Methylation of Ethyl 3-Nitro-2-thienylpyruvate.—A mixture of 4.24 g. (0.017 mole) of ethyl 3-nitro-2-thienylpyruvate, 2.60 g. of anhydrous potassium carbonate, 15 ml. of methyl iodide, and 300 ml. of acetone was heated at reflux for 12 hr. During the reflux period, the initially red mixture became light orange. The mixture then was cooled and filtered to remove inorganic salts. After removal of the acetone, the residual oil was chromatographed on alumina with benzene as eluent. The first band to be eluted contained 3.58 g. of an oil which slowly crystallized. Recrystallization from ethanol–water afforded 1.06 g. (24%) of the enol methyl ether, ethyl 2-methoxy-3-(3-nitro-2-thienyl)acrylate (IVb). A second recrystallization gave an analytical sample of yellow needles, m.p. 74.5–75.5°. The material failed to give a ferric chloride test for enols. An infrared spectrum (KBr pellet) contained peaks at 1725 (ester carbonyl) and 1612 cm.$^{-1}$ (enol C=C).

Anal. Calcd. for $C_{10}H_{11}NO_5S$: C, 46.70; H, 4.28; N, 5.45. Found: C, 46.67: H, 4.36; N, 5.30.

The filtrate from the first recrystallization of IVb was evaporated and again chromatographed on alumina. Fractionation of the benzene eluent afforded a trace of crystalline solid, m.p. 40–42°, which was assigned the structure of 2-ethyl-3-nitrothiophene (IIIb) on the basis of infrared spectra.

Reduction of Ethyl 2-Methoxy-3-(3-nitro-2-thienyl)acrylate (IVb).—Reduction of IVb under conditions employed for the reductive cyclization of Ib to IIb, afforded ethyl 2-methoxy-3-(3-amino-2-thienyl)acrylate (VII), a yellow solid, which was purified by recrystallization from benzene–petroleum ether (30–60°), m.p. 89.5–90.5°.

Anal. Calcd. for $C_{10}H_{13}NO_3S$: C, 52.91; H, 5.73; N, 6.17. Found: C, 52.75; H, 5.88; N, 5.97.

Reaction of Ethyl 3-Nitro-2-thienylpyruvate with *p*-Nitrobenzyl Chloride.—To a stirred solution of 0.1 g. (0.0043 g.-atom) of sodium metal in 15 ml. of absolute ethanol was added a solution of 1.0 g. (0.0041 mole) of the pyruvate Ia in 25 ml. of ethanol. The mixture was brought to reflux temperature and a solution of 0.71 g. (0.0041 mole) of *p*-nitrobenzyl chloride in 20 ml. of ethanol then was added over a 10-min. period. The resulting mixture was refluxed for 19 hr. Most of the ethanol was evaporated, and the solution was diluted with water and acidified with hydrochloric acid. The brown solid which precipitated was collected, dried, and recrystallized from absolute ethanol. A yellow solid, 0.354 g. (24%), which separated from the solution was identified through analysis and infrared spectroscopy as ethyl 2-(*p*-nitrobenzoxy)-3-(3-nitro-2-thienyl)acrylate (IVc). Another recrystallization from ethanol provided an analytical sample, m.p. 168.5–169°.

Anal. Calcd. for $C_{16}H_{14}N_2O_7S$: C, 50.80; H, 3.73; N, 7.40. Found: C, 50.98; H, 3.69; N, 7.44.

The filtrate from the first recrystallization of IVc yielded 0.185 g. (12%) of another yellow solid identified as 1-(3-nitro-2-thienyl)-2-(*p*-nitrophenyl)ethane (IIIc). An analytical sample from ethanol–water melted at 120–121°.

Anal. Calcd. for $C_{12}H_{10}N_2O_4S$: C, 51.80; H, 3.62; N, 10.08. Found: C, 51.63; H, 3.61; N, 10.35.

Cyanomethylation of Ethyl 3-Nitro-2-thienylpyruvate.—The pyruvate Ia (0.50 g.), sodium iodide (0.31 g.), and chloroacetonitrite (0.156 g.) were dissolved in 25 ml. of absolute ethanol. To this solution at reflux temperature was added a solution of sodium metal (0.051 g.) in 25 ml. of absolute ethanol. The mixture was heated at reflux for 24 hr., then reduced in volume, acidified with dilute hydrochloric acid, and extracted with ether. An oil which remained after removal of the ether was taken up in cyclohexane, treated with Darco, filtered, and chilled. 3-(3-Nitro-2-thienyl)propionitrile (IIId) was obtained in 15% yield as white needles, m.p. 77.5–78.3°. In the infrared (KBr pellet) the material does not absorb in the carbonyl region but exhibits a nitrile absorption at 2240 cm.$^{-1}$.

Anal. Calcd. for $C_7H_6N_2O_2S$: C, 46.20; H, 3.32; N, 15.40. Found: C, 45.94; H, 3.12; N, 15.18.

