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THE REACTION OF TRIMETHOXYBOROXINE WITH SOME ARYL GRIGNARD REAGENTS

Thesis for the Degree of M. S.
MICHIGAN STATE UNIVERSITY
Thomas Paul Povlock

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By

Thomas Paul Povlock

A THESIS

Submitted to the College of Science and Arts of Michigan
State University of Agriculture and Applied Science
in partial fulfillment of the requirements
for the degree of

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Department of Chemistry

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AN ABSTRACT

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ABSTRACT

The reaction of trimethoxyboroxine with some aryl Grignard reagents was studied in an attempt to find a new method for the synthesis of borinic acids. As a result of a study of the effect of temperature and the effect of changing the mole ratio of trimethoxyboroxine to phenyl magnesium bromide, it was found that the highest yield was obtained when the reaction proceeds at 25°C. and with the mole ratio of boroxine to Grignard of one to nine.

Using the reaction conditions developed for the preparation of diphenylborinic acid, di(o-tolyl), di(m-tolyl), di(p-tolyl), di(p-anisyl), di(p-chlorophenyl), di(α-naphthyl), and di(p-biphenyl) borinic acids were prepared. Of these acids, di(o-tolyl), di(m-tolyl), di(p-tolyl), and di(p-biphenyl) have not been reported in the literature. As a result of a study to determine the most successful method of preparation and isolation of aminoethyl diphenylborinate, it was found that the boronic acid must be completely removed before attempting the esterification with ethanolamine.

Melting points, neutralization equivalents, and elemental analysis were used to characterize the borinic esters. The melting points of the boronic acids were correlated with the literature values.

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INTRODUCTION

I. Purpose

This study was undertaken to examine the reaction of trimethoxyboroxine with aryl Grignard reagents in order to find a new method for synthesis of aryl borinic acids, and to improve the yields over the currently used methods. In an attempt to elucidate a possible mechanism for the reaction, a study of the effects of certain electrical and steric factors was made.

From this study eight aryl borinic acids and eight aryl boronic acids were obtained from the reaction of the appropriate Grignard reagent with trimethoxyboroxine. Of the compounds prepared, four borinic acids and one boronic acid have not been reported in the literature. The yield of borinic acid isolated as the aminoethyl ester was found to be approximately two times that obtained from currently used methods (1). The effect of temperature, ratio of trimethoxyboroxine to Grignard reagent, steric effects, and electrical factors were studied along with the methods of isolation and purification of the borinic acids and their esters. It was found that steric factors and both electron donating and withdrawing groups decrease the yield of borinic acid. A mechanism has been suggested to account for some of these facts.

II. Historical

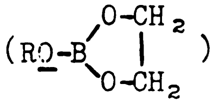
A. Borinic Acids

Aryl borinic acids, having the general formula R_2BOH, have been known since 1894 when Michaelis (2) described the isolation of diphenylborinic acid from the hydrolysis of the corresponding chloride. Since the methods of isolation and characterization were doubtful, it was not known whether or not the earlier workers had actually prepared the reported compounds. In the case of the diphenylborinic acid, it was not until 1955 that Letsinger (1) isolated and characterized this acid. The yield of borinic acid was nonspecified in some of the early work and when reported ranged from 20-40 percent.

Table I lists the alkyl and aryl borinic acids for which the melting or boiling points have been reported. Other borinic acids have been prepared and isolated as an alkyl ester, but were not converted to the acid. The boiling points of the acids which have been recorded are actually those of the anhydride. Letsinger (1) has showed that when diphenylborinic acid was distilled, the anhydride was recovered.

In some cases there are discrepancies in the reported physical constants of the borinic acids as shown in Table I. Di(*p*-bromophenyl) borinic acid is listed with two different melting points. Di(*p*-biphenyl) borinic acid (6) is listed as melting above 300°C, but the isolated compound was never proved to be the borinic acid. It was found as a by-product in the preparation of the boronic acid and was assumed to be the borinic acid.

Borinic acids have been prepared by use of one of the following reactions, followed by hydrolysis.

1. Moist air oxidation of trialkylborines (R_3B)(8).
2. Reaction of trialkylborines with iodine to prepare the dialkyliodoborines (9).
3. Reaction of trialkylborates [($(RO)_3B$] or cyclic borates  with an excess of alkyl or aryl Grignard reagents at -60°C. (10).

Of these preparations, method 3 gives the best yields and is the most widely used procedure.

Two of the main difficulties in the preparation of borinic acids are their separation from the boronic acid and the preparation of a suitable derivative for characterization. Borinic esters obtained from the above methods were separated from the boronic ester by use of a method developed by Letsinger (1). This method consists of treating the mixture of esters in ether solution with ammonia. The borinic ester complexes with ammonia and precipitates from solution. The complex is then treated with a solution of ethanolamine in water or toluene to prepare the aminoethyl borinate. This ester is an excellent derivative because it can be prepared easily, recrystallizes readily from an ethanol-water mixture, melts sharply, analyzes well, and over a period of months shows no sign of decomposing.

B. Boronic Acids

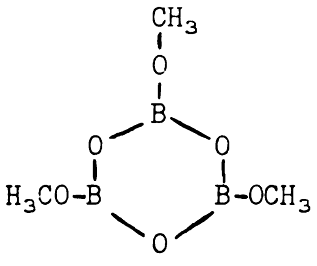
Boronic acids, having the general formula $RB(OH)_2$, have received far more attention in the literature than the borinic acids. In a review article by Lappert (11), seventy alkyl and aryl boronic acids were reported along with their melting points. As in the case of the borinic acids, there are reported different melting points for some of the boronic acids (Table III).

The most important methods for the preparation of alkyl or aryl boronic acids depends on one of the following procedures.

1. The addition of a metal alkyl or aryl to a trialkyl borate and the hydrolysis of the boronic ester (12).
2. The addition of a metallic alkyl or aryl to a boron trihalide to obtain the alkyl or aryl boron dihalide, which on hydrolysis gives the boronic acid (13).
3. Anhydrous air oxidation of a trialkylborine to a boronic ester and the hydrolysis of the latter (13).

C. Trimethoxyboroxine

Trimethoxyboroxine, I, is believed to be a six-membered ring



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compound containing alternate boron and oxygen atoms with one methoxy group attached to each boron atom. This structure was verified by molecular weight determinations, elemental analysis, Raman spectra and the solubility in anhydrous ether while one of its components, boric anhydride, is insoluble as determined by Ogle (14).

