SYNTHESIS OF ORGANOBORON COMPOUNDS FOR NEUTRON-CAPTURE THERAPY

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SYNTHESIS OF ORGANOBORON COMPOUNDS

FOR NEUTRON-CAPTURE THERAPY

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CHAPTER I

INTRODUCTION

The use of boron-10 neutron-capture therapy in the treatment of certain tumors has been limited because a boron compound suitable for use in this type of treatment is not available. For a boron compound to be useful in this type of therapy the compound must 1) be stable to hydrolysis in a biological system, 2) be selectively absorbed by the fast-growing tumor cells, and 3) be non-toxic at high dose levels.

A limited number of boron compounds have been synthesized and screened for use in neutron-capture therapy. Those that have been reported lack one or more of the desired properties listed previously. Little work has been done in synthesizing boron analogs of the biologically important pyrimidines. If the boron atom is incorporated into the pyrimidine ring adjacent to a nitrogen atom this analog should have the desired properties listed. With boron in the ring adjacent to nitrogen the compound may have some aromatic character and be stabilized by it. By being similar to the pyrimidine bases, the compounds should have low toxicity and high affinity for the fast-growing tumor cells. They may also act as antimetabolites.

The goals of this study were to synthesize new

organoboron compounds that may be useful in neutron-capture therapy, to investigate and record the physical and chemical properties of these new compounds, to determine the structures of the new compounds, and to make the compounds available for biological testing.

CHAPTER II

HISTORICAL

The element boron, atomic number 5, exists in nature in two isotopic forms, boron-10 and boron-11. The percent abundance of each is 20 and 80, respectively. The boron-10 isotope has the nuclear property of being able to capture thermal neutrons. The cross section for neutron capture by boron-10 is 3850 barns compared to 0.05 barns for the boron-11 isotope. This high neutron-capture cross section of boron-10 has made it the subject of investigation in the treatment of certain malignant tumors.[1]

The nuclear reaction for the capture of a neutron by boron-10 is:

$$^{10}_{5}B + {}^{1}_{0}n \rightarrow \left[{}^{11}_{5}B\right] \rightarrow {}^{7}_{3}Li + {}^{4}_{2}He + 2.4 \text{ Mev}$$

The particles that result from the fission of the unstable boron-11 nucleus, $^{7}_{3}Li$ and $^{4}_{2}He$, are large by nuclear standards and therefore have limited penetrating ability. They expend their kinetic energy within a few microns. If this reaction could be made to occur in the interior of a cell, the result would be destruction of that cell with the possibility of slight or no damage to those cells adjacent to it.

If boron-10 could be incorporated into a molecule that would be selectively absorbed by a fast-growing malignant cell, subsequent bombardment of this cell by thermal neutrons would result in the selective destruction of that cell. This approach to therapy of certain tumors was proposed by Locher[2] in 1936; Kruger[3] in 1940, from survival time experiments with mice bearing transplanted tumors, reported that boron-10 thermal-neutron therapy could be used to selectively destroy these tumors.

Other non-radioactive nuclides with high neutron-capture cross sections have been considered for use in this type of therapy. These are listed with their cross sections.

^{6}Li (870 barns)	^{157}Gd (200,000 barns)
^{113}Cd (24,000 barns)	^{164}Dy (2620 barns)
^{149}Sm (46,000 barns)	^{199}Hg (2500 barns)
^{155}Eu (14,000 barns)	^{235}U (549 barns)

Of these isotopes, the ^{6}Li and ^{235}U are the only ones that undergo neutron capture without the emission of gamma radiation. The emission of gamma radiation by the other isotopes makes them useless. The relatively small cross sections for neutron capture for ^{6}Li and ^{235}U, the lack of hydrolytic stability of organolithium compounds and the high toxicity of the uranyl ions and their complexes have made them useless. Boron-10 is therefore the isotope of choice.

Three requirements must be considered in the use of boron-10 neutron-capture therapy. First, a large concentration of boron-10 must be evenly distributed throughout the neoplasm. Second, a source of thermal neutrons must be available. Third, and this is the most important consideration, the boron-10 must be more concentrated in the neoplasm than in adjacent tissue.

