procedure removed the propyl borate. Some ester cleavage by hydrogen bromide occurred during the reaction under pressure, shown by isolation of propyl bromide.

Previous radical additions to dibutyl vinylboronate have led to polyhalo compounds,[4] structures unlikely to have desirable biological properties. In the present work, we have examined the addition of bromomalononitrile to dibutyl vinylboronate (1) and obtained dibutyl 1-bromo-3,3-dicyanopropane-1-boronate (5) in 85% yield. The initiator was azobisisobutyronitrile. and the chain-carrying radical is believed to be the dicyanomethyl radical.

$$\underset{\mathbf{1}}{CH_2{=}CH{-}B(OBu)_2} \xrightarrow{(NC)_2\dot{C}H} (NC)_2CH{-}CH_2\dot{C}HB(OBu)_2 \xrightarrow{(NC)_2CHBr} \underset{\mathbf{5}}{(NC)_2CHCH_2CHBrB(OBu)_2} + (NC)_2\dot{C}H$$

We subsequently tried to add bromomalononitrile to other olefins. Vinyl acetate, 1-octene, acrylonitrile, and ethyl acrylate yielded only polymeric residues.

Dibutyl bromomalonate also added to dibutyl vinylboronate. The yield of dibutyl 1-bromo-3,3-dicarbobutoxypropane-1-boronate (6) was about 40%.

$$\underset{\mathbf{6}}{(BuO_2C)_2CHCH_2CHBrB(OBu)_2}$$

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(1) (a) Supported by Grants No. CA-05513-02 to -05 from the National Institutes of Health, U. S. Public Health Service. (b) National Defense Education Act Fellow, 1961–1964. Abstracted from the Ph.D. Thesis of G. D. S.

(2) (a) A. H. Soloway, *Science*, **128**, 1572 (1958); (b) D. S. Matteson, A. H. Soloway, D. W. Tomlinson, J. D. Campbell, and G. A. Nixon, *J. Med. Chem.*, **7**, 640 (1964).

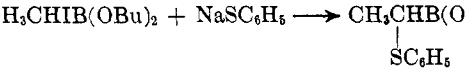
(3) D. S. Matteson and R. W. H. Mah, *J. Am. Chem. Soc.*, **85**, 2599 (1963).

(4) D. S. Matteson, *ibid.*, **82**, 4228 (1960).

(5) D. S. Matteson and J. D. Liedtke, *Chem. Ind.* (London), 1241 (1963).

Reactions.—Because it is much more easily prepared, dibutyl 2-bromopropane-2-boronate[5] (**7**), $(CH_3)_2CBrB(OBu)_2$, was chosen in preference to the 1-haloethaneboronic esters (**2** and **4**) for exploratory studies of the reactions of these halides. The reaction of **7** with sodium butoxide to yield dibutyl 2-butoxypropane-2-boronate has been reported previously.[5] It was hoped that mercaptide ions would displace bromide ion from **7**, but treatment with sodium thiophenolate in butanol yielded dibutyl 2-butoxypropane-2-boronate, $(CH_3)_2C(OBu)B(OBu)_2$.[6] From the infrared spectrum of the crude product, it appeared that a few per cent of the phenylthio-substituted boronic ester had been formed, but there was insufficient material to isolate.

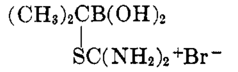
In contrast to the 2-bromopropane-2-boronic ester (**7**), dibutyl 1-iodoethaneboronate (**2**) reacted with sodium thiophenolate in butanol to yield dibutyl 1-phenylthioethaneboronate (**8**). Dipropyl 1-bromoethaneboronate (**4**) behaved similarly. However, sodio derivatives of 2-mercaptopyrimidine or 6-mercaptopurine did not yield the desired sulfides. It appeared likely that butoxide ion was dominating the competition, since the basicity was neutralized and 6-mercaptopurine was recovered, but the boron-containing product was not isolated for proof.



$$CH_3CHIB(OBu)_2 + NaSC_6H_5 \longrightarrow CH_3\underset{\displaystyle SC_6H_5}{\underset{|}{C}}HB(OBu)_2$$

2 **8**

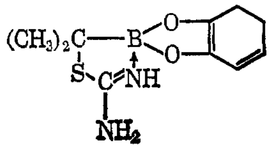
Thiourea in acetonitrile did displace bromide ion from dibutyl 2-bromopropane-2-boronate (**7**) to yield, after hydrolysis with water, S-(2-borono-2-propyl)-thiourea hydrobromide (**9**). Dipropyl 1-bromoethaneboronate and thiourea similarly yielded S-1-boronoethylthiourea hydrobromide. Neither of these highly water-soluble thiourea derivatives could be recrystallized, and the latter yielded an only partially satisfactory elemental analysis. The nmr and infrared spectra were in accord with the assigned structures.



$$(CH_3)_2\underset{\displaystyle SC(NH_2)_2{}^+Br^-}{\underset{|}{C}}B(OH)_2$$

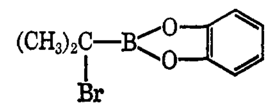
9

Treatment of an aqueous solution of the thiourea derivative **9** with catechol led to formation of aqueous hydrobromic acid and the crystalline catechol ester of S-(2-borono-2-propyl)thiourea. On the basis of this remarkable elimination of acid, we have assigned the chelated structure **10** to this compound.