Quill and co-workers (15,16) studied the reaction of trimethoxyboroxine with alcohols and aryl amines. The reaction with alcohols is illustrated in the following equation:

$$6ROH + (CH_3OBO)_3 \longrightarrow 3(RO)_2B\text{-}OCH_3 + 3H_2O$$

The following reaction illustrates the reaction of trimethoxyboroxine with aniline:

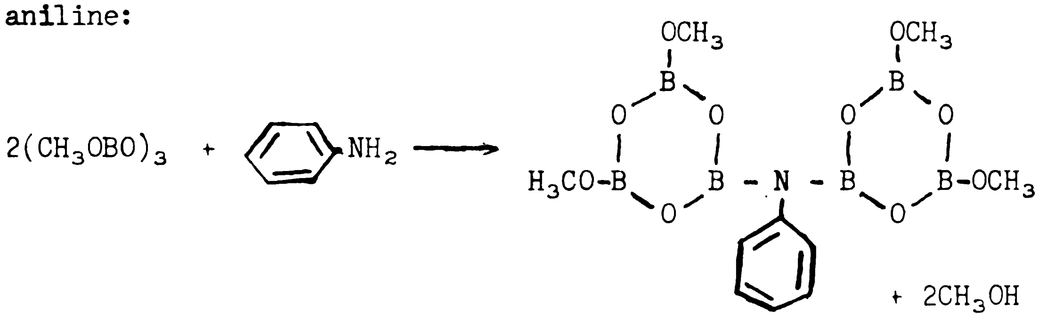

TABLE I

PHYSICAL CONSTANTS OF BORINIC ACIDS

R in R_2BOH	Melting Point	Boiling Point	Reference
C_2H_5-	-51 to -48	35-37/75 mm.	3
CHCl=CH-		66-68/3 mm.	4
C_6H_5-		210-213/1 mm.	2
p-Cl-C_6H_4-	75		5
p-Br-C_6H_4-	113		7
	82-84		2
p-CH_3O-C_6H_4	107		7
p-C_6H_5-C_6H_4	>300		6
2-CH_3-5-Cl-C_6H_3-	81		5
β-$C_{10}H_7$-	172		7
α-$C_{10}H_7$-	105-106		8
C_6H_5-α-$C_{10}H_7$-*			8

*Isolated as the ethanolamine ester melting at 228°C.

EXPERIMENTAL

I. General Procedure

Grignard reagents from bromobenzene, o-bromotoluene, m-bromotoluene, p-bromotoluene, p-bromoanisole, p-chlorobromobenzene, α-bromonaphthalene, p-bromobiphenyl, and bromomesitylene were prepared in anhydrous ether solution. Trimethoxyboroxine, prepared from trimethyl borate and boric anhydride, was dissolved in anhydrous ether and added to each Grignard reagent. The reaction mixture was hydrolyzed and the ether layer removed and distilled yielding an oil containing a mixture of boronic and borinic acids. The boronic acid was removed by heating this oil with hot water. The borinic acid was dissolved in ether and converted to the aminoethyl ester by adding a mixture of ethanolamine in water.

II. Reagents

Bromobenzene - Eastman Kodak Company. Practical grade. Redistilled and the fraction boiling at 62° and 30 mm. was used.

o-Bromotoluene - Eastman Organic Chemicals. White label. Redistilled and the fraction boiling at 65° and 15 mm. was used.

m-Bromotoluene - Eastman Kodak Company. White label. Redistilled and the fraction boiling at 67° and 15 mm. was used.

p-Bromotoluene - Dow Chemical Company. Redistilled and the fraction boiling at 85° and 30 mm. was used.

p-Bromoanisole - Eastman Kodak Company. White label. Redistilled and the fraction boiling at 98-99° and 16 mm. was used.

_α_-Bromonaphthalene- Eastman Kodak Company. White label. Redistilled and the fraction boiling at 137° and 15 mm. was used.

_p_-Bromobiphenyl - Eastman Kodak Company. White label. Used as received.

Ethanolamine - Eastman Kodak Company. White label. Used as received.

Diethyl ether - Anhydrous grade dried over sodium metal for three days.

Trimethyl borate - Anderson Chemical Company. Used as received.

Boric anhydride - Baker Chemical Company. Used as received.

Mesitylene - Matheson-Coleman-Bell. Used as received.

Bromine - Mallinckrodt Chemical Company. Used as received.

_p_-Chloroaniline - Eastman Kodak Company. White label. Used as received.

III. Preparation of Intermediates

A. Preparation of Bromomesitylene

Bromomesitylene was prepared from the method described in Organic Syntheses (17). In a 1-liter three-necked flask equipped with a stirrer, dropping funnel, and a parallel side arm holding a thermometer and a reflux condenser were placed 213 g. (1.77 moles) of mesitylene and 150 ml. of carbon tetrachloride. A rubber tube from the top of the condenser to the water drain was used to remove the hydrogen bromide vapors. The flask was cooled to 10°C in an ice-salt bath. Ninety-six milliliters (1.87 moles) of bromine in 190 ml. of carbon tetrachloride were added over a period of two and one-half hours while the temperature was maintained between 10-15°C. After all the bromine was added, the mixture was refluxed for one hour. The reaction mixture was washed with a saturated sodium bisulfite solution, two 200 ml. portions of water, and two 250 ml. of a 5 percent sodium hydroxide solution. The reaction mixture was dried over calcium chloride and the carbon tetrachloride distilled at atmospheric pressure through a 40 cm. Fenske column. The residue was then added to 1-liter of 95 percent ethyl alcohol which had previously reacted with 17 g. of sodium metal. The reaction mixture was refluxed for two hours, allowed to stand overnight, and then diluted with 3-liters of water and separated. The water layer was washed with three 100 ml. portions of carbon tetrachloride removed from the first distillation. The extracts were combined with the crude product and dried over calcium chloride. After the carbon tetrachloride had been removed by distilling through the Fenske column at reduced pressure, there was collected 200.6 g. of bromomesitylene at 101-102° and 15 mm. Yield 58% based on mesitylene.

B. Preparation of Trimethoxyboroxine

The boroxine was prepared following a procedure of Goubeau and Keller (18). In a 500 ml. one-neck flat-bottomed flask were placed 69.4 g.(1 mole) of boric anhydride and 103.8 g. (1 mole) of trimethyl borate along with a glass covered stirring bar. The flask was connected to a reflux condenser and placed in a heating mantle on top of a magnetic stirrer. The reaction mixture was stirred and refluxed from two to four hours or until the boric anhydride dissolved. The flask was cooled to room temperature and then immersed in a dry ice-isopropyl alcohol bath until the contents of the flask froze. The flask was removed from the bath, permitted to warm to room temperature, and the trimethoxyboroxine stored in a glass stoppered Erlenmeyer flask.

At one time during this research it became necessary to prepare trimethoxyboroxine from boric anhydride obtained from other companies. Boric anhydride from Matheson-Coleman-Bell and Anderson Chemical Company were used, but in both cases the boric anhydride would not dissolve in the trimethyl borate even after prolonged reflux periods of 50 hours. It was believed that the boric anhydride contained water, so a sample was heated in a vacuum oven for 24 hours at 200°C and at a pressure of 30 mm. of mercury using phosphoric anhydride as the dehydrating agent. The boroxine could not be prepared using the boric anhydride derived in this manner.

Boric anhydride was then prepared by dehydrating boric acid using a vacuum oven at 200°C and at a pressure of 30 mm. of mercury with phosphoric anhydride as the dehydrating agent. The sample was heated for 40 hours. Trimethoxyboroxine was prepared from the boric anhydride obtained from the dehydration of boric acid.