The first requirement can be achieved only by injection of the compound into the blood stream. The poorly defined boundaries of a tumor makes impossible the uniform distribution of the compound throughout the tumor by injection of a boron compound directly into the tumor. Even distribution of the boron compound can be achieved only by transportation through the blood stream. Since injection is necessary, the compound must be hydrolytically stable in the biological environment of pH 7.4, otherwise degradation will occur. As more work is being done in the area of organoboron synthesis, compounds with higher hydrolytic stability are becoming available.

The second consideration, a high flux of thermal neutrons, can be obtained in a nuclear reactor. The third requirement of a high concentration of boron-10 relative to adjacent tissue is of utmost importance. This requires that the boron compound have a high affinity for malignant cells.

Boron compounds that have been evaluated for neutron-capture therapy can be classified as inorganic boron

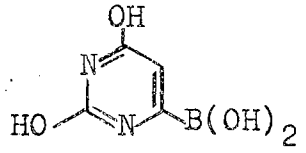
compounds and organic boron compounds.

Of the inorganic boron compounds that have been examined, boric acid and its derivatives have received the most extensive review. Locksly and Sweet[4] have studied the possible use of boric acid. Using a transplanted mouse brain tumor induced by 3-methylcholanthrene these workers found that the concentration of boron in the tumor reached a maximum in thirty minutes after injection of boric acid, at which time the tumor/adjacent tissue boron ratio was 3. Sweet and Farr[6] obtained disappointing results using 96% enriched boron-10 sodium tetraborate and irradiating a brain tumor in man through the skull. All patients receiving this treatment eventually succumbed to the malignancy although there was some lengthening of life in these patients. Farr and Konikowski[7] have recently reported the results of a study using boron-10 enriched sodium pentaborate decahydrate to treat a transplanted intramuscular neoplasm in mice. The sodium pentaborate decahydrate is less toxic than the tetraborate and its toxicity is reduced further when it is used in a solution of D-glucose at a borate:glucose molar ratio of 2. By varying the dosage of the borate and the exposure time no difference was obtained. The important factor was the neutron flux.

At a dosage of 35 mg./kg. of body weight, a neutron flux range of 0.8-3.2 x 10^{12} $cm.^{-2}$ and an irradation time of 100 milliseconds, these workers obtained permanent regression of neoplasms in 29 of 38 cases.

Of the inorganic borohydrides tested, the perhydrodecaborate ion, $B_{10}H_{10}^{2-}$ and the perhydroduodecaborate ion, $B_{12}H_{12}^{2-}$, have received the most attention.[8,9] These ions have low toxicity as determined in terminal cancer patients. The tumor/adjacent tissue ratios were 3.9 in 15 minutes and 7.3 in 108 minutes for the perhydrodecaborate ion.

Two general types of organoboron compounds have received the most attention: the boronic acids, $R\text{-}B(OH)_2$, and the heterocyclic organoboron compounds. The boronic acids have received much attention due to the oxidative and hydrolytic stability of the boron-carbon bond, especially when R = alkyl. Soloway and coworkers[10,11,12] studied a large number of benzene boronic acids to determine whether substituents on the phenyl ring affected the localization of these compounds in mouse brain tumors. Compounds with high lipid solubility penetrated the brain readily and produced toxic symptoms in the central nervous system. Compounds with low lipid solubility had low toxicity and favorable tumor/adjacent tissue ratios. An exception was the p-chlorobenzene boronic acid which was highly toxic. Cheng[18] prepared the substituted pyrimidine boronic acid,

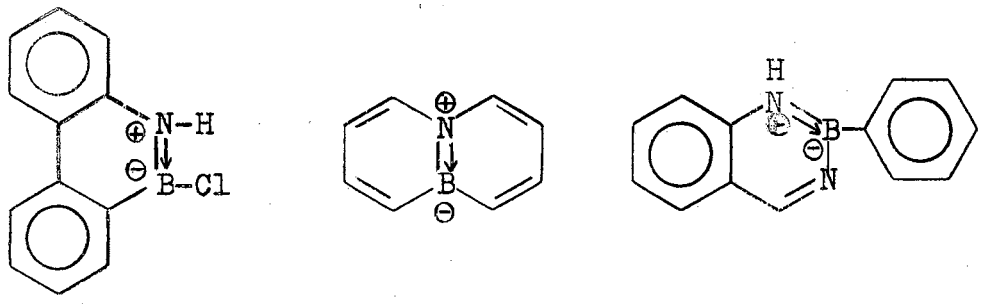


but no biological data have been reported for it.