10

In the hope that it would undergo desired displacement reactions, crystalline catechyl 2-bromopropane-2-boronate (**11**) was prepared by transesterification of the butyl ester (**7**) with catechol. However, this substance (**11**) proved unstable on storage, turning to a black liquid. Similarly, catechyl 1-bromoethaneboronate was unstable and we were unsuccessful in attempts to obtain a pure sample. Catechyl vinylboronate was also prepared from dibutyl vinylboronate (**1**) and catechol and found to polymerize within minutes of its isolation, even in the presence of large quantities of phenothiazine.

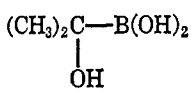


11

Reaction of catechyl 1-bromoethaneboronate or 2-bromopropane-2-boronate with aniline in ether yielded aniline hydrobromide, indicating that the desired displacement to form an α-anilinoalkaneboronic ester did not occur.

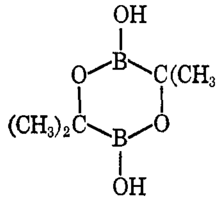
Dibutyl 2-bromopropane-2-boronate (**7**) reacted with sodium thiocyanate in acetone, but the product appeared on infrared examination to be a mixture of thiocyanate and isothiocyanate, and deteriorated to tar and butyl borate on attempted molecular distillation. Potassium cyanate in dimethylformamide yielded a mixture of products, including dibutyl 2-butoxypropane-2-boronate and, after treatment with butanol, what appeared to be butyl carbamate. Dipropyl 1-bromoethaneboronate (**4**) behaved similarly toward cyanate.

Solvolysis of dibutyl 2-bromopropane-2-boronate in 50% aqueous ethanol at room temperature yielded crystalline 2-hydroxypropane-2-boronic acid (**12**). This compound dehydrated very easily to a substance having the composition and molecular weight of the dimeric cyclic ester **13**.



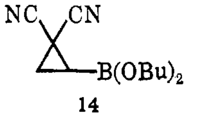
$$(CH_3)_2\underset{\displaystyle OH}{\underset{|}{C}}-B(OH)_2$$

12



13

Treatment of dibutyl 1-bromo-3,3-dicyano-propane-1-boronate (**6**) with pyridine yielded dibutyl 2,2-dicyanocyclopropaneboronate (**14**). Sodium butoxide or *t*-butylamine also converted **6** to **14**, but yields were lower. Derivatives prepared from **14** included the boronic acid and the diethanolamine ester.



14

Kinetics.—The profound effect of the boron atom in accelerating the rate of displacement of the neighboring halogen atom by bases has been reported previously in a study of dibutyl 1-bromo-3,3,3-trichloropropane-1-boronate.[3] However, the extraneous trichloromethyl group introduced some uncertainty into the interpretation. Accordingly, we have now examined the behavior of simple α-haloalkaneboronic esters toward sodium iodide in acetone and toward solvolysis in aqueous ethanol.

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[6] Previous to this finding, R. A. Bowie (to be published) observed that treatment of dibutyl 1-bromo-1-phenylethaneboronate with sodium thiophenolate in butanol yields dibutyl 1-butoxy-1-phenylethaneboronate, not the expected sulfide.

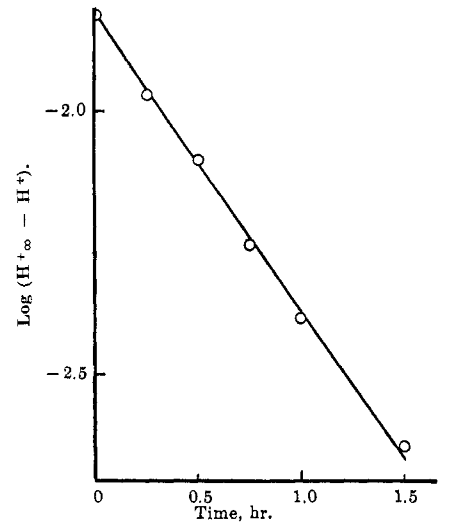


Figure 1.—First-order plot for the solvolysis of dibutyl 2-bromopropane-2-boronate in 50% aqueous ethanol at 25°.

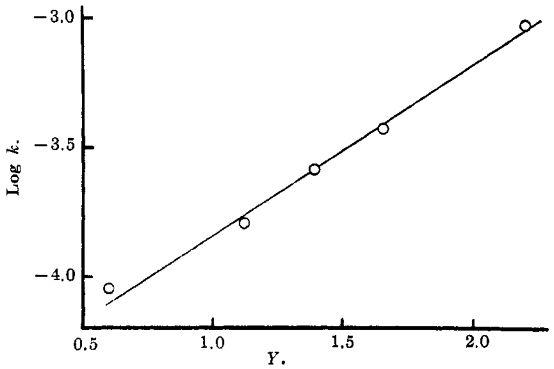


Figure 2.—Plot of log k vs. Y for dibutyl 2-bromopropane-2-boronate in 40–70% ethanol at 25°.