Ethyl 1-Pyrrolidino-2-(3-nitro-2-thienyl)acrylate (VI).—In a two-necked 100-ml. flask were placed 55 ml. of dry benzene, 2.00 g. (0.0082 mole) of ethyl 3-nitro-2-thienylpyruvate, 0.62 g. (0.0088 mole) of dry redistilled pyrrolidine, and 40 mg. of *p*-toluenesulfonic acid monohydrate. The flask was fitted with a nitrogen inlet and with a Soxhlet extractor containing a thimble filled with molecular sieve, as recommended by Stork[9] for the efficient removal of water in conversions of ketones to enamines. The mixture was refluxed vigorously under nitrogen. After 12 hr., the reaction was shown to be complete by infrared analysis. The mixture absorbed strongly at 1730 (ester carbonyl of enamine), while peaks due to unchanged pyruvate at 1700 (bonded ester carbonyl) and 3400 cm.$^{-1}$ (enolic hydroxyl) were weak or absent. Removal of the benzene and excess pyrrolidine *in vacuo* afforded a viscous, dark red oil, principally the enamine, which was used directly in attempted alkylations.

When the sulfonic acid catalyst was omitted, considerable cleavage of the pyruvate to 2-methyl-3-nitrothiophene occurred.

Ethyl 3-Nitro-2-thienylbromopyruvate (Id).—A solution of 3.35 g. (0.021 mole) of bromine in 80 ml. of chloroform was added slowly to a stirred solution of 5.00 g. (0.020 mole) of ethyl 3-nitro-2-thienylpyruvate in 100 ml. of chloroform. The temperature of the reaction mixture was held between −5 and −10° with an ice–salt bath. Moist litmus paper indicated the evolution of hydrogen bromide. When the addition was complete, the chloroform was removed *in vacuo*. The residue was dissolved in ethyl ether and treated with Darco. The ether solution was reduced in volume and hot petroleum ether (b.p. 30–60°) was added to effect crystallization. A yield of 5.4 g. (82%) of light yellow crystals was obtained, m.p. 66–68°. For analysis, the material was recrystallized twice from ethyl ether–petroleum ether (b.p. 30–60°), m.p. 67–68°.

An infrared spectrum of a 10% chloroform solution of the product exhibited a carbonyl absorption at 1730 cm.$^{-1}$. There was no band for enolic hydroxyl in the region 3200–4000 cm.$^{-1}$.

Anal. Calcd. for $C_9H_8BrNO_5S$: C, 33.55; H, 2.50; N, 4.35. Found: C, 33.44; H, 2.48; N, 4.38.

Arylboronic Acids. VII. Some Reactions of *o*-Formylbenzeneboronic Acid[1]

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The behavior of *o*-formylbenzeneboronic acid towards various aldehyde reagents is described. Reaction with secondary diamines, malononitrile, sodium bisulfite, and Girard's reagent T provides the usual products, while the 2,4-dinitrophenylhydrazone is isolated as the diethyl boronate ester. The boronic acid function participates in condensation reactions with semicarbazide and *p*-carboxyphenylhydrazine hydrochlorides to give the corresponding 4-hydroxyborazaroisoquinolines. α-Substituted boronophthalides are formed with isopropylidene malonate, nitromethane, and sodium cyanide.

The formation of the stable boron-containing compounds, bis(4,3-borazaro-4-isoquinolinyl) ether (Ia) and bis(3-phenyl-4,3-borazaro-4-isoquinolinyl) ether (Ib), from the reaction of *o*-formylbenzeneboronic acid (II) with hydrazine and phenylhydrazine hydrochloride, respectively, was recently reported by Dewar.[2] Although II also reacted with hydroxylamine to form a cyclic derivative (III), the aldehyde appeared to be

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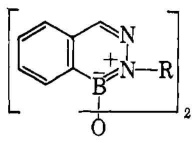
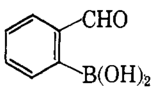
(1) This work was supported by a grant [AT(11-1)-314] from the Atomic Energy Commission; report COO-314-8.

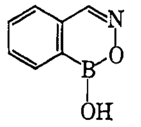
(2) M. J. S. Dewar and R. C. Dougherty, *J. Am. Chem. Soc.*, **84**, 2648 (1962); **86**, 433 (1964).



Ia, R = H
b, R = C_6H_5
c, R = $CONH_2$



II

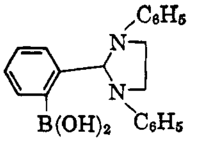


III

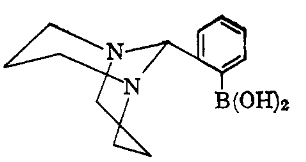
less reactive than its *para* isomer, presumably owing to interaction of the formyl and boronic acid groups.[3]

The purpose of the present investigation was the further study of the behavior of II towards aldehyde reagents to determine whether any uncyclized derivatives could be obtained, and also to see if the boronic acid function were capable of entering into any of the reactions to produce novel structures.

When II reacted with methanolic solutions of N,N'-diphenylethylene diamine[4] (IV) and 1,5-diazacyclooctane[5] (V), the respective products, 1,3-diphenyl-2-(*o*-boronophenyl)tetrahydroimidazole (VI) and 9-(*o*-boronophenyl)-1,5-diazabicyclo[3.3.1]nonane (VII), were obtained. The structures of VI and VII were indicated by the disappearance of the infrared carbonyl band of II at 1668 cm.$^{-1}$ and by microanalysis. Reaction of 1 mole of II with 2 moles of IV or V led to the isolation of only VI or VII, indicating that the boronic acid group was inactive towards these diamines. The boroxoles of VI and VII were obtained by dehydration.