Some interesting aliphatic boronic acids have been prepared by Matteson.[13,14,15,16,17] These compounds in

general either lack selectivity for tumor absorption or are quite toxic. For example, β-thioacetoxyethyleneboronic acid was toxic in mice at doses as low as 9 mg. B/kg. body weight.

Dewar[19] has done extensive theoretical and synthetic work in heteroaromatic boron compounds. The $\bar{B}\leftarrow\!\!=\overset{+}{N}$ bond system is isoelectronic with the C=C bond system and it is reasoned that replacement of the C=C bond by the $\bar{B}\leftarrow\overset{+}{N}$ system in an aromatic ring should result in a stable compound. This has been used to explain the stability of the compounds shown below.[20,21,22]



However, no organoboron molecules of this type have been synthesized that are of biological significance.

CHAPTER III

AN APPROACH TO THE PROBLEM

Several compounds have been synthesized and screened for possible application in boron-10 neutron-capture therapy of cancer.[1]

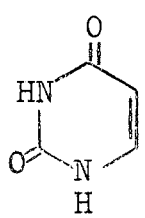
1. Triisopropanolamine borate
2. 3-Amino-4-carboxybenzeneboronic acid
3. m-Boronosuccinanilic acid
4. 2-Acetamindobenzene-1,4-diboronic acid
5. α-Sulfo-o-tolylboronic acid

The majority of these compounds are substituted benzene boronic acids, and although they are non-toxic and give favorable tumor/adjacent tissue boron ratios, they are excreted rapidly through the urinary tract. Excretion is much faster than absorption by the tumor. A considerable concentration of these compounds remains in the blood which has led to damage of blood vessels on neutron irradiation. Therefore it appears that another desirable property, in addition to those discussed earlier, is that the compound become irreversibly bound to the tumor.

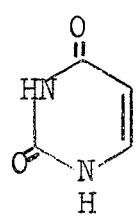
Tumor cells can be distinguished from ordinary cells by having impaired or distorted respiration.[23,24] Cancer cells are proliferating at a much greater rate than most normal

cells and preferentially absorb compounds necessary for metabolism and for the synthesis of vital cell components. If a heterocyclic boron compound could be prepared that would mimic the function of a naturally occurring compound, it should be selectively absorbed and bound to/in the cancer cell. In this sense the boron heterocyclic compound may act as an antimetabolite in addition to its being useful in neutron-capture therapy.

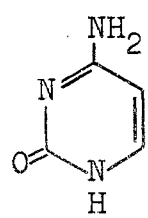
It is well known that uracil is found in high concentrations in tumor tissue.[50] Uracil is the primary pyrimidine found in RNA, and the important pyrimidines found in DNA, thymine and cytosine, are formed from uracil.[51] Some of the biologically important pyrimidines are given below. Orotic acid is the precursor of the pyrimidines.



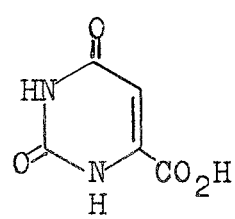
Uracil



Thymine



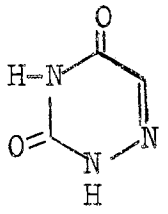
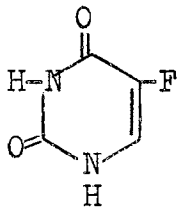
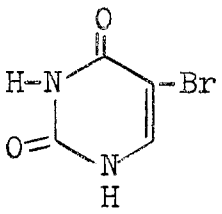
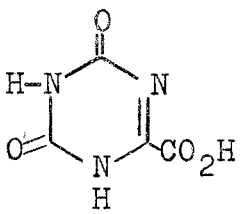
Cytosine



Orotic acid

Uracil is formed from it by enzymatic decarboxylation. Methylation of uracil gives thymine and amination gives cytosine.