C. Preparation of p-Chlorobromobenzene

p-Chlorobromobenzene was prepared following the procedure from Organic Syntheses (19). A mixture of 127.5 g. (1 mole) of p-chloroaniline and 300 ml. (2.5 moles) of 48 percent hydrobromic acid were placed in a 2-liter flask. The flask was cooled to 0° in an ice-salt bath. A solution of 70 g. (1 mole) of sodium nitrite in 125 ml. of water was added rapidly keeping the temperature below 10° by adding ice to the solution. While the diazonium solution was being made, a mixture of 79 g. (0.55 mole) of cuprous bromide and 80 ml. (0.6 mole) of 48 percent hydrobromic acid were heated to boiling in a 5-liter three-necked flask equipped with a steam inlet tube, a dropping funnel, and a condenser set for distillation and provided with a 2-liter receiving flask. The diazonium solution was added to the cuprous bromide-hydrobromic acid solution by way of the dropping funnel while a current of steam was passed through the mixture. The addition was over a period of 45 minutes. When the addition was complete, the mixture was steam distilled until no more oil was recovered. The distillate was cooled in an ice-water bath. The solid recovered from the distillate was filtered and recrystallized twice from ethanol-water mixture. The yield of p-chlorobromobenzene was 137 g., 71.6% based on p-chloroaniline. Melting point 67°C (lit. m.pt. 67.4°(20)).

IV. Preparation of Grignard Reagents

A. General Procedure

Grignard reagents from bromobenzene, o-bromotoluene, m-bromotoluene, p-bromotoluene, p-bromoanisole, p-chlorobromobenzene, α-bromonaphthalene, and bromomesitylene* were prepared following the procedure from Organic Syntheses (21). In a 1-liter three-necked flask equipped with a stirrer, dropping funnel, and a parallel side arm holding a reflux condenser and a thermometer were placed 9.7 g. (0.4 mole) of magnesium turnings. The condenser and dropping funnel were protected with calcium chloride

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*Five tenths of a milliliter of ethyl bromide was added as an initiator.

drying tubes. Ten milliliters of anhydrous ether and 5 ml. of the bromide were added to the flask. After the reaction was initiated, the stirring started, and the remainder of 62.8 g. (0.4 mole) of bromobenzene, 68.4 g. (0.4 mole) of o-bromotoluene, 68.4 g. (0.4 mole) of m-bromotoluene, 68.4 g. (0.4 mole) of p-bromotoluene, 74.8 g. (0.4 mole) of p-bromoanisole 76.4 g. (0.4 mole) of p-chlorobromobenzene 82.8 g. (0.4 mole) of α-bromonaphthalene, or 80.0 g. (0.4 mole) of bromomesitylene, which had previously been diluted with 170 ml. of anhydrous ether, was added to the flask over a period of one hour. After the addition, the reaction mixture was refluxed for two hours. The contents of the flask **was** cooled to room temperature, a 5 ml. aliquot was removed for analysis, and the ether solution of trimethoxyboroxine was added to the remainder of the Grignard reagent as described in section V.

The 5 ml. aliquot was analyzed following a procedure of Fieser (22). Twenty milliliters of distilled water was added along with an excess of standard 0.4531 N hydrochloric acid to the aliquot, and the excess of acid was neutralized with standard 0.4532 N sodium hydroxide to a methyl orange end point. The following is a sample calculation using the Grignard reagent from bromobenzene as the example.

40.70 ml. of 0.4531 N HCl = 0.0184

20.09 ml. of 0.4532 N NaOH = $\underline{0.0095}$

0.0089 moles of Grignard in aliquot

220 ml. total volume

$\frac{220}{X} = \frac{5}{0.0089}$ x = 0.398 moles of Grignard reagent prepared.

B. Preparation of the Grignard Reagent From p-Bromobiphenyl

In a 1-liter three-necked flask equipped with a stirrer, dropping funnel, and parallel side arm holding a reflux condenser and thermometer were placed 9.7 g. (0.4 mole) of magnesium turnings. The condenser and dropping funnel were protected with calcium chloride drying tubes. One hundred sixty milliliters of anhydrous ether was saturated with p-bromobiphenyl. Twenty milliliters of the ether solution and 0.5 ml. of ethyl bromide were added to the flask. After the reaction was initiated, the remainder of the solid 93.2 g. (0.4 mole) of p-bromobiphenyl was added through the side arm at a rate fast enough to keep the ether refluxing. The reaction mixture was not stirred. The remaining 140 ml. of the saturated ether solution was added simultaneously with the solid. Twenty milliliters of ether was used to wash the dropping funnel and added to the flask. After the addition was complete, the reaction mixture was stirred and refluxed for three hours. The contents of the flask were cooled to room temperature, a 5 ml. aliquot was removed for analysis, and the ether solution of trimethoxyboroxine was added to the remainder of the Grignard reagents as described in section V. The aliquot was analyzed following the procedure of Fieser (22).

V. Reaction of the Aryl Magnesium Bromide With Trimethoxyboroxine

A. General Procedure

The addition of trimethoxyboroxine to the aryl Grignard reagent was carried out in exactly the same manner for all the reactions. The following is the general procedure and the reaction with phenyl magnesium bromide will be used as the example.

To a 1-liter three-necked flask containing the phenyl magnesium bromide equipped with a stirrer, dropping funnel, and a parallel side arm holding a reflux condenser and a thermometer was added 100 ml. of anhydrous ether. The condenser and dropping funnel were protected with calcium chloride drying tubes. The contents of the flask were cooled to 25°C by placing the flask in a water bath. Analysis showed that 0.398 mole of phenyl magnesium bromide had been prepared. To this solution 7.7 g. (0.044 mole) of trimethoxyboroxine (9 to 1 mole ratio of Grignard reagent to trimethoxyboroxine) was dissolved in 150 ml. of anhydrous ether and added dropwise over a period of two hours while the temperature was maintained between 24-26°C. The temperature was kept constant by adding ice to the water bath. After the addition of the boroxine, the reaction mixture was stirred for three hours at the same temperature. Forty milliliters of concentrated hydrochloric acid in 300 ml. of water was used to hydrolyze the reaction mixture. The ether layer was separated and washed twice with 100 ml. portions of water. Diphenylborinic acid was isolated from the ether solution by the procedure given in Part VI and converted to the aminoethyl ester. The yield of ester from this reaction was 19 g., 62.4%. A summary of the yields of the other borinates is given in Table II.

B. Effect of Temperature

The effect of temperature on the percent of aminoethyl diphenylborinate isolated was studied. The procedure was the same as given in the preceding paragraph except that the temperatures of -60°, 6°, 16°

TABLE II

YIELD OF AMINOETHYL BORINATES*

Compound	Grams Obtained	Grams Theoretical	Percent Yield
Aminoethyl diphenylborinate	19.0	30.4	62.4
Aminoethyl di(o-tolyl)borinate	18.9	31.9	59.3
Aminoethyl di(m-tolyl)borinate	18.6	30.8	60.3
Aminoethyl di(p-tolyl)borinate	10.0	30.3	33.0
Aminoethyl di(p-anisyl)borinate	13.0	34.2	38.0
Aminoethyl di(α-naphthyl)borinate	25.0	40.3	62.0
Aminoethyl di(p-biphenyl)borinate	11.0	26.4	41.7
Aminoethyl dimesitylborinate	0.0	34.0	0.0
Aminoethyl di(p-chlorophenyl)borinate	5.3	37.5	14.2

*One to 9 mole ratio of boroxine to Grignard reagent at 24-26°C.

and 35° were used. The temperature was controlled at -60° by immersing the reaction flask in a dry ice-isopropyl alcohol bath with the temperature range between -65 to -55°C. At 6° the temperature was controlled by a salt-ice bath with the range between 5-7°C. At 16° the reaction flask was immersed in a circulating water bath and the temperature controlled between two degrees, and at 35° the reaction mixture was heated to the reflux temperature of ether with the temperature remaining constant over the reaction period. These results are summarized in part I of the result section.