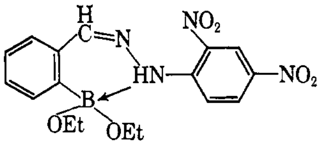
VI



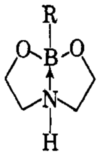
VII

o-Formylbenzeneboronic acid reacted with sodium bisulfite to provide the expected addition product, sodium α-hydroxy(*o*-borono)benzylsulfonate (VIII). The α-hydroxy group of VIII could not be made to form a lactone with the boronic acid function by means of vacuum desiccation at elevated temperatures, however. The condensation of II with malononitrile in dimethyl sulfoxide or dimethylformamide provided *o*-boronobenzalmalononitrile (IX). The presence of a conjugated structure rather than a lactone was indicated by the infrared spectrum of IX, which revealed a band at 2235 cm.$^{-1}$ (conjugated dinitrile),[6] and by the absence of strong bands near 1000 (C–O stretch)[7] and 1100 cm.$^{-1}$ (cyclic ether).[8]

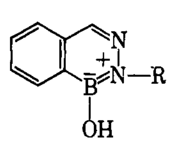
Although Girard's reagent T (betaine hydrazide hydrochloride) gave the normal hydrazone with II, the 2,4-dinitrophenylhydrazone, prepared in ethanol and phosphoric acid according to the method of Fieser,[9] was isolated as its diethyl boronate ester (X), as shown by microanalysis and infrared and nuclear magnetic resonance spectra. The hydrolytic stability of this ester was sufficient to enable it to resist atmospheric moisture over a period of weeks, which was unexpected for an ethyl ester of an arylboronic acid[10,11] and might be due to boron–nitrogen coordination similar to that reported for the thiosemicarbazone and isonicotinylhydrazone of II.[12] Evidence for such an interaction was provided by the infrared spectrum of X, which revealed that the N–H stretching bands had been lowered in frequency to 3250 and 3090 cm.$^{-1}$, similar to the observation made by Serafinowa and Makosza.[12] Although the electron-withdrawing effect of the 2,4-dinitrophenyl group would be expected to negate a large part of the donor ability of the nitrogen atom, comparison with the properties of the boronic acid esters (XI) of diethanolamine, which are stable to neutral hydrolysis because of boron–nitrogen coordination,[13] seems to require the structure X.



X



XI



XII
a, R = p-$C_6H_4CO_2H$
b, R = $CONH_2$

Evidence of the participation of the boronic acid group in condensation reactions of the aldehyde II was provided by the isolation of 3-(*p*-carboxyphenyl)-4-hydroxy-4,3-borazaroisoquinoline (XIIa) from the reaction of II with *p*-carboxyphenylhydrazine hydrochloride. Similarly, semicarbazide hydrochloride gave 3-formamido-4-hydroxy-4,3-borazaroisoquinoline (XIIb), which was converted to bis(3-formamido-4,3-borazaro-4-isoquinolinyl) ether (Ic) by extended dehydration. The structures of XIIa, XIIb, and Ic were supported by microanalyses in conjunction with molecular weight determinations. These three compounds resisted deboronation by concentrated hydrochloric acid at room temperature for 24 hr.

The ability of the boronic acid group of II to incorporate itself into a heterocycle was also manifested in the reaction of isopropylidene malonate[14] with II in dioxane. Instead of the expected *o*-boronocinnamic acid, there was obtained a product (XIIIa) whose infrared spectrum revealed a strong carbonyl band at 1743 cm.$^{-1}$, indicative of an unsaturated aliphatic acid, and strong bands at 1091 and 1002 cm.$^{-1}$, characteristic of the boronophthalide structure. A partial nuclear magnetic resonance spectrum of XIIIa in dimethyl sulfoxide also favored the assignment to boronophthalidylacetic acid.[15] This compound was also produced by the reaction of malonic acid with II in dioxane.

A similar structure, α-(nitromethyl)boronophthalide (XIIIb), was formed in the reaction of II with nitromethane, as evidenced by the presence of boronophthalide bands (see Table I) in the infrared spectrum. The nuclear magnetic resonance spectrum of XIIIb

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[3] H. R. Snyder, A. J. Reedy, and W. J. Lennarz, *J. Am. Chem. Soc.*, **80**, 835 (1958).

[4] H. W. Wanzlick and W. Löchel, *Chem. Ber.*, **86**, 1463 (1953).

[5] J. H. Billman and L. C. Dorman, *J. Org. Chem.*, **27**, 2419 (1962).

[6] R. E. Kitson and N. E. Griffith, *Anal. Chem.*, **24**, 334 (1952).

[7] W. J. Lennarz and H. R. Snyder, *J. Am. Chem. Soc.*, **82**, 2172 (1960).

[8] W. J. Dale and J. E. Rush, *J. Org. Chem.*, **27**, 2598 (1962).

[9] L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1957, p. 316.