These compounds have served as models in the synthesis of cancer chemotherapeutic agents. Some of the more important pyrimidine antagonists are given below.

6-Azauracil 5-Fluorouracil 5-Bromouracil 5-Azaorotic acid

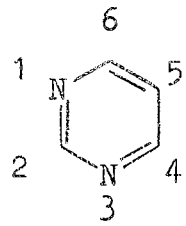
6-Azauracil has been shown to have antitumor activity,[52] but has considerable toxicity to the central nervous system. Its mechanism of activity appears to involve inhibition of de novo pyrimidine synthesis since E. coli treated with 6-azauracil were found to have an increased concentration of orotic acid.[53]

One of the more effective uracil-like compounds that has been useful in cancer chemotherapy is 5-fluorouracil. In cells in culture, 5-fluorouracil inhibits DNA synthesis but not RNA synthesis.[53]

5-Bromouracil was synthesized using thymine as a model. The steric requirements of the bromo group are similar to that of the methyl group.[50] 5-Bromouracil is readily incorporated into DNA but its use clinically is limited because it is mutagenic.[50]

The symmetrical triazine, 5-azaorotic acid, has been found to inhibit the metabolism of orotic acid in tumor cell extracts.[53] It inhibits decarboxylation of orotic acid in human patients with the latter compound being excreted in the urine. 5-Azaorotic acid is being considered for clinical application to liver and kidney tumors.

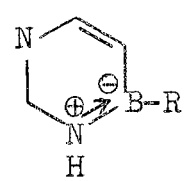
It was proposed to synthesize a compound that in a biological system may mimic the pyrimidine bases.



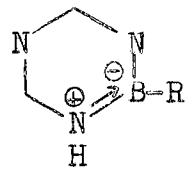
Pyrimidine

In order for it to do this the compound must have the boron atom built into the ring. By building the boron atom in the ring adjacent to a nitrogen atom, maximum stability should result due to dative bond formation between the unshared electron pair of nitrogen and the vacant p orbital of boron. It is well established that the boron-nitrogen bond in aminoboranes, $R_2N-BR'_2$, has double bond character.[20] Experimental and theoretical evidence present the double bond character as being the result of delocalization of the p electrons of nitrogen to the vacant p orbital of boron. By building the boron-nitrogen bond into the six-membered pyrimidine ring, the resulting heterocyclic compound should have greater hydrolytic stability than the aminoboroanes.

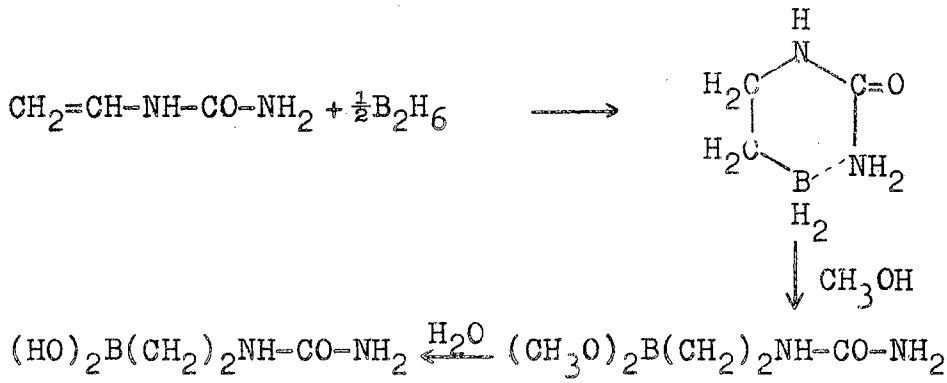
This problem has been approached in two ways. The first method involved replacing the carbon atom at position 4 with boron. This would give the 2-borapyrimidine ring system given below. The second approach was to replace the



carbon atom in position 4 with boron and the carbon of position 5 with nitrogen. This, essentially, involves replacing a carbon-carbon double bond with a boron-nitrogen system giving the 2-bora-s-triazine ring system given below.



An attempted synthesis of the first ring system was reported by Soloway and Butler.[27] Their ingenious approach is outlined below.



All attempts to cyclize the ureidoboronic acid were unsuccessful.