Rates of reaction with sodium iodide in acetone were determined by allowing allyl bromide to compete with the haloalkaneboronic ester for a deficient amount of sodium iodide, then determining the allyl bromide/allyl iodide ratio by gas chromatography. Values of $k_{\text{boronic ester}}/k_{\text{allyl bromide}}$ were calculated to be 0.419 for dibutyl 2-bromopropane-2-boronate (**7**), 1.44 for dibutyl 1-bromoethaneboronate (**15**), and 1.46 for dibutyl 1-bromo-3,3,3-trichloropropane-1-boronate. The last agrees well with the previously estimated value,[3] 1.5. For this study, dibutyl 1-bromoethaneboronate (**15**) was prepared by transesterification of the propyl ester (**4**) with butanol. Dibutyl 2-iodopropane-2-boronate was prepared by addition of hydrogen iodide to dibutyl propane-2-boronate and shown by infrared spectra to be identical with the product from sodium iodide and the bromo compound **7**.

The rate of solvolysis of dibutyl 2-bromopropane-2-boronate (**7**) in aqueous ethanol was followed by determining the amount of hydrobromic acid liberated with a pH meter. Conventional titration procedures for following solvolyses could not be used in this case, since the boronoalkyl halide reacts so rapidly with base that no end point can be reached in the useful range, above pH 3 or 4, without titrating the boronoalkyl halide as well as the free acid. However, the acid liberated in the solvolysis quickly lowers the pH to where hydroxide ion does not interfere, and good pseudo-first-order plots have been obtained out to about two half-lives, as illustrated in Figure 1. The error in k determined between successive pairs of points was ±10%. Rate constants were similarly determined for dipropyl 1-bromoethaneboronate (**4**) which solvolyzed too slowly for convenient measurement except at high water concentrations (90–100%). Observed rate constants are summarized in Table I.

TABLE I

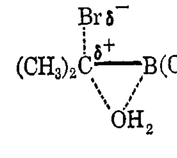
FIRST-ORDER RATE CONSTANTS FOR THE SOLVOLYSIS OF α-HALOALKANEBORONIC ESTERS IN AQUEOUS ETHANOL

Compound	Solvent, % ethanol	Temp, °C	10^4k, sec^{-1}
$(CH_3)_2CBrB(OBu)_2$	70	25.0	0.895
	60	25.0	1.56
	55	25.0	2.58
	50	25.0	3.67, 4.06
	40	25.0	9.41, 9.80
	50	17.7	1.72
	50	35.0	10.9
$CH_3CHBr(OPr)_2$	10	25.0	0.858
	0	25.0	1.37
	10	35.0	2.50
	10	45.0	6.63

For dibutyl 2-bromoethane-2-boronate (**7**) in 50% ethanol, ΔH^* is 17.5 kcal/mole and ΔS^* is −15.5 cal/deg mole. Plotting the data in 40–70% ethanol according to the Grunwald–Winstein equation,[7] $\log k = mY + \log k_0$, yields a line with a slope m of 0.68 ± 0.13, shown in Figure 2. The curvature appears to be greater than experimental error. For the solvolysis of dipropyl 1-bromoethaneboronate (**4**) in 10% ethanol, ΔH^* is 17.7 kcal/mole and ΔS^* is −17.8 eu.

Discussion

Mechanism of Solvolysis.—The solvolysis of dibutyl 2-bromopropane-2-boronate (**7**) shows considerable carbonium ion character in the transition state, but it appears that a free carbonium ion is not involved. The slope, m, of the Grunwald–Winstein plot,[7] 0.68, may be contrasted with that expected for a carbonium ion process, near 1, and those found for concerted displacements such as the solvolysis of methyl bromide, 0.26, and ethyl bromide, 0.34,[8] or the concerted solvolytic elimination, the deboronobromination of dibutyl 2-bromoethaneboronate, 0.40.[9] The heat and entropy of activation, 17.5 kcal and −15.5 eu, differ significantly from those parameters for t-butyl chloride, 21.6 kcal and −1.4 eu in 50% ethanol,[10] and may be interpreted on the basis of involvement of a tightly bound water molecule in the transition state.



$$(CH_3)_2\overset{Br\delta^-}{\underset{OH_2}{C^{\delta+}}}\!-\!B(OR)_2$$

The solvolysis of dipropyl 1-bromoethaneboronate (**4**) in 10% ethanol is evidently a concerted nucleophilic displacement. The entropy of activation, −17.8

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(7) E. Grunwald and S. Winstein, *J. Am. Chem. Soc.*, **70**, 846 (1948).
(8) S. Winstein, E. Grunwald, and H. W. Jones, *ibid.*, **73**, 2700 (1951).
(9) D. S. Matteson and J. D. Liedtke, *ibid.*, **87**, 1526 (1965).
(10) S. Winstein and A. H. Fainberg, *ibid.*, **79**, 5937 (1957).

eu, is remote from that of a typical carbonium ion process, *t*-butyl chloride in 10% ethanol,[10] +11.7 eu. The two points available for a Grunwald–Winstein correlation, 10% ethanol and pure water, yield an *m* value of 1.1, unreasonably high. Anomalous behavior was similarly found for dibutyl 2-bromoethaneboronate at the other extreme of solvent composition and was attributed to shifts in the equilibrium concentrations of the various boronic acid and ester functions present.[9]

The rate constants for these solvolyses reveal considerable acceleration by the borono function. Data available for *t*-butyl bromide[7] and isopropyl bromide[8] may be used to calculate rough rate constants for 50% ethanol at 25°. The relative magnitudes are *t*-butyl bromide, 10^2; dibutyl 2-bromopropane-2-boronate (**7**), 1; and isopropyl bromide, 10^{-2}. Assuming its Grunwalt–Winstein slope drops to 0.7, dibutyl 1-bromoethaneboronate (**4**) should have a relative magnitude around 10^{-2}.