[10] M. F. Lappert, *Chem. Rev.*, **56**, 998 (1956).

[11] W. Gerrard, "The Organic Chemistry of Boron," Academic Press, New York, N. Y., 1961, p. 71.

[12] B. Serafinowa and M. Makosza, *Roczniki Chem.*, **35**, 937 (1961).

[13] R. L. Letsinger and J. R. Nazy, *J. Org. Chem.*, **24**, 93 (1959).

[14] J. A. Hedge, C. W. Kruse, and H. R. Snyder, *ibid.*, **26**, 3166 (1961).

[15] Based on the analogous phthalidyl radical, o-$C_6H_4COOCH\cdot$: *Chem. Abstr.*, **51** (Subject Index), 11R (1957).

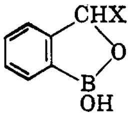
TABLE I

SELECTED INFRARED BANDS OF α-SUBSTITUTED BORONOPHTHALIDES[a]

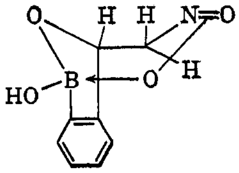
α-Substituent	Infrared bands, cm.$^{-1}$ B–O stretch[b]	Cyclic ether	C–O stretch
$-CH_2CO_2H$	1397–1358	1091	1002
$-CH_2NO_2$	1386–1356	1096	1015
$-CN$	1330	1076	978
$-CO_2H$	1340	1090	970

[a] All infrared spectra were obtained in KBr disks by the staff of the Spectroscopy Laboratory of the Department of Chemistry and Chemical Engineering of the University of Illinois, using a Perkin-Elmer Model 21 infrared spectrophotometer (equipped with sodium chloride optics). [b] L. J. Bellamy, W. Gerrard, M. F. Lappert, and R. L. Williams, *J. Chem. Soc.*, 2412 (1958).

in dimethyl sulfoxide (containing single proton quartets at τ 4.07, 4.57, and 5.38) revealed that the nitromethyl protons were nonequivalent. The unusually low τ-value of 0.31 for the BO–H proton (normally found at 1.9 to 2.4 for boronophthalides),[16] in conjunction with a single nitro stretching band[17] at 1551 cm.$^{-1}$ and a lowered BO–H stretch at 3175 cm.$^{-1}$ (3250–3440 cm.$^{-1}$ is the normal range)[7] found in the infrared spectrum of XIIIb, suggest the existence of a coordinated structure like XIV for this compound.



XIIIa, X = CH_2CO_2H
b, X = CH_2NO_2
c, X = CN
d, X = CO_2H
e, X = CH_3
f, X = CH_2Br



XIV

Sodium cyanide reacted with II to produce *o*-boronomandelonitrile, which lost water to form α-cyanoboronophthalide (XIIIc) when heated to 65°. This boronolactone was quantitatively hydrolyzed by concentrated hydrochloric acid to α-carboxyboronophthalide (XIIId). The α-substituted boronophthalides mentioned were not deboronated when allowed to stand in concentrated hydrochloric acid for 24 hr., which was not unexpected in view of the unusual stability of the boronophthalide ring.[7]

Previous to this study, the only α-substituted boronophthalides on record have been those of Dale,[8] who prepared α-methylboronophthalide (XIIIe) and α-(bromomethyl)boronophthalide (XIIIf) by dehydrobromination of *o*-(1-bromoethyl)benzeneboronic anhydride and *o*-(1,2-dibromoethyl)benzeneboronic anhydride, respectively. Although the aromatic ring of boronophthalide has been nitrated in the 3- and 5-positions,[7,18] the protons of the methylene group of boronophthalide and its benzene ring-substituted derivatives have proven resistant to substitution,[7,18,19] presumably because of the deactivating influence of the adjacent ether linkage.

Experimental[20]

Preparation of *o*-Formylbenzeneboronic Acid.—This reaction was run *in the hood*. From a magnetically stirred solution of 23.6 g. (66.7 mmoles) of *o*-tolueneboronic anhydride in 550 ml. of carbon tetrachloride in a 1000-ml., one-necked round-bottomed flask (equipped with a Claisen head, a condenser, and receiver protected by a drying tube), was distilled 50 ml. of carbon tetrachloride to insure the absence of water from the solution. The distillation apparatus was then removed and (while the solution was still boiling) in its place was quickly fitted a parallel side-arm connecting tube equipped with a 150-ml. pressure-equalizing addition funnel and a reflux condenser (protected with a drying tube). Bromine (64.2 g., 401 mmoles) was diluted with 100 ml. of dry carbon tetrachloride and placed in the addition funnel, and a 150-w. tungsten light bulb was situated a few inches from the flask. The bromine solution was added dropwise over a period of 2–2.5 hr. to the boronic anhydride solution, which was vigorously stirred and maintained at a gentle reflux during the addition. The pale yellow dibromide solution thus obtained was then stripped of solvent and any unchanged bromine *in vacuo*. To the cream-colored residue were then added 300 ml. of carbon tetrachloride and 100 ml. of water, and the resulting mixture was placed in a cold water bath (5–10°) and magnetically stirred. To this cooled slurry was added dropwise cold 15% aqueous sodium hydroxide until all the dibromide was dissolved in the aqueous layer (*ca.* pH 10). After filtration and separation, the yellow aqueous layer (maintained at 10–15°) was acidified with concentrated hydrochloric acid until a pH of 4 was reached. The precipitate resulting from the acidification was filtered and dried *in vacuo* over calcium chloride and weighed 25.6 g. (88% yield). The product was treated with Darco in water, resulting in 23.1 g. of white needles, which were observed to lose water at 110–120° and to resolidify at 125–130° before melting with decomposition at 163–165°. An analytical sample was prepared by recrystallizing the aldehyde twice from water and drying *in vacuo* for 24 hr. over calcium chloride.