Synthesis of the 2-bora-s-triazine ring system has been reported by Boone.[28] No evidence for the existence of this system is given; only elemental analysis and molecular weight data are given for the reaction product. Cragg and Lappert[29] report that this ring system is formed in the reaction of phenyl isocyanate and B,B',B''-tris-(diethylamino)-N,N',N''-triethylborazine, $[(C_2H_5)_2NB-NC_2H_5]_3$. Infrared data are given for the compound along with other

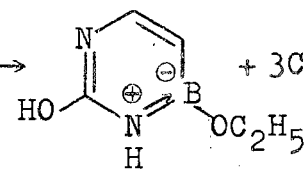
experimental data for this reaction. In neither report is there a statement regarding the stability of this ring system.

The proposed syntheses for the first ring system are outlined below.

Method I

$$BrCH_2CH(OC_2H_5)_2 + Mg \longrightarrow BrMgCH_2CH(OC_2H_5)_2$$

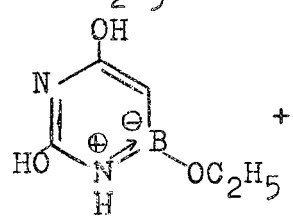
$$BrMgCH_2CH(OC_2H_5)_2 + B(OC_2H_5)_3 \rightarrow (C_2H_5O)_2BCH_2CH(OC_2H_5)_2 + BrMgOC_2H_5$$

$$(C_2H_5O)_2BCH_2CH(OC_2H_5)_2 + NH_2CONH_2 \longrightarrow$$  $$+ 3C_2H_5OH$$

Method II

$$BrCH_2CO_2C_2H_5 + Zn \longrightarrow BrZnCH_2CO_2C_2H_5$$

$$BrZnCH_2CO_2C_2H_5 + B(OC_2H_5)_3 \longrightarrow (C_2H_5O)_2BCH_2CO_2C_2H_5 + BrZnOC_2H_5$$

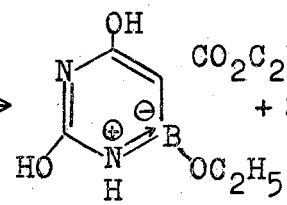
$$(C_2H_5O)_2BCH_2CO_2C_2H_5 + NH_2CONH_2 \longrightarrow$$  $$+ 2C_2H_5OH$$

Method III

$$CH_2(CO_2C_2H_5)_2 + KOC(CH_3)_3 \longrightarrow KCH(CO_2C_2H_5)_2 + HOC(CH_3)_3$$

$$KCH(CO_2C_2H_5)_2 + B(OC_2H_5)_3 \longrightarrow (C_2H_5O)_2BCH(CO_2C_2H_5)_2 + KOC_2H_5$$

$$(C_2H_5O)_2BCH(CO_2C_2H_5)_2 + NH_2CONH_2 \longrightarrow$$



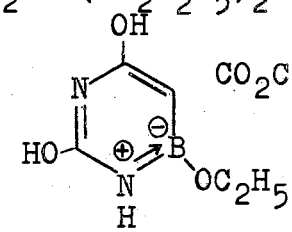
$$+ 2C_2H_5OH$$

Method IV

$$CH_2(CO_2C_2H_5)_2 + NaH \longrightarrow H_2 + NaCH(CO_2C_2H_5)_2$$

$$NaCH(CO_2C_2H_5)_2 + B(OC_2H_5)_3 \longrightarrow (C_2H_5O)_2BCH(CO_2C_2H_5)_2 + NaOC_2H_5$$

$$(C_2H_5O)_2BCH(CO_2C_2H_5)_2 + NH_2CONH_2 \longrightarrow$$



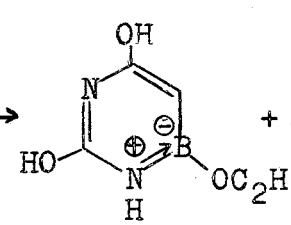
$$+ 2C_2H_5OH$$

Method V

$$CH_2(CO_2C_2H_5)_2 + Mg + C_2H_5OH \longrightarrow H_2 + C_2H_5OMgCH(CO_2C_2H_5)_2$$