Two factors appear to be accelerating the solvolyses of **4** and **7**. The electron-donating inductive effect of the borono function, postulated on theoretical grounds, stabilizes positive charge at the adjacent carbon atom. The other factor, partial bonding of the attacking nucleophile through the vacant orbital of boron, has been fully discussed previously.[3] The relative contribution of each factor to the total effect cannot be estimated from the present data.

Halide Exchange.—It was unexpected that dibutyl 1-bromoethaneboronate (**15**) would react no faster than dibutyl 1-bromo-3,3,3-trichloropropane-1-boronate with sodium iodide in acetone. Comparison with literature values for simple alkyl halide[11] gives the following relative rate constants: isopropyl bromide, 1.0; ethyl bromide, 40; dibutyl 2-bromopropane-2-boronate, 1600; allyl bromide, 4000; and dibutyl 1-bromoethaneboronate, 6000. Thus, even though the effect of the neighboring boron is not so extraordinary as it first seemed,[3] it must still be regarded as large. This acceleration is consistent with the same factors which accelerate the solvolytic displacements.

Hydrogen Iodide Addition.—The direction of hydrogen iodide addition to dibutyl vinylboronate (**1**) may result from slightly greater stability of the α-carbonium ion than that of the β ion, as postulated previously.[5] If this addition has concerted character,

$$CH_3\overset{+}{C}HB(OBu)_2 \quad \textit{vs.} \quad {}^{+}CH_2CH_2B(OBu)_2$$

iodide attack at the α-carbon would be facilitated by the vacant orbital of boron. However, a high degree of concerted character in the addition would require a transition state which retained much carbon–carbon π-bond character, and the π-electron-withdrawing effect of the boron would direct the halide to the β position. This opposing factor governs hydroboration of **1**,[12] though it should be noted that the differing results represent only a slight shift in thermodynamic balance.

In summary, the solvolysis, halide exchange, and hydrogen iodide addition reactions reported in this work all fit a consistent picture of two primary effects, electron donation from boron to carbon and partial bond formation by nucleophiles with the vacant boron orbital.

Other Reactions.—The reaction of dibutyl 2-bromopropane-2-boronate (**7**) with thiophenoxide, in which the basic butoxide ion rather than the more nucleophilic mercaptide displaces the halide, is consistent with results previously published.[3] The two methyl groups of **7** would tend to increase the carbonium ion character of the displacement, as noted in the foregoing discussion of the solvolysis, making the carbon atom less sensitive to the relative nucleophilicities of competing reagents. However, a reagent as highly nucleophilic but weakly basic as thiourea does not release butoxide sufficiently for effective competition by the latter.

The formation of dicyanocyclopropaneboronic ester **14** from dibutyl 1-bromo-3,3-dicyanopropane-1-boronate (**5**) is remarkable, especially with bases such as butoxide, which normally attack the α-haloalkylboron function very rapidly. This is the only known alkylation of an α-haloalkaneboronic ester by a carbanion. In addition to the usual rapidity of three-membered ring closure, this reaction is probably aided by the linearity of the cyano group, which keeps the nucleophilic nitrogen away from the boron atom. The analogous malonic ester **6** does not yield a cyclopropane derivatives, and malononitrile fails to alkylate α-haloethaneboronic esters.

Biological testing of the new boronic acids reported in this article is in progress, but none has shown useful properties.[13]

Experimental Section

Dibutyl 1-Iodoethaneboronate (**2**).—A 36.8-g sample of dibutyl vinylboronate[4] was added dropwise in 30 min to 24 ml of stirred, refluxing anhydrous hydrogen iodide (bp −35°) in a bath at −35°. The solution was stirred 30 min with the bath at −45 to −35°, 1.5 hr with the bath at −10 to −20° (refluxing). The solution was then allowed to warm to room temperature and the hydrogen iodide was allowed to escape. Simple distillation yielded 38.0 g (61%) of a mixture of dibutyl 1-iodoethaneboronate (**2**) and 2-iodoethaneboronate (**3**), bp 71–73° (0.1 mm). A 20.0-g portion of this mixture was stirred with 25 ml of water and 35 ml of ethanol under nitrogen at 25° for 45 min. The solution was saturated with sodium chloride and extracted with two 60-ml portions of 1:1 butanol–ether. The organic extracts were washed with saturated sodium chloride solution, dried over magnesium sulfate, and distilled to yield 6.8 g of dibutyl 1-iodoethaneboronate. The analytical sample was fractionated through a short column, bp 62–65° (0.1 mm), $n^{31}\text{D}$ 1.4646.