Anal. Calcd. for $C_7H_7BO_3$: C, 56.07; H, 4.70. Found: C, 56.11; H, 4.79.

Earlier reports[3,21] have placed the melting point of this compound at 115–123°, which was the range in which the crystals were observed under the microscope to dissolve in the water resulting from the formation of *o*-formylbenzeneboronic anhydride; the figure of 163–165° reported here actually represented the melting point of the boroxin.

Preparation of *o*-Formylbenzeneboronic Anhydride.—To 150 ml. of dry benzene in a 200-ml. one-necked flask equipped with a heating mantle, magnetic stirrer, Dean-Stark water separator, condenser, and drying tube was added 1.50 g. (10 mmoles) of *o*-formylbenzeneboronic acid. The stirred suspension was refluxed for 24 hr., during which time *ca.* 0.20 ml. of water had accumulated in the trap. The benzene was removed *in vacuo* to yield 1.31 g. of a white hygroscopic powder (m.p. 165–166° dec.), representing a virtually quantitative yield of pure *o*-formylbenzeneboronic anhydride.

Anal. Calcd. for $C_7H_5BO_2$: C, 63.71; H, 3.82; mol. wt., 396. Found: C, 63.44; H, 3.78; mol. wt. (in benzene), 401.

Preparation of 1,3-Diphenyl-2-(*o*-boronophenyl)tetrahydroimidazole.—To a solution of 0.53 g. (23 mmoles) of N,N′-diphenylethylenediamine monohydrate in 5 ml. of absolute methanol in a 25-ml. beaker was added with stirring, in one portion, a solution of 0.33 g. (22 mmoles) of *o*-formylbenzeneboronic acid in 1 ml. of absolute methanol. A white crystalline precipitate appeared after a few seconds of continued stirring. After standing in the refrigerator for an hour, the reaction mixture was filtered and air-dried. The product was then washed with 1 ml. of water and again air-dried to yield 0.749 g. (99% yield) of white crystals, m.p. 144–146°, with dehydration at 105–115°. One recrystallization from chloroform–benzene raised the melting point to 146–148°.

An analytical sample was prepared by recrystallizing once more from chloroform–benzene.

Anal. Calcd. for $C_{21}H_{21}BN_2O_2$: C, 73.27; H, 6.15; N, 8.14; mol. wt., 344. Found: C, 73.36; H, 6.26; N, 8.03; mol. wt. (in chloroform), 320.

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(16) R. T. Hawkins, W. J. Lennarz, and H. R. Snyder, *J. Am. Chem. Soc.*, **82**, 3053 (1960).

(17) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1960 p. 297.

(18) R. R. Haynes, Ph.D. Thesis, University of Illinois, 1963.

(19) R. K. Kurz, Ph.D. Thesis, University of Illinois, 1961.

(20) Microanalyses and molecular weight determinations (using a Mechrolab Model 301A vapor pressure osmometer) were performed by Mr. Josef Nemeth and his associates. All melting points were taken on a Kofler hot stage microscope and are uncorrected.

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

The anhydride, m.p. 146–148° was prepared by drying a sample of the acid at 110° *in vacuo* overnight.

Anal. Calcd. for $C_{21}H_{19}BN_2O$: C, 77.32; H, 5.87; N, 8.59. Found: C, 77.18; H, 5.99; N, 8.71.

Preparation of 9-(*o*-Boronophenyl)-1,5-diazabicyclo[3.3.1]nonane.—A warmed, agitated suspension of 293 mg. (7.33 mmoles) of sodium hydroxide and 1.00 g. (3.62 mmoles) of 1,5-diazacyclooctane dihydrobromide in 4 ml. of methanol was treated with several drops of water until the neutralization reaction was completed. This solution was filtered into a solution of 542 mg. (3.62 mmoles) of *o*-formylbenzeneboronic acid in 1 ml. of methanol. After being thoroughly mixed, the resulting solution was placed on a steam bath and allowed to evaporate overnight. The residue was washed with 5 ml. of 50% aqueous methanol, filtered, and air-dried to yield 0.75 g. (84% yield) of white crystals, m.p. 294–298°, with loss of water at 105–110°. Recrystallization from 75% methanol resulted in 0.58 g. (65% yield) of purified product, m.p. 297–299°.

An analytical sample was obtained by another recrystallization from 75% methanol, followed by drying at 110° *in vacuo* overnight, to give the anhydride.