C. Effect of Ratio Change

The effect of changing the mole ratio of trimethoxyboroxine to Grignard reagent was also studied. Here the reaction procedure was identical with that given above except that the mole ratios of trimethoxyboroxine to Grignard reagent of 1 to 3, 1 to 6, and 1 to 12 were used. The results are summarized in Part II of the result section.

VI. Isolation and Purification of Reaction Products

A. General Procedure for Borinates

The following isolation and purification method, adapted from a procedure of Letsinger (1), was used in all of the reactions. The ether solution from the reaction of trimethoxyboroxine with the Grignard reagent was heated on a steam bath to remove the solvent. One hundred milliliters of water was added to the resultant oil and the mixture was heated on a steam bath for 15 minutes to remove the boronic acid that had dissolved in the ether. The oil was separated from the water and diluted to 250 ml. with ether. The water layer was evaporated to recover the boronic acid. A mixture of ethanolamine in an equal volume of water was added to the ether solution and stirred until the precipitate, aminoethyl borinate, ceased to form. The solid was filtered, washed with three 50 ml. portions of water, and dried. The solid was recrystallized by dissolving in the least amount of hot ethyl alcohol, and water was added until the first appearance of a solid. The beaker was cooled in an ice-water bath and filtered through a Buchner funnel. The solid was washed with two 50 ml. portions of water and dried in a vacuum desiccator.

B. Other Methods

A study was made in effort to find a satisfactory procedure for the isolation and purification of the aminoethyl diphenylborinate. The best procedure found is given in part A. The following are other methods tried:

1) Preparation of the ester without removal of the boronic acid. The ether solution was placed in a one-neck flask equipped with a stirrer. An equal volume of ethanolamine and water was placed in the flask, and the contents of the flask stirred for one hour. The aminoethyl diphenylborinate was filtered, washed with water, and recrystallized.
2) Removal of the borinic acid by preparation of the potassium salt followed by esterification. In a two-necked flask equipped with a stirrer and reflux condenser were placed the ether solution and an excess of 1 N potassium hydroxide. The reaction

mixture was stirred and refluxed for three hours. The water layer was separated and acidified with dilute hydrochloric acid. The resulting oil was extracted with three 75 ml. portions of ether and treated with a solution of ethanolamine in water. The aminoethyl diphenylborinate was filtered, washed with water, and recrystallized.

3) Direct removal of the boronic acid by treatment with water. In a two-necked flask equipped with a stirrer and reflux condenser were placed the ether solution and 100 ml. of water. The reaction mixture was refluxed for one hour. After cooling, the ether layer was separated and treated with ethanolamine in an equal volume of water. The aminoethyl diphenylborinate was filtered, washed with water, and recrystallized.

The results obtained from the study of different methods of isolation are summarized in Part III of the result section.

C. Purification of the Boronic Acids

Phenylboronic acid, o-tolylboronic acid, m-tolylboronic acid, p-tolylboronic acid, p-anisylboronic acid, and p-biphenylboronic acid isolated from the reaction mixture were recrystallized from water. α-Naphthylboronic acid and mesitylboronic acid were recrystallized from a benzene solution. Table III summarized the observed and the literature melting points for these acids.

TABLE III

MELTING POINTS OF BOROINC ACIDS*

Compound	Melting Point		Reference
	Obs.	Lit.	
Phenylboronic acid	214-215	216	12
o-Tolylboronic acid	167-168	168	7
m-Tolylboronic acid	156-157	157	7
		137-140	23
p-Tolylboronic acid	238-239	240	12
		245	7
p-Anisylboronic acid	207-208	209-210	7
α-Naphthylboronic acid	215-216	219	24
		202	7
p-Biphenylboronic acid	229-231	232-234	24
Mesitylboronic acid	170-171	--	

*Melting points were obtained using a modified Thiele apparatus with mineral oil as the bath liquid.

VII. Analysis of the Products

A. Neutralization Equivalents

Neutralization equivalents of the aminoethyl borinates were determined using a procedure of Stone (25) for the calculation of total amines. Samples ranging from 0.4-0.9 g. (20 meq.) were weighed into a 250 ml. beaker and 100 ml. of isopropyl alcohol was added. The solution was titrated with standard 0.2405 N hydrochloric acid in isopropyl alcohol to a sharp decrease in apparent pH as measured with a pH meter using glass and calomel electrodes. A plot of change in apparent pH per change in volume against volume was used to determine the exact neutralization equivalent. The results are given in Table IV. The following is a sample calculation using aminoethyl diphenylborinate as the example.

Wt. of sample	799.5 mg.
Volume of 0.2405 N HCl	17.75 ml.
Meq.	3.545 meq.
Eq. wt. (obs.)	225.3
Eq. wt. (calc.)	225

B. Melting Points

A modified Thiele apparatus with mineral oil as the bath liquid was used to determine the melting point of the esters. The thermometer was calibrated using a Jenaer Normalglas calibrated thermometer. The results are summarized in Table IV.

C. Carbon, Nitrogen, and Hydrogen Analysis

Micro-analysis were by Micro-Tech Laboratories, Skokie, Illinois. The results are summarized in Table V.

D. Boron Analysis

Boron analysis were obtained following a procedure of Johnson (26). A sample ranging from 0.2-0.4 g. (equivalent to 0.15 g. of boric acid) was placed in a 25 ml. flask fitted with a parallel side arm holding a small Allihn condenser and a small dropping funnel. Through the addition tube 0.5 ml. of a saturated sodium hydroxide solution was added, and while the apparatus was shaken 10 ml. of 5 percent hydrogen peroxide was added dropwise from the funnel. On completion of the additions the solution was warmed gently to decompose the peroxide. One and five tenths milliliters of saturated sodium hydroxide was then added followed by the slow addition of 2-3 ml. of 30 percent hydrogen peroxide. During the addition the flask was warmed and shaken. The mixture was then heated to reflux for one-half hour. The flask was removed and its contents transferred to a nickel crucible (40 x 45 mm). The flask was washed with 5 ml. portions of water until the rinsings were neutral to litmus. The crucible was heated on a steam bath until the rate of evaporation became extremely slow, about three hours. The sample was carefully heated with a micro burner until the material solidified. The crucible was heated slightly stronger until the effervesence ceased. The crucible was finally heated to red heat for ten minutes. After cooling, the crucible was placed in a 300 ml. beaker with 75 ml. of water. After the salts had dissolved, the crucible was removed and rinsed carefully. The solution was heated to boiling and filtered into a 500 ml. flask fitted with a reflux condenser. Two drops of a methyl red solution were added followed by 3 N hydrochloric acid until an excess of 3-5 ml. was present. The solution was refluxed for one-half hour. The flask was cooled and the condenser rinsed thoroughly, the rinsings added to the flask. The solution was roughly neutralized with 10 percent sodium hydroxide, and the exact neutrality with 0.2080 N hydrochloric acid and 0.1971 N sodium hydroxide. To the neutral solution were added three drops of phenolphthalein and 10 g. of mannitol. The solution was then titrated with 0.1971 N sodium hydroxide to the first faint pink color by the phenolphthalein. The percent of boron was then calculated from the amount of alkali consumed between the methyl red and phenolphthalein end points. The results are summarized in Table V. The following is a sample calculation using aminoethyl diphenylborinate as the example.