Anal. Calcd for $C_{10}H_{22}BIO_2$: C, 38.49; H, 7.11; B, 3.47; I, 40.67. Found:[14] C, 38.73; H, 7.30; B, 3.66; I, 40.89.

Dipropyl vinylboronate was prepared from the butyl ester *via* vinylboronic acid,[15] which was esterified by distillation of the propanol–benzene–water azeotrope through a 30-cm packed column. In a previous preparation,[16] characterization was incomplete. The product was fractionated, bp 56–58° (20 mm), $n^{24}\text{D}$ 1.4050.

Anal. Calcd for $C_8H_{17}BO_2$: C, 61.60; H, 10.98; B, 6.94. Found: C, 61.66; H, 11.06; B, 6.73.

Dipropyl 1-Bromoethaneboronate (**4**).—Thirty grams of dipropyl vinylboronate was added dropwise rapidly to 50 ml of anhydrous hydrogen bromide under nitrogen with stirring at −75°. The mixture was then transferred rapidly to a cooled

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[11] A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 12, 13.

[12] D. S. Matteson and J. G. Shdo, *J. Org. Chem.*, **29**, 2742 (1964).

[13] A. H. Soloway, personal communication.

[14] Microanalyses were by Galbraith Laboratories, Knoxville, Tenn.

[15] D. S. Matteson, *J. Org. Chem.*, **27**, 3712 (1962).

[16] D. S. Matteson and K. Peacock, *J. Organometal. Chem.*, **2**, 190 (1964).

Parr A428HC4 Monel-8 bomb fitted with a monel needle valve. The bomb was closed and allowed to stand 18 hr at 20–25°. The hydrogen bromide was vented and the residue was poured into 125 ml of 1-propanol. (Much polymeric residue and lower yields resulted if the propanol was omitted.) Distillation yielded a mixture of dipropyl 1-bromoethaneboronate (**4**), dipropyl 2-bromoethaneboronate, and tripropyl borate. This mixture was treated with 25 ml of propanol and 25 ml of water for 2 hr at 25° to solvolyze the 2 isomer. The organic product was salted out with sodium bromide and extracted with two 50-ml portions of ether and one 50-ml portion of propanol, then washed with saturated sodium bromide solution and dried over magnesium sulfate. Distillation yielded 7.3 g (16%) of dipropyl 1-bromoethaneboronate, bp 41–46° (0.1 mm). The analytical sample was distilled through a spinning-band column, bp 75–78° (20 mm), $n^{24.5}$D 1.4334.

Anal. Calcd for $C_8H_{18}BBrO_2$: C, 40.55; H, 7.65; B, 4.57; Br, 33.73. Found: C, 40.51; H, 7.71; B, 4.60; Br, 33.91.

Dibutyl 1-bromoethaneboronate (**15**) was prepared from 6.5 g of the propyl ester **4** by transesterification with 25 ml of butanol and distillation through a short column: yield 5.5 g, bp 52–53° (0.02 mm), $n^{25.5}$D 1.4356.

Anal. Calcd for $C_{10}H_{22}BBrO_2$: C, 45.33; H, 8.37; B, 4.07; Br, 30.15. Found: C, 45.50; H, 8.57; B, 4.23; Br, 29.96.

Dibutyl 2-Bromopropane-2-boronate (**7**).[17]—A 4.2-g sample of dibutyl propene-2-boronate[4] was added dropwise to 15 ml of anhydrous hydrogen bromide stirred under nitrogen at −75° in the dark. After 2 hr at −75°, the hydrogen bromide was evaporated by allowing the solution to warm to room temperature. Simple distillation yielded 4.2 g (71%) of dibutyl 2-bromopropane-2-boronate (**7**), bp 50–51° (0.1 mm), analysis previously reported.[5]

Dibutyl 2-iodopropane-2-boronate was prepared from 5.4 g of sodium iodide and 10.0 g of dibutyl 2-bromopropane-2-boronate in 100 ml of acetone for 4 hr. Alternately, 20 g of dibutyl propene-2-boronate was added to 25 ml of hydrogen iodide as described for the preparation of the crude iodoethaneboronic ester (**2**), yield 53%, bp 68–71° (0.1 mm), n^{24}D 1.4684, shown by infrared to be identical with the other sample.

Anal. Calcd for $C_{11}H_{24}BIO_2$: C, 40.52; H, 7.42; B, 3.32; I, 38.93. Found: C, 40.55; H, 7.42; B, 3.38; I, 38.83.

Dibutyl 1-Bromo-3,3-dicyanopropane-1-boronate (**5**).—A 13.6-g portion of dibutyl vinylboronate nearly saturated with azobisisobutyronitrile (~0.1 g) was added over 45 min to 10.7 g of bromomalononitrile[18] and 0.1 g of the azonitrile stirred at 75° under nitrogen. A second 0.2-g portion of azonitrile was added after 1 hr and heating was continued a total of 4 hr after which the infrared spectrum of the black product indicated no unsaturation at 6.1 μ. After distillation of volatile impurities up to a bath temperature of 80° (0.1 mm), the residue was passed through a falling-film molecular still twice to yield 21.0 g (87%) of dibutyl 1-bromo-3,3-dicyanopropane-1-boronate, n^{31}D 1.4581, weak infrared C≡N band at 4.42 μ.