Anal. Calcd. for $C_{13}H_{17}BN_2O$: C, 68.45; H, 7.52; N, 12.28. Found: C, 68.28; H, 7.34; N, 12.46.

Preparation of Sodium α-Hydroxy(*o*-borono)benzylsulfonate.—To 450 mg. (3 mmoles) of *o*-formylbenzeneboronic acid was added 1.0 ml. of a freshly prepared 3.1 *M* solution of sodium bisulfite, resulting in a rapid exothermic dissolution of the aldehyde. The water was removed *in vacuo* and the residue was extracted with two 10-ml. portions of boiling absolute ethanol. The filtrate was evaporated *in vacuo,* and to the glassy residue was added 2 ml. of water, and the resulting solution was concentrated under reduced pressure. In this manner a yield of 665 mg. (87% yield) of slightly hygroscopic crystals, m.p. 275–287° dec., was obtained.

A sample was purified for analysis by extracting with cold absolute ethanol, evaporating the filtrate, adding water to the residue, re-evaporating, and finally drying over phosphorus pentoxide for 24 hr. *in vacuo.*

Anal. Calcd. for $C_7H_8SBO_6Na$: C, 33.10; H, 3.17. Found C, 33.35; H, 3.26.

Preparation of *o*-Boronobenzalmalononitrile.—A solution of 450 mg. (3 mmoles) of *o*-formylbenzeneboronic acid, 198 mg. (3 mmoles) of freshly distilled malononitrile, and a drop of pyridine in 2 ml. of dimethyl sulfoxide was heated on a steam bath for 24 hr. in a 5-ml. flask equipped with a reflux condenser protected by a drying tube. The reaction mixture was then cooled to room temperature, triturated with 20 ml. of water, and placed in the refrigerator overnight. After filtering, washing with 5 ml. of water, and air-drying, a yield of 783 mg. (98% yield) of white crystals, m.p. 208–212° dec. with dehydration at 110–115°, was obtained. Two recrystallizations from water provided a product melting at 217–219° dec.

A sample of analytical purity was obtained by recrystallizing twice more from water.

Anal. Calcd. for $C_{10}H_7BN_2O_2$: C, 60.66; H, 3.56; N, 14.15. Found: C, 60.88; H, 3.83; N, 14.14.

The anhydride, m.p. 217–219° dec., was obtained by dehydrating at 110° for 48 hr. over phosphorus pentoxide *in vacuo.*

Anal. Calcd. for $C_{10}H_5BN_2O$: C, 66.72; H, 2.80; N, 15.56. Found: C, 66.44; H, 3.03; N, 15.83.

The substitution of dimethylformamide for dimethyl sulfoxide in this reaction provided an 89% yield of product which showed no change in melting point when mixed with the dicyanide prepared in dimethyl sulfoxide.

Preparation of *o*-Formylbenzeneboronic Acid (Carboxymethyl)-trimethylammonium Chloride Hydrazone.—To 5 ml. of 95% ethanol in a 10-ml. flask equipped with a reflux condenser were added 765 mg. (5.1 mmoles) of *o*-formylbenzeneboronic acid and 838 mg. of Girard's reagent T, followed by a drop of glacial acetic acid. The resulting solution was refluxed for 1 hr., and then cast into 50 ml. of ether. After standing in the refrigerator for 1 hr., the solution was filtered. The precipitate obtained was dried, dissolved in ethanol, treated with Darco, and reprecipitated with ether. The resulting white crystals were dissolved in 1 ml. of water and the solution was evaporated *in vacuo* to give 1.38 g. (87% yield) of white crystals, m.p. 198–202° dec., with dehydration at 95–105°.

An analytical sample was prepared by twice repeating the above ethanol–ethyl ether–water treatment, and was dried *in vacuo* over calcium chloride. Inasmuch as the elemental composition of a sample prepared in this manner was found to be consistent with the monohydrate of the expected compound, a more severe dehydration (110° for 48 hr. at 0.05 mm. over phosphorus pentoxide) was used, providing a hygroscopic white solid, m.p. 202–203° dec., of the expected composition.

Anal. Calcd. for $C_{12}H_{19}N_3BClO_3$: C, 48.11; H, 6.39; N, 14.03. Found: C, 48.44; H, 6.10; N, 13.99.

Preparation of the Diethyl Ester of *o*-Formylbenzeneboronic Acid 2,4-Dinitrophenylhydrazone.—To a solution of 450 mg. (3 mmoles) of *o*-formylbenzeneboronic acid in 10 ml. of 95% ethanol was added dropwise with stirring 12.5 ml. of 0.25 *M* (3.12 mmoles) 2,4-dinitrophenylhydrazine (prepared by the method of Fieser[9]), and the reaction mixture was chilled in the refrigerator for an hour. After filtration and air-drying, there was obtained 1.12 g. of orange crystals, m.p. 247–249° dec., 97% yield. Recrystallization from ethanol raised the melting point to 249–250° dec.

The analytical sample was obtained by three further recrystallizations from ethanol and subsequent drying over calcium chloride.

Anal. Calcd. for $C_{17}H_{19}BN_4O_6$: C, 52.87; H, 4.96; N, 14.51. Found: C, 52.70; H, 4.87; N, 14.64.