1 ml. of 0.1971 N NaOH = 0.00216 g. of boron
5.12 ml. of 0.1971 N NaOH = 0.0101 g. of boron
Wt. of sample 0.210 g.
Percent boron 4.80%

TABLE IV

MELTING POINTS AND NEUTRALIZATION EQUIVALENTS OF BORINATES*

Name	Melting Points		Neut. Eq.	
	Obs.	Lit.	Obs.	Calc.
Aminoethyl diphenylborinate	189	190(1)	225.3	225
Aminoethyl di(o-tolyl)borinate	181-181.5	--	255	253
Aminoethyl di(m-tolyl)borinate	180-181	--	256	253
Aminoethyl di(p-tolyl)borinate	186-187	--	251	253
Aminoethyl di(p-anisyl)borinate	173-174	--	287	285
Aminoethyl di(α-naphthyl)borinate	202-203	--	326.5	325
Aminoethyl di(p-biphenyl)borinate	217-218	--	381	377
Aminoethyl di(p-chlorophenyl)-borinate	223-224	--		

*Melting points were obtained using a modified Thiele apparatus with mineral oil as the bath liquid. Neutralization equivalents were obtained from following a procedure of Stone (25).

TABLE V

ANALYSIS OF AMINOETHYL BORINATES*

Name	Percent Composition							
	Found				Calculated			
	C	H	N	B	C	H	N	B
Aminoethyl diphenyborinate	74.67	7.36	6.22	4.80	74.63	7.15	6.22	4.88
Aminoethyl di(*o*-tolyl)borinate	75.62	8.36	5.46	4.33	75.90	7.91	5.53	4.34
Aminoethyl di(*m*-tolyl)borinate	75.37	8.09	5.43	4.40	75.90	7.91	5.53	4.34
Aminoethyl di(*p*-tolyl)borinate	75.60	8.32	5.27	4.40	75.90	7.91	5.53	4.34
Aminoethyl di(*p*-anisyl)borinate	67.43	7.21	4.75	3.82	67.30	7.02	4.91	3.85
Aminoethyl di(*α*-naphthyl)borinate	80.84	6.39	4.01	3.35	81.20	6.15	4.31	3.38
Aminoethyl di(*p*-biphenyl)borinate	79.95	6.30	4.69	2.92	82.75	6.36	3.71	2.92

*Carbon, hydrogen, and nitrogen analysis were by Micro-Tech Laboratories, Skokie, Illinois. Boron analysis obtained from following a procedure of Johnson (26).

RESULTS

I. Effect of Temperature

Table VI and Graph I summarize the results obtained by varying the temperature in the preparation of aminoethyl diphenylborinate. These results indicate that a maximum yield of the borinate is obtained when the reaction proceeds at 25°. The small yield of borinate at -60° and 6° may be explained by reasoning that the activation energy is too high to form an appreciable amount of the borinic acid at these temperatures.

The boronic acid was not isolated from these reactions because it is quite soluble in the aqueous acid used for hydrolysis and also because it oxidizes readily to phenol in water. Since the water extract contains magnesium salts and boric acid produced by decomposition of unreacted boroxine, the problem of isolation becomes exceedingly difficult. It was observed, however, that at -60° the yield of boronic acid isolated is the same as the yield of the borinate.

II. Effect of Ratio of Boroxine to Grignard Reagent

Table VII and Graph II summarizes the results obtained by changing the mole ratio of trimethoxyboroxine to phenyl magnesium bromide in the preparation of aminoethyl diphenylborinate at 25°. These results indicate that a maximum in yield is obtained when the mole ratio of trimethoxyboroxine to phenyl magnesium bromide of 1 to 9. The low yield at the mole ratio of 1 to 3 could be explained by reasoning that the concentration of Grignard reagent is too low to force the reaction

TABLE VI

TEMPERATURE EFFECT IN THE REACTION OF TRIMETHOXYBOROXINE WITH PHENYL MAGNESIUM BROMIDE[*]

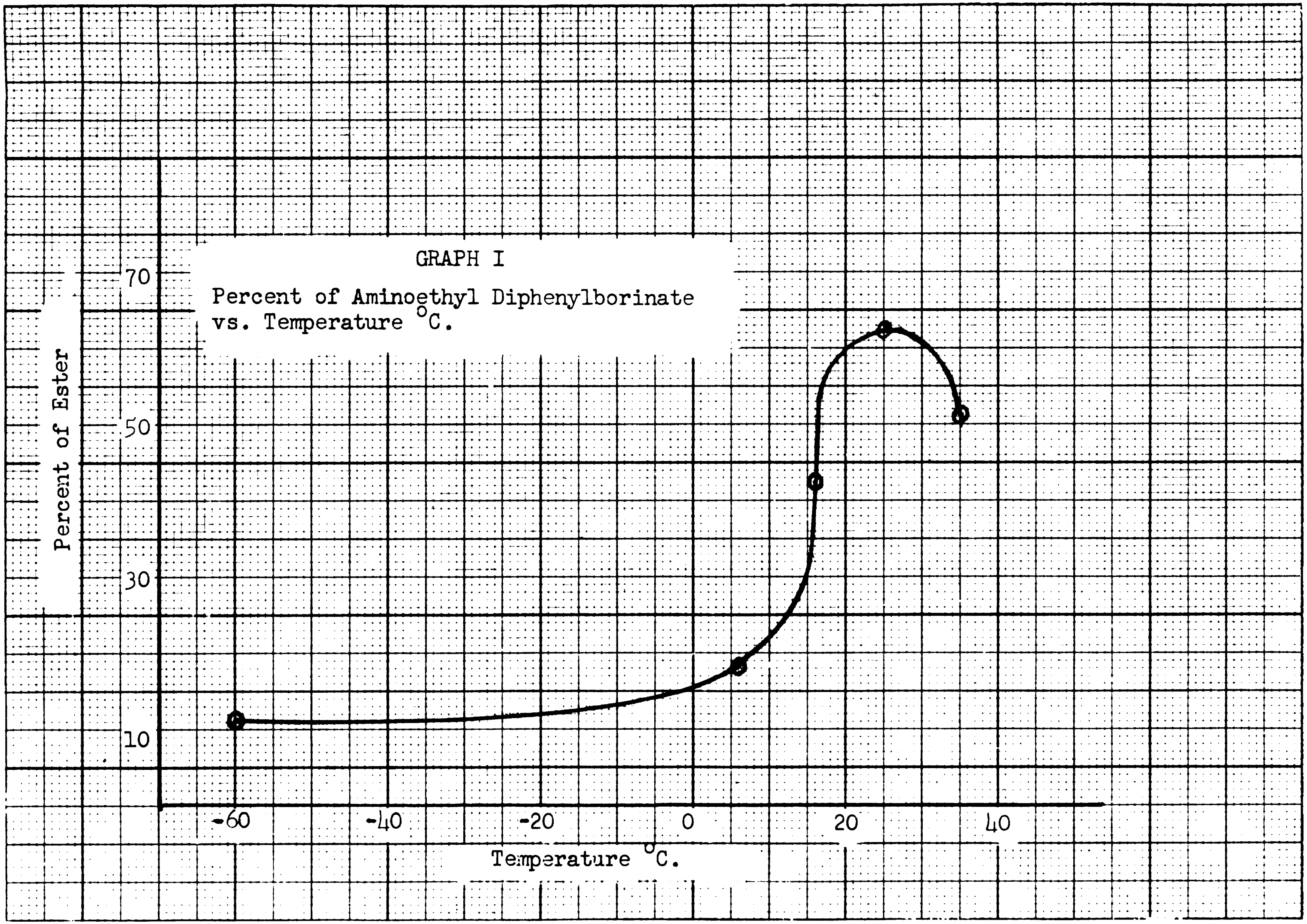
Temperature °C.	Percent Yield of Aminoethyl Diphenylborinate
-60	11.2
6	18.4
16	42.6
25	62.4
35	51.7