Anal. Calcd for $C_{13}H_{22}BBrN_2O_2$: C, 47.43; H, 6.74; B, 3.29; Br, 24.29; N, 8.52. Found: C, 47.43; H, 6.95; B, 3.29; Br, 24.49; N, 8.73.

Dibutyl 1-Bromo-3,3-dicarbobutoxypropane-1-boronate (**6**).—Dibutyl vinylboronate (9.2 g) saturated with azobisisobutyronitrile was added to dibutyl bromomalonate[19] (14.8 g) at 80° following the procedure described in the preceding section for the synthesis of **5**, except that an additional 0.2-g portion of azonitrile was required and the total heating period was 13 hr. Unreacted dibutyl bromomalonate was distilled and the residue was passed through a falling-film molecular still to yield 9.7 g (50%) of dibutyl 1-bromo-3,3-dicarbobutoxypropane-1-boronate (**6**), n^{24}D 1.4513.

Anal. Calcd for $C_{21}H_{40}BBrO_6$: C, 52.61; H, 8.41; B, 2.26; Br, 16.68. Found: C, 52.27; H, 8.25; B, 2.47; Br, 16.82.

Dibutyl 1-Butoxyethaneboronate.—The crude mixture of iodoethaneboronates **2** and **3** obtained directly from hydrogen iodide and dibutyl vinylboronate was treated with sodium butoxide in butanol in the usual manner.[3,5] The product contained much butyl borate, which was removed by adding methanol and distilling the methanol–methyl borate azeotrope until the flame test for boron in the distillate was negative. The residue yielded 32% of dibutyl 1-butoxyethaneboronate, bp 67° (0.1 mm), n^{24}D 1.4171. The structure was proved by hydrogen peroxide deboronation[4] to acetaldehyde in 77% yield as the 2,4-dinitrophenylhydrazone.

Anal. Calcd for $C_{14}H_{31}BO_3$: C, 65.12; H, 12.10; B, 4.19. Found: C, 65.35; H, 12.25; B, 4.39.

Dipropyl 1-Phenylthioethaneboronate.—The procedure previously described[3] for the reaction of dibutyl 1-bromo-3,3,3-trichloropropane-1-boronate with butyl mercaptan was followed, substituting dipropyl 1-bromoethaneboronate (**4**), thiophenol, and 1-propanol for the reactants and solvent. Dipropyl 1-phenylthioethaneboronate was obtained in 65% yield, bp 80–81° (0.02 mm), n^{22}D 1.5055. Hydrogen peroxide deboronation[4] yielded 100% of acetaldehyde 2,4-dinitrophenylhydrazone.

Anal. Calcd for $C_{14}H_{23}BO_2S$: C, 63.19; H, 8.71; B, 4.06; S, 12.05. Found: C, 63.01; H, 8.75; B, 4.18; S, 12.15.

Dibutyl 1-phenylthioethaneboronate was similarly prepared from crude dibutyl 1-iodoethaneboronate (**2**), and butyl borate was removed by distillation of the methanol–methyl borate azeotrope. The yield was 26% after short-path distillation, n^{24}D 1.5034.

Anal. Calcd for $C_{16}H_{27}BO_2S$: C, 65.31; H, 9.25; B, 3.68; S, 10.90. Found: C, 65.05; H, 9.16; B, 3.73; S, 11.01.

S-2-Borono-2-propylthiourea Hydrobromide (**9**).—Five grams of dibutyl 2-bromopropane-2-boronate (**7**) was added dropwise to a stirred solution of 1.37 g of thiourea in 50 ml of anhydrous acetonitrile, then heated at 80° for 3 hr under nitrogen. The solution was cooled, treated with 50 ml of water, and evaporated under vacuum to yield 3.73 g (86%) of S-2-borono-2-propylthiourea hydrobromide, mp 130–200° dec. The infrared spectrum in a potassium bromide pellet showed a broad OH band at 3.0 μ, a C=N band at 6.05 μ, and strong B–O absorption at 7–8 μ. The nmr spectrum in deuterium oxide showed an OH singlet at τ 5.35 and a methyl singlet at τ 8.63 in the ratio 1:1. This compound could not be recrystallized, but yielded a correct analysis for the corresponding boronic anhydride after repeated washing with ether and prolonged drying under vacuum.

Anal. Calcd for $C_4H_{12}BBrN_2OS$: C, 21.35; H, 4.48; B, 4.80; Br, 35.40; N, 12.44; S, 14.25. Found: C, 21.65; H, 4.71; B, 4.78; Br, 35.50; N, 12.04; S, 14.50.

S-1-Boronoethylthiourea hydrobromide was similarly prepared from dipropyl 1-bromoethaneboronate (**4**). The nmr spectrum showed an OH singlet at τ 5.42, a CH_3 doublet at τ 8.82, and a CH quartet at τ 7.40 in the expected ratios. The infrared spectrum was in accord with the assigned structure. Two of the elemental analyses were off for the anhydride, as might be expected for a substance which could not be recrystallized.