The ester was hydrolyzed with hot water to provide the acid form of the 2,4-dinitrophenylhydrazone, m.p. 226–227° dec.

Anal. Calcd. for $C_{13}H_{11}BN_4O_6$: C, 47.30; H, 3.36; N, 16.98. Found: C, 47.51; H, 3.24; N, 16.78.

Preparation of 3-(*o*-Carboxyphenyl)-4-hydroxy-4,3-borazaroisoquinoline.—To a solution of 450 mg. (3 mmoles) of *o*-formylbenzeneboronic acid in 10 ml. of 50% ethanol was added dropwise with agitation 12.5 ml. of 0.25 *M* (3.12 mmoles) *p*-carboxyphenylhydrazine hydrochloride in water. After cooling in the refrigerator for 1 hr., the tan-colored product was filtered and washed with 5 ml. of water and air-dried. After recrystallization from ethanol–water, a yield of 712 mg. (89%) of tan crystals, m.p. 288–289° dec., was obtained.

The analytical sample was obtained by twice recrystallizing from water–ethanol and drying over calcium chloride *in vacuo.*

Anal. Calcd. for $C_{14}H_{11}BN_2O_3$: C, 63.19; H, 4.17; N, 10.53; mol. wt., 266. Found: C, 62.86; H, 4.25; N, 10.80; mol. wt. (in acetone), 257.

Preparation of 3-Formamido-4-hydroxy-4,3-borazaroisoquinoline.—To a solution of 450 mg. (3 mmoles) of *o*-formylbenzeneboronic acid in 10 ml. of 50% ethanol was added dropwise with agitation 12.5 ml. of 0.25 *M* semicarbazide hydrochloride in water. After being chilled in the refrigerator for an hour, the reaction mixture was filtered, and the product was washed with 5 ml. of water and air-dried. The white crystals were recrystallized from ethanol–water, resulting in 571 mg. (92% yield) of product, m.p. 295–299° dec., with sintering at 275–290°.

An analytical sample was prepared by two further recrystallizations from ethanol–water, followed by drying over calcium chloride *in vacuo.*

Anal. Calcd. for $C_8H_8BN_3O_2$: C, 50.84; H, 4.27; N, 22.23; mol. wt., 189. Found: C, 51.27; H, 4.25; N, 22.54; mol. wt. (in dioxane), 201.

Dehydration of this compound (140° at 0.25 mm. over phosphorus pentoxide for 48 hr.) provided bis(3-formamido-4,3-borazaro-4-isoquinolinyl) ether.

Anal. Calcd. for $C_{16}H_{14}B_2N_6O_3$: C, 53.39; H, 3.92; N, 23.35; mol. wt., 360. Found: C, 53.19; H, 4.09; N, 23.12; mol. wt. (in acetone), 347.

Preparation of Boronophthalidylacetic Acid.—To a 10-ml. flask equipped with a reflux condenser and a drying tube were added 750 mg. (5 mmoles) of *o*-formylbenzeneboronic acid, 865 mg. (6 mmoles) of isopropylidene malonate, 5 ml. of reagent dioxane, and a drop of pyridine. The solution was heated on a steam bath for 24 hr. and then evaporated *in vacuo.* The resulting yellow glass was treated with Darco in water, and the aqueous solution obtained from this treatment was concentrated under reduced pressure to a thick sirup, which was then triturated with benzene to yield 308 mg. (32%) of white crystals, m.p. 127–130°.

Two recrystallizations from chloroform provided an analytical sample, m.p. 129–130°.

Anal. Calcd. for $C_9H_9BO_4$: C, 56.30; H, 4.73. Found: C, 56.31; H, 4.69.

Substitution of malonic acid for isopropylidene malonate in this reaction provided a 17% yield of boronophthalidylacetic acid.

Preparation of α-(Nitromethyl)boronophthalide.—To a magnetically stirred, cooled (15–20°) solution of 850 mg. (21 mmoles) of sodium hydroxide in water was added 3.00 g. (20 mmoles) of *o*-formylbenzeneboronic acid. After the solution was stirred for 5 min., there was added dropwise 1.09 ml. (1.22 g., 20 mmoles) of nitromethane. This solution was stirred for 15 min., after which time it was cooled to 5° while 20% hydrochloric acid was added dropwise until a pH of 3 was attained. After standing in the refrigerator for an hour, the reaction mixture was filtered. The precipitate, upon air-drying, provided 3.72 g. (96% yield) of product, m.p. 110–114°. Treatment with Darco in water gave white needles, m.p. 117–119°.

Two more recrystallizations from water provided a sample of analytical purity.

Anal. Calcd. for $C_8H_8BNO_4$: C, 49.78; H, 4.18; N, 7.26. Found: C, 49.81; H, 4.28; N, 7.09.

Preparation of α-Cyanoboronophthalide.—To a magnetically stirred, cooled (15–20°) solution of 1.04 g. (20 mmoles) of 95% sodium cyanide in water was added 3.00 g. (20 mmoles) of *o*-formylbenzeneboronic acid. After stirring for 15 min., the solution was cooled to 5° and acidified with concentrated hydrochloric acid to a pH of 5. The white precipitate thus formed was removed by filtration, and the filtrate was further acidified with 10% acid until no more precipitate formed. The two crops thus obtained were found to weigh 3.52 g. (99+% yield) upon air-drying. A recrystallization from water provided 2.81 g. (88% yield) of purified *o*-boronomandelonitrile (dehydration range, 60–65°). Dehydration of this material either by heating to 65° or by vacuum desiccation was found sufficient to cause lactone formation.