[*] One to nine mole ratio of trimethoxyboroxine to Grignard Reagent.

TABLE VII

EFFECT OF CHANGING THE MOLE RATIO OF TRIMETHOXYBOROXINE TO PHENYL MAGNESIUM BROMIDE AT 25°

Ratio of Boroxine to Grignard	Percent Yield of Aminoethyl Diphenylborinate
1-3	16.7, 15
1-6	56.2
1-9	62.4
1-12	43.7, 45

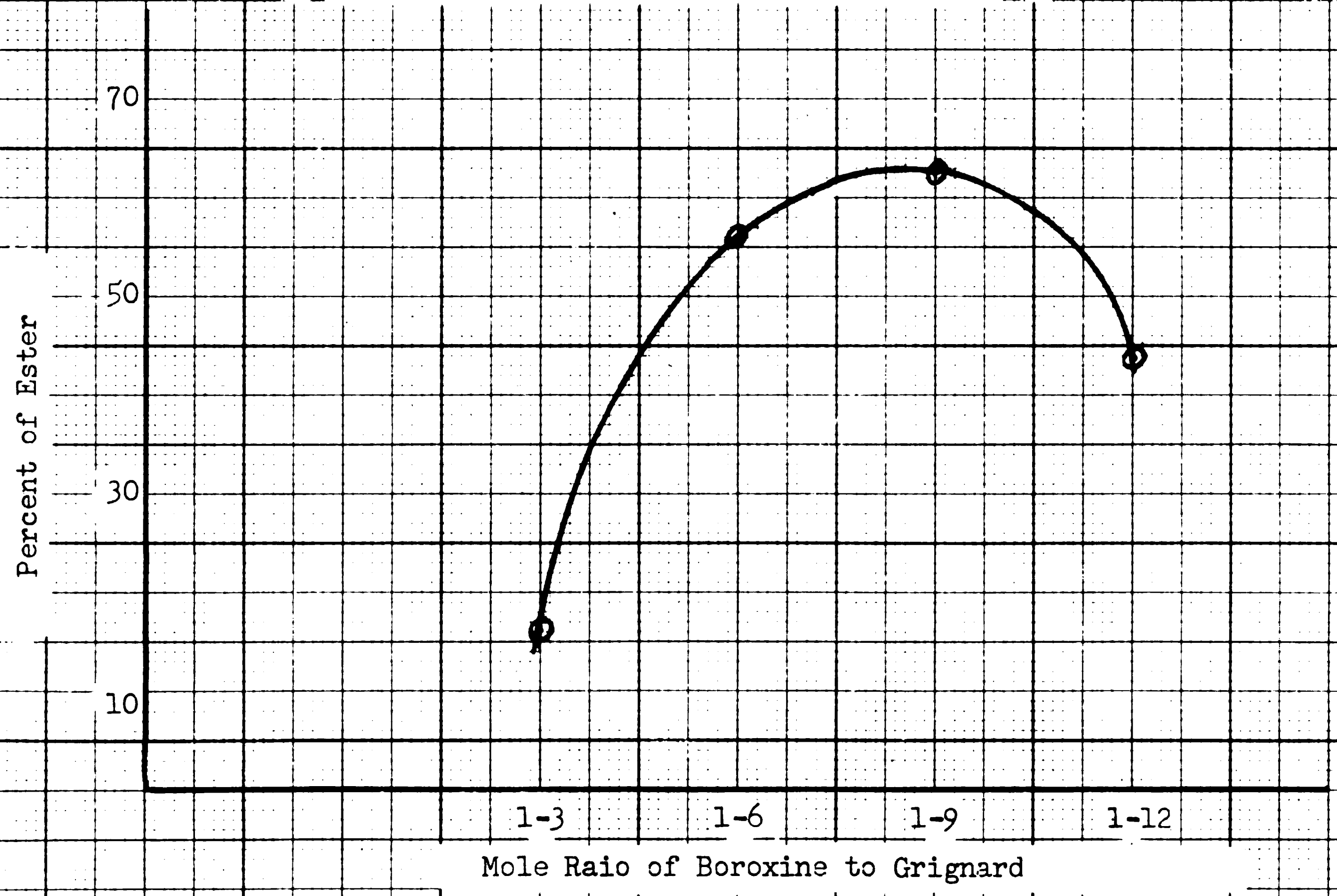


GRAPH I

Percent of Aminoethyl Diphenylborinate vs. Temperature °C.

GRAPH II

Percent of Aminoethyl Diphenylborinate vs. Mole Ratio of Boroxine to Grignard Reagent



in favor of the borinic acid. This is reasonable because boric acid was isolated from the reaction mixture after hydrolysis and was not found in any of the other reactions of this series. Since boric acid is soluble in aqueous solutions, any boric acid formed from the hydrolysis of the unreacted boroxine would dissolve in the acid solution used for hydrolysis. Boric acid was recovered only when it was present in larger amounts than that required to saturate the solution.

III. Methods of Isolation

Four methods were studied in an attempt to find the most satisfactory method of isolation of aminoethyl diphenylborinate. These methods were described in section VI of the Experimental. The results from this study are summarized in Table VIII. Method 1, removal of the solvent and boronic acid followed by esterification, which gave the highest yield of ester (62.4%) was used to isolate the borinic acids in all subsequent reactions of Grignard reagents with the boroxine. The yield obtained by method 2 (preparation of the ester without removal of the boronic acid) is slightly more than one-half that of method 1, and shows the necessity of removing the boronic acid before attempting esterification. Method 3, which attempts to remove the borinic acid from ether by extracting with aqueous potassium hydroxide, gives surprisingly low yields (40.7%) of the ester. This is difficult to explain but suggests that extraction with aqueous base is quite inefficient. Method 4, removal of boronic acid from the reaction mixture by boiling with water and subsequent esterification of the remaining

TABLE VIII

COMPARISON OF SEVERAL METHODS FOR ISOLATION OF BORINIC ACIDS*

Method**	Aminoethyl Diphenylborinate		
	Grams Obtained	Grams Theoretical	Percent Ester Obtained
1	11.1	17.7	62.4
2	6.2	17.7	35.0
3	7.2	17.7	40.7
4	8.3	17.7	46.9

*Identical and optimum reaction conditions were used in each case.