Anal. Calcd for $C_3H_8BBrN_2OS$: C, 17.1; H, 3.82; B, 5.1; Br, 37.9; N, 13.3; S, 15.2. Found: C, 18.5; H, 4.16; B, 5.0; Br, 36.2; N, 13.0; S, 15.0.

Catechyl Ester of S-2-Borono-2-propylthiourea (**10**).—Addition of 0.55 g of catechol in 5 ml of water to 1.21 g of S-2-borono-2-propylthiourea hydrobromide in 10 ml of water precipitated 0.95 g (89%) of the catechyl ester **10**. The filtrate was highly acidic, and the product (**10**) gave a negative test for bromide ion with alcoholic silver nitrate and with sodium iodide in acetone. The analytical sample was sublimed at 100° (0.05 mm) and did not melt up to 280°. The nmr spectrum in perdeuteriodimethyl sulfoxide showed three singlets at τ 3.57, 6.62, and 8.74 due to aromatic, exchangeable NH, and methyl protons, respectively.

Anal. Calcd for $C_{10}H_{13}BN_2O_2S$: C, 50.87; H, 5.55; B, 4.58; N, 11.87; S, 13.58. Found: C, 50.87; H, 5.60; B, 4.76; N, 11.63; S, 13.38.

Catechyl 2-Bromopropane-2-boronate (**11**).—A 5.7-g portion of catechol was stirred with 14.0 g of dibutyl 2-bromopropane-2-boronate (**7**), the butanol liberated was distilled under vacuum, and the residue was fractionated to yield 9.9 g of catechyl 2-bromopropane-2-boronate, bp 63° (0.1 mm), after sublimation, mp 42–43°. The nmr spectrum showed aromatic CH at τ 2.84 and a CH_3 singlet at τ 7.99.

Anal. Calcd for $C_9H_{10}BBrO_2$: C, 44.87; H, 4.18; B, 4.49; Br, 33.19. Found: C, 44.67; H, 4.13; B, 4.61; Br, 32.91.

2-Hydroxypropane-2-boronic Acid (**12**).—Five grams of dibutyl 2-bromopropane-2-boronate (**7**) was dissolved in 10 ml of ethanol, and 10 ml of water was added. After 8 hr under nitrogen at 25°, the crystalline product (**12**) was collected, mp 151–153° dec, yielded 1.13 g (61%) including second crop. The nmr spectrum in perdeuteriodimethyl sulfoxide showed a single

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(17) J. D. Liedtke, Ph.D. Thesis, Washington State University, 1964. Details were omitted in the preliminary note, ref. 4.

(18) B. C. Hesse, *Am. Chem. J.*, **18**, 723 (1896).

(19) H. P. Gallus and A. K. Macbeth, *J. Chem. Soc.*, 1810 (1937).

OH peak at τ 6.57 and a methyl singlet at τ 8.81. Drying the analytical sample yielded the cyclic dimeric ester **13**.

Anal. Calcd for $C_6H_{14}B_2O_4$: C, 41.94; H, 8.22; B, 12.59; mol wt, 172. Found: C, 42.02; H, 8.27; B, 12.49; mol wt, 169.

Dibutyl 2,2-Dicyanocyclopropaneboronate (14).—A solution of 9.9 g of dibutyl 1-bromo-3,3-dicyanopropane-1-boronate in 75 ml of ether was added over a period of 1 hr to 25 ml of anhydrous pyridine stirred at 0° under nitrogen, then allowed to stand 3 hr at room temperature. Treatment with 100 ml of ether and 50 ml of water was followed by washing the organic phase with 1 *M* hydrochloric acid, extracting the washings with butanol, and drying the combined organic phase with magnesium sulfate. Distillation yielded 5.4 g (72%) of dibutyl 2,2-dicyanocyclopropaneboronate (**14**), bp 109–112° (0.02 mm), $n^{31}\text{D}$ 1.4441. The infrared spectrum showed a well-defined cyclopropyl C–H band at 3.22 μ and a strong C$\equiv$N band at 4.45 μ; there was no C$\equiv$C band in the 6.1-μ region.

Anal. Calcd for $C_{13}H_{21}BN_2O_2$: C, 62.87; H, 8.53; B, 4.36; N, 11.29. Found: C, 62.93; H, 8.57; B, 4.38; N, 11.15.

2,2-Dicyanocyclopropaneboronic Acid.—The butyl ester **14** (3.75 g) was treated with water (20 ml) and the volatile material was distilled under vacuum to yield 87% of 2,2-dicyanocyclopropaneboronic acid, mp 124–126°. The nmr spectrum at 60 Mc in deuterium oxide showed the HDO peak at 274.5 cps downfield from external tetramethylsilane and two groups of peaks attributed to three nonequivalent cyclopropyl hydrogens at 135, 131, 124, 122, 119.5, 112.5, and 108 cps (integrals 0.1, 0.3, 0.3, 0.2, 0.4, 0.4, 0.3; total 2.0) and at 95, 85.5, 83, and 74 cps (integrals 0.5, 0.3, 0.25, 0.15; total 1.2).

Anal. Calcd for $C_5H_5BN_2O_2$: C, 44.20; H, 3.71; B, 7.96; N, 20.62. Found: C, 44.05; H, 3.86; B, 7.77; N, 20.38.