The analytical sample of the lactone (m.p. 107–109°) was prepared by twice recrystallizing from water, followed by drying over phosphorus pentoxide for 24 hr. *in vacuo*.

Anal. Calcd. for $C_8H_6BNO_2$: C, 60.43; H, 3.80; N, 8.81; mol. wt., 159. Found: C, 60.26; H, 3.79. N, 8.75; mol. wt. (in benzene), 160.

Preparation of α-Carboxyboronophthalide.—To a 15-ml. beaker containing 10 ml. of concentrated hydrochloric acid was added 159 mg. (1 mmole) of α-cyanoboronophthalide, and the mixture was allowed to stand for 24 hr. in the hood. The white crystalline product was separated by filtration, washed with two 10-ml. portions of acid, and dried, to provide 175 mg. (98% yield) of α-carboxyboronophthalide (m.p. 141–142°), which proved to be analytically pure.

Anal. Calcd. for $C_9H_7BO_4$: C, 53.99; H, 3.96; mol. wt., 178. Found: C, 53.76; H, 4.08; mol. wt. (in dioxane), 171.

The Interconversion of 2-Substituted 2-Oxazolines and 2-Thiazolines

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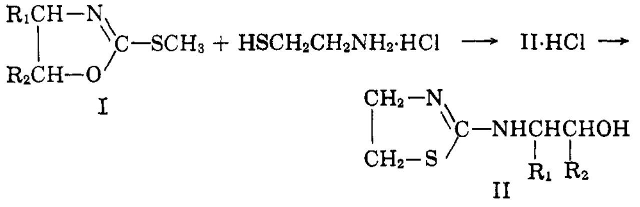
The anomalous products obtained from the reaction of two 2-methylthio-2-oxazolines with 2-mercaptoethylamine hydrochloride were identified as 2-(2-hydroxyethylamino)-2-thiazolines. On standing in solution, the latter compounds undergo rearrangement to 2-(2-mercaptoethylamino)-2-oxazolines, isolated as the disulfides. The interconversion of 2-oxazolines containing a 2-mercaptoethylamino side chain and 2-thiazolines containing a 2-hydroxyethylamino side chain, possibly through a bicyclic intermediate, is thus demonstrated.

In a previous paper[1] we have reported that products with anomalous properties are obtained from the reaction of 2-mercaptoethylamine hydrochloride with both 2-methylthio-2-oxazoline (Ia) and 2-methylthio-4-methyl-5-phenyl-2-oxazoline (Ib). The crystalline bases, IIa and IIb, afforded by these reactions have empirical formulas of $C_5H_{10}N_2OS$ and $C_{12}H_{16}N_2OS$. We have now demonstrated that these compounds are 2-(2-hydroxyethylamino)-2-thiazoline and 2-(2-hydroxy-1-methyl-2-phenylethylamino)-2-thiazoline, respectively, as shown.



a, $R_1 = R_2 = H$
b, $R_1 = CH_3$; $R_2 = C_6H_5$

As reported previously,[1] the nuclear magnetic resonance spectrum of IIb contained a single sharp band that represented two protons at a frequency assignable to NH. This observation had suggested the possibility that a spiran such as V had been isolated, although the infrared spectrum strongly indicated that an unsaturated heterocyclic ring was present. The n.m.r. spectrum of the unsubstituted base, IIa, has been found to contain an analogous sharp signal with an intensity corresponding to two protons. In both cases, this band shifted to higher field as a single sharp peak on dilution. However, in the n.m.r. spectrum of 2-ethylaminoethanol,[2] the NH and OH protons are assigned to a single band, presumably as a result of rapid proton exchange.[3] We have found that the singularity of the NH–OH signal in 2-ethylaminoethanol is maintained over a wide range of concentrations and temperatures. Thus these two-proton signals in the spectra of IIa and IIb could arise from NH and OH rather than from two NH groups.

The infrared spectrum of IIb in chloroform had failed to show the presence of hydroxyl,[1] possibly, as previously suggested, because of hydrogen bonding. In dilute carbon tetrachloride solution it was indeed possible to observe a rather weak, though definite, free OH band at 2.76 μ. That both IIa and IIb contained an OH group was clearly demonstrated by near-infrared spectroscopy. The near-infrared spectra of the compounds showed the first overtone bands of both OH and NH.[4,5]

Additional evidence for the presence of hydroxyl in IIa and IIb was obtained by acetylation with acetic anhydride and pyridine. In both cases the spectrum of

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(1) R. C. Clapp, L. Long, Jr., and T. Hasselstrom, *J. Org. Chem.*, **28**, 1308 (1963).

(2) "Varian N.M.R. Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, no. 92.

(3) Other systems in which OH and amine NH protons undergo rapid proton exchange and give a single signal are discussed by J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp. 440 and 455.

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