**The four methods studied are:

1. Removal of the solvent and boronic acid followed by esterification.
2. Preparation of the ester without removal of the boronic acid.
3. Removal of the borinic acid by preparation of the potassium salt followed by esterification.
4. Direct removal of the boronic acid by treatment with water.

borinic acid, gave a 46.7% yield of ester. This suggests that the boronic acid cannot be successfully removed with boiling water.

IV. Effect of Steric Factors

The study of steric effects in this reaction is illustrated in Table IX. Results of reacting phenyl, o-tolyl, α-naphthyl, and mesityl Grignard reagents with the boroxine gave a clear indication of the susceptibility of this reaction to steric factors. Substitution of one o-methyl group has virtually no effect on the yield of borinate, whereas blocking both ortho positions of the Grignard completely prevents the reaction. No reaction between mesityl magnesium bromide and boroxine was evidenced even after increasing the reaction time to fifteen hours, five times the usual procedure. It is interesting to note that the yield of the di(o-tolyl)borinic ester is nearly twice that of the di(p-tolyl)borinic ester. Since electrical factors are nearly the same in these two compounds, the steric effect of the single o-methyl group appears opposite to that of the two o-methyl groups. The yield of ester from the α-naphthyl Grignard is almost identical with that obtained from the o-methyl compound.

V. Effect of Electrical Factors

The influence of electron donating and electron withdrawing substituents in the Grignard reagent has been studied with phenyl, p-tolyl, m-tolyl, p-anisyl, p-chlorophenyl, p-biphenyl, and α-naphthyl Grignard reagents. These results are summarized in Table X. In general, the results indicate that the highest yields of ester (62% of theoretical)

TABLE IX

EFFECT OF STERIC FACTORS*

Compound	Percent Yield of Borinate
Aminoethyl diphenylborinate	62.4
Aminoethyl di(*o*-tolyl)borinate	59.3
Aminoethyl di(*α*-naphthyl)borinate	62.0
Aminoethyl dimesitylborinate	0.0

*One to nine mole ratio of boroxine to Grignard reagent at 25°.

TABLE X

EFFECT OF ELECTRICAL FACTORS*

Compound	Percent Yield of Borinate
Aminoethyl diphenylborinate	62.4
Aminoethyl di(*α*-naphthyl)borinate	62.0
Aminoethyl di(*p*-biphenyl)borinate	41.7
Aminoethyl di(*p*-anisyl)borinate	38.0
Aminoethyl di(*p*-tolyl)borinate	33.0
Aminoethyl di(*p*-chlorophenyl)borinate	14.2**
Aminoethyl di(*m*-tolyl)borinate	60.3

*One to nine mole ratio of boroxine to Grignard reagent at 25°.

**Low yield due in part to air oxidation of the borinic acid.

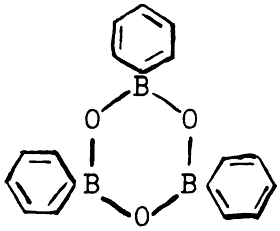
are obtained with the phenyl and α-naphthyl compounds. The p-biphenyl and p-anisyl Grignards gave approximately the same yield (40% of theoretical), somewhat lower than that obtained from the first two members of the series. The yield in the case of the p-tolyl compound was 33%, somewhat less than the p-anisyl and p-biphenyl and significantly less than the m-tolyl which was 60.2%. Finally, the p-chlorophenyl Grignard reagent gave a poor yield (14.2%). The actual yield is probably somewhat higher than this, but the di(p-chlorophenyl) borinic acid is especially susceptible to autoxidation. This oxidation accounts in part for the low yield.

In general, it appears that both electron donating and electron withdrawing substituents decrease the yield of borinic acid in this reaction.

DISCUSSION

The study of the effect of temperature, mole ratio of boroxine to Grignard reagent, steric, and electrical factors were made to gain insight into the nature of this new reaction, to explore its scope, and to attempt to elucidate a possible mechanism.

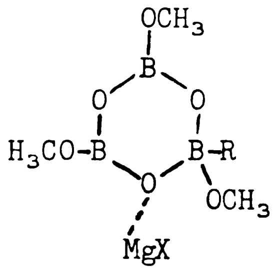
The significance of the effect of temperature suggests that triphenylboroxine,



could be found at low temperatures. This observation is founded on the following facts. First, the isolated yield of boronic acid is the same as that of the ester of the borinic acid. If the boronic acid is present before hydrolysis, it should react with the excess Grignard reagent. This reaction has been shown to proceed at these conditions by Letsinger (8). The second reason for the suggested compound is that the boroxine ring should be stable at this temperature as it is formed under similar conditions.

At higher temperatures increased yields of borinic acids were obtained. It is conceivable that the initial reaction is the preparation of triphenylboroxine. Two facts suggest that this may not be the case. First, the isolation of boric acid from the reaction mixture. This can be obtained from the hydrolysis of either trimethoxyboroxine or a mono- or di-substituted phenyl boroxine, but not from triphenylboroxine which would give only phenylboronic acid. Second, at the higher temperatures the boroxine ring becomes unstable as shown by its decomposition at 68°.

The increased yield of borinic acid could be explained by the increase in energy acquired by the Grignard reagent which facilitates its reaction with the boron compound. The attacking reagent could do one of two things. The Grignard reagent could cause complex formation, as shown in Figure I, or cause the ring to rupture, as shown in Figure II.



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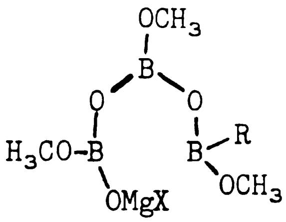


II

The significance of changing the ratio of boroxine to Grignard reagent, in addition to supporting the Law of Mass Action, lies in the observation that considerable amounts (15%) of borinic ester are formed at a 3 to 1 ratio of Grignard reagent to boroxine. Since the yield of borinic acid exceeds that of boronic acid, it appears that the reaction of the Grignard reagent occurs more readily at the boron atom containing a phenyl group than at a boron atom containing a methoxy group. This suggests that a phenyl group on boron activates the boron for further attack. This activation is not noticeable at the lower temperatures.

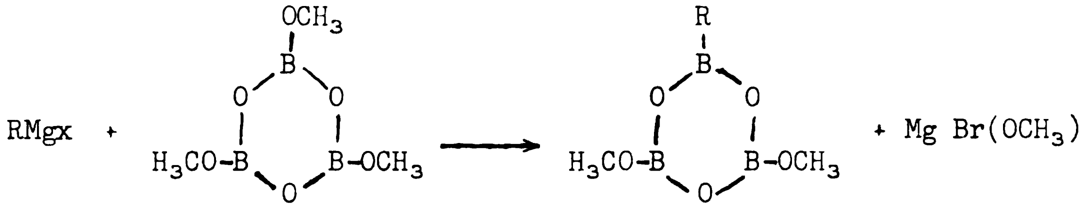
Further support for this picture comes from the studies at 6 to 1 and 9 to 1 ratios of Grignard reagent to trimethoxyboroxine. In these two cases, even though there is enough Grignard reagent to form the theoretical amount of borinic acid, boronic acid and boric acid are isolated after hydrolysis.