The diethanolamine ester of 2,2-dicyanocyclopropaneboronic acid was prepared from the acid and diethanolamine in acetone and was recrystallized from ethyl acetate, mp 190–192°.

Anal. Calcd for $C_9H_{12}BN_3O_2$: C, 52.72; H, 5.90; B, 5.28; N, 20.49. Found: C, 52.77; H, 6.00; B, 5.07; N, 20.70.

Relative Rates of Displacement of Bromide by Iodide.—A solution of sodium iodide in acetone was added to a solution of the α-bromoalkaneboronic ester and allyl bromide to make the concentration of each of the three reactants 0.25 *M*. The mixture was allowed to stand at 22–24° until no further change of composition was shown by analysis; 1 hr was sufficient. Allyl bromide and allyl iodide were determined by gas chromatography on a 5-ft SE-30 silicone rubber on Chromosorb W column at 0°. Relative rate constants were calculated assuming that reactions were first order in each reactant and that all the sodium iodide had been consumed.

Kinetics of Solvolyses.—Solvents were measured volumetrically and solutions were made approximately 0.05 *M* in the α-bromoalkaneboronic ester. Temperature control was ±0.1°. The pH was determined to ±0.02 unit with a Leeds and Northrup pH meter. The pH value measured at "infinite" time generally differed from the theoretical value by 0.2–0.5 unit. It was assumed that hydrobromic acid concentrations calculated from the pH measurements followed a linear function of the true values.

Rearrangements of *o*-Aminophenyl Esters

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Received August 18, 1965

The hydrogenolysis of several N-benzyloxycarbonyl-*o*-aminophenyl esters resulted in isolation of the rearranged N-acyl- or N-alkoxycarbonyl-*o*-aminophenols. The unstable, intermediate *o*-aminophenyl esters could not be isolated. However, hydrogenolysis of some of the original compounds in the presence of acetic anhydride produced N-acetyl-*o*-aminophenyl esters, presumably because acetylation of the amino group formed was more rapid than rearrangement.

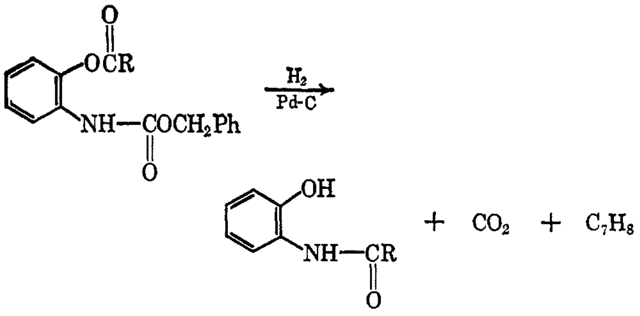
Following the work of Böttcher,[2] there have been several reports on the reduction of *o*-nitrophenyl (or analogous nitronaphthyl) esters by treatment with metal–acid combinations.[2] In all cases the intermediate *o*-aminophenyl esters were not isolated. Presumably these unstable intermediates were first produced and then rapidly rearranged to the N-acyl-*o*-aminophenols, the products actually obtained. Indeed, Ransom[3] and Ransom and Nelson[4] were able to isolate an unrearranged *o*-aminophenyl alkyl carbonate from the reduction of an *o*-nitrophenyl alkyl carbonate at low temperature. These unstable compounds readily rearranged to the N-alkoxycarbonyl-*o*-aminophenols on standing. This type of rearrangement does not occur when the amino and ester groups are *meta* or *para* to each other.[3,5]

Pelczar[6] isolated the unstable intermediate N-methyl-*o*-aminophenyl acetate from the hydrogenolysis of N-methyl-N-benzyloxycarbonyl-*o*-aminophenyl acetate. This compound also readily isomerized to N-methyl-*o*-acetamidophenol.

These facts suggested that *o*-aminophenyl esters might be isolated from the hydrogenolysis of N-benzyloxycarbonyl-*o*-aminophenyl esters. In any event, this reaction appeared to be a convenient way of studying the O to N migration of *o*-aminophenyl esters.

Discussion and Results

Hydrogenolysis of several N-benzyloxycarbonyl-*o*-aminophenylcarboxylate and carbonate esters resulted in isolation of the rearranged N-acyl- or N-alkoxycarbonyl-*o*-aminophenols. The unstable, intermediate *o*-aminophenyl esters could not be obtained.



R = CH_3, C_2H_5, C_6H_5, *i*-C_4H_9O

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[1] Abstracted in part from the Ph.D. Thesis of C. Ambrosio, The University of Connecticut, 1965.

[2] (a) W. Böttcher, *Ber.*, **16**, 629 (1883); (b) A. Einhorn and B. Pfyl, *Ann.*, **34**, 311 (1900); (c) J. H. Ransom, *Ber.*, **31**, 1055 (1898).

[3] J. H. Ransom, *Am. Chem. J.*, **23**, 1 (1900).

[4] J. H. Ransom and R. E. Nelson, *J. Am. Chem. Soc.*, **36**, 390 (1914).

[5] K. Auwers, *Ber.*, **33**, 1923 (1900).

[6] F. A. Pelczar, M.S. Thesis, The University of Connecticut, 1963.