One interpretation of this observation is that two Grignard molecules attack a given boron atom before the ring ruptures. In fact two (or even all three boron atoms) may be doubly substituted by phenyl groups before ring rupture occurs. Rupture of the ring gives rise to borate type structures which can react slowly with the Grignard to give boronates and ultimately borinates. That the entire reaction cannot proceed by an instantaneous decomposition of the ring to the borate structure followed by reaction of this structure with Grignard reagent is shown by the fact that borates react with Grignard reagents under these conditions to give yields of borinates less than half those obtained in the present reaction.

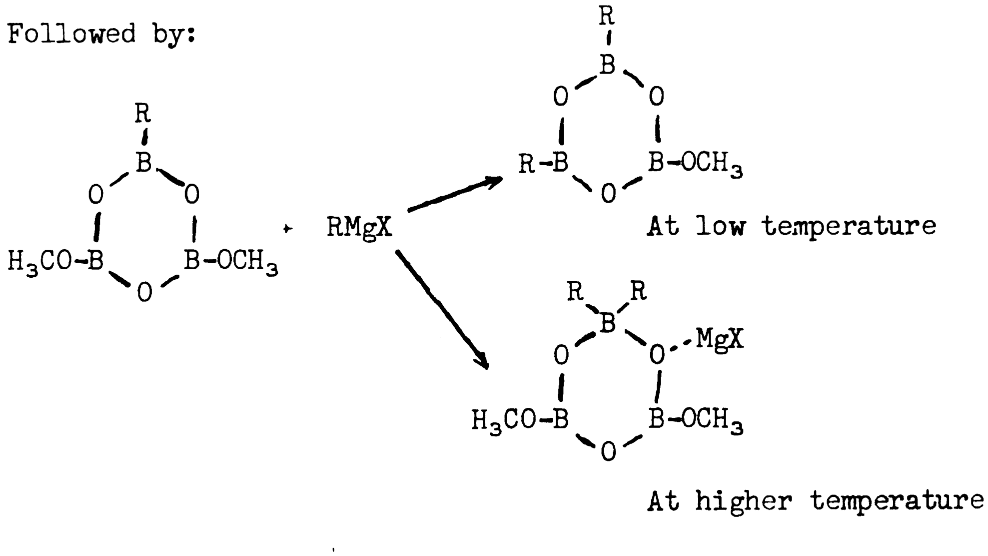
The significance of the steric effect is illustrated by the reaction of mesityl magnesium bromide with the boroxine. Only mesitylboronic acid is isolated. This accentuates the importance of blocking the area around the small boron atom thus preventing attack by a second substituent. In the case of _o_-tolyl magnesium bromide the yield is approximately equal to that obtained from the phenyl Grignard and nearly twice that from the _p_-tolyl compound. The high yield from the _o_-tolyl compound, clearly opposite to its expected behavior on the basis of both steric and electrical grounds can be explained by reasoning that the ortho methyl group weakens the carbon-magnesium bond by steric hindrance. This assists the reaction by making the magnesium more available for coordination with the oxygen atom of the boroxine.

On the basis of the above reasoning, the following general mechanism is proposed. This mechanism has not been established but is included partly as a working guide toward a better understanding of the reaction and partly to stimulate thinking on future research in this area.

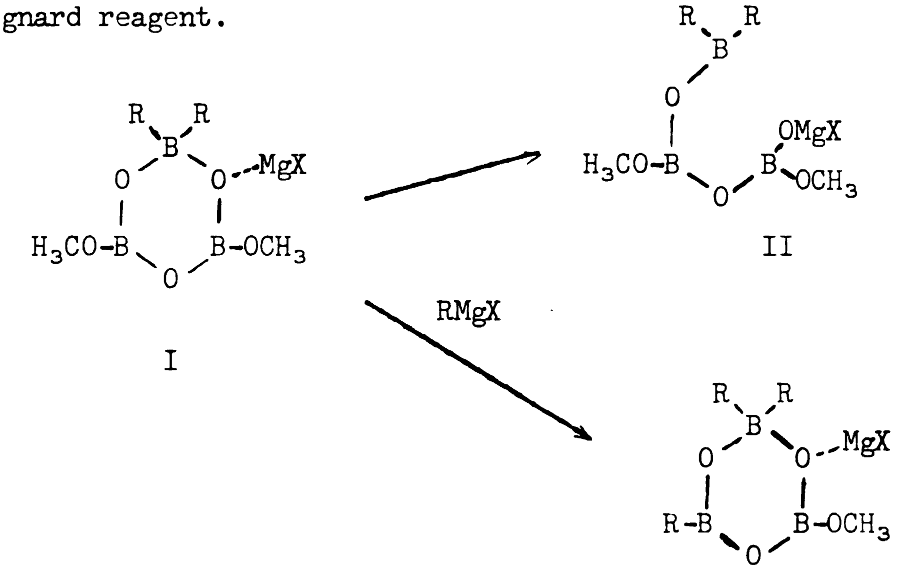
The initial reaction is probably



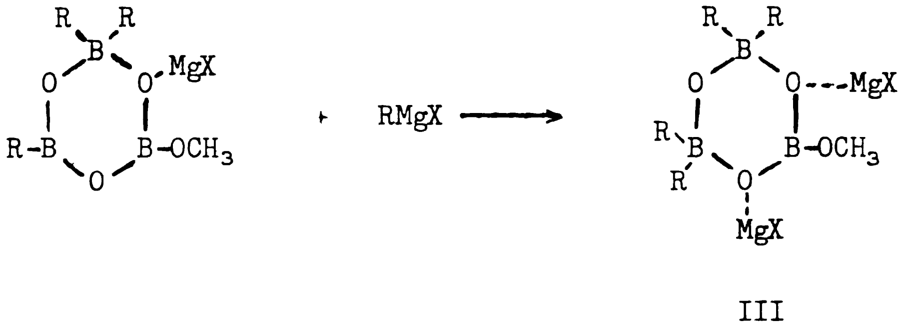
Followed by:



The complex, I, may decompose by ring rupture or react with more Grignard reagent.



Compound II reacts slowly to yield boronic and borinic acids.



Complex III on hydrolysis gives two molecules of borinic acid and one of boric acid.

CONCLUSION

1. The reaction between trimethoxyboroxine and aryl Grignard reagents is found to proceed to give aryl boronic and aryl borinic acids.

2. The yields of borinic acids isolated as the aminoethyl ester ranged from 14-62 percent.

3. A mechanism is proposed which is supported by studies of effect of temperature, effect of changing ratio of boroxine to Grignard reagent, and effect of steric and electrical factors.

4. Aminoethyl esters of di-(*o*-tolyl), di-(*p*-tolyl), di-(*m*-tolyl), and di-(*p*-biphenyl) borinic acids and mesitylboronic acid were prepared by this reaction. These acids have not previously been reported in the literature.

5. Aminoethyl esters of diphenyl, di-(*α*-naphthyl), di-(*p*-anisyl), and di-(*p*-chlorophenyl) borinic acids and phenyl, *o*-tolyl, *m*-tolyl, *p*-tolyl, *p*-anisyl, *α*-naphthyl, and *p*-biphenyl boronic acids were also prepared by this method. These boronic and borinic acids have been reported.

6. The yields of the borinic esters obtained from this reaction were in nearly all cases twice that obtained from currently used methods.

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