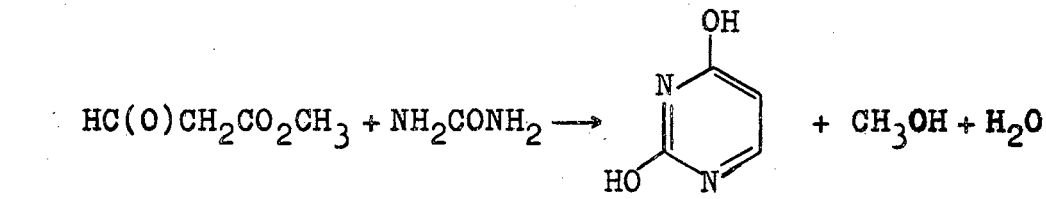
$$C_2H_5OMgCH(CO_2C_2H_5)_2 + B(OC_2H_5)_3 \longrightarrow (C_2H_5O)_2BCH(CO_2C_2H_5)_2 + Mg(OC_2H_5)_2$$

$$(C_2H_5O)_2BCH(CO_2C_2H_5)_2 + NH_2CONH_2 \longrightarrow$$



$$+ 2C_2H_5OH$$

The synthetic routes proposed are analogous to the synthesis of uracil from methyl formylacetate and urea.[30]



They involve the preparation of a functional boronic acid ester that will cyclize with urea to form a uracil-like boron-containing six-membered ring. The preparations of the boronic acid ester intermediates were proposed from known reactions involving displacements of alkoxy groups from boron by organometallic intermediates. The Grignard reagent, $BrMgCH_2CH(OC_2H_5)_2$, of Method I was reported by Yoffe and Nesmeyanov.[31] The organometallic intermediates in the Methods II-V are well known intermediates of various displacement reactions.[30,32] Displacement of alkoxy groups by organometallic reagents, an example of transmetalation, is the most direct method of preparation of boronic acids and their esters.

If the intermediate, $(C_2H_5O)_2BCH_2CH(OC_2H_5)_2$, in Method I cannot be prepared by direct displacement of the ethoxy group from the borate, it may be possible to prepare this intermediate by an indirect route devised by Matteson and Peacock.[49] These workers found that bases would cause elimination of ethylene and bromide ion with substitution of the base for the 2-bromoethyl group of di-n-butyl 2-bromoethaneboronate as shown in the equation below.

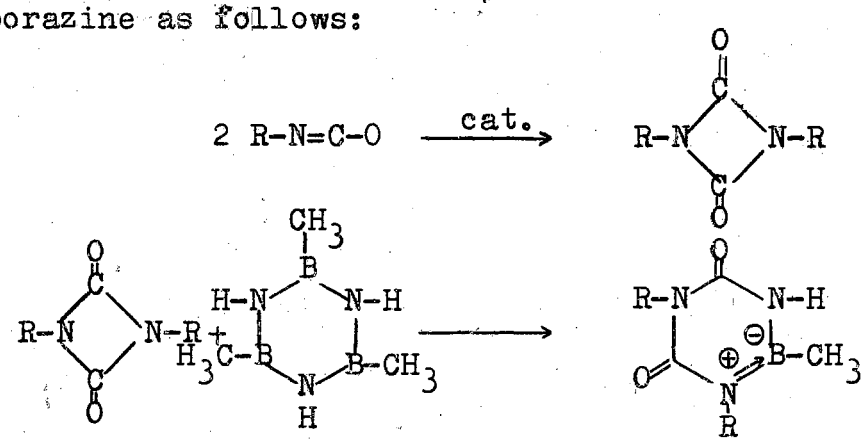
$$BrCH_2CH_2B(OC_4H_9)_2 + Z^- \longrightarrow Br^- + C_2H_4 + ZB(OC_4H_9)_2$$

This reaction provides a route to boronates that otherwise resist synthesis by conventional means.

It may be possible to displace the 2-bromoethyl group from di-n-butylethaneboronate with the Grignard intermediate in Method I. The equation for this reaction is given below.

$$BrMgCH_2CH(OC_2H_5)_2 + BrCH_2CH_2B(OC_4H_9)_2 \longrightarrow MgBr_2 + C_2H_4$$
$$(C_4H_9O)_2BCH_2CH(OC_2H_5)_2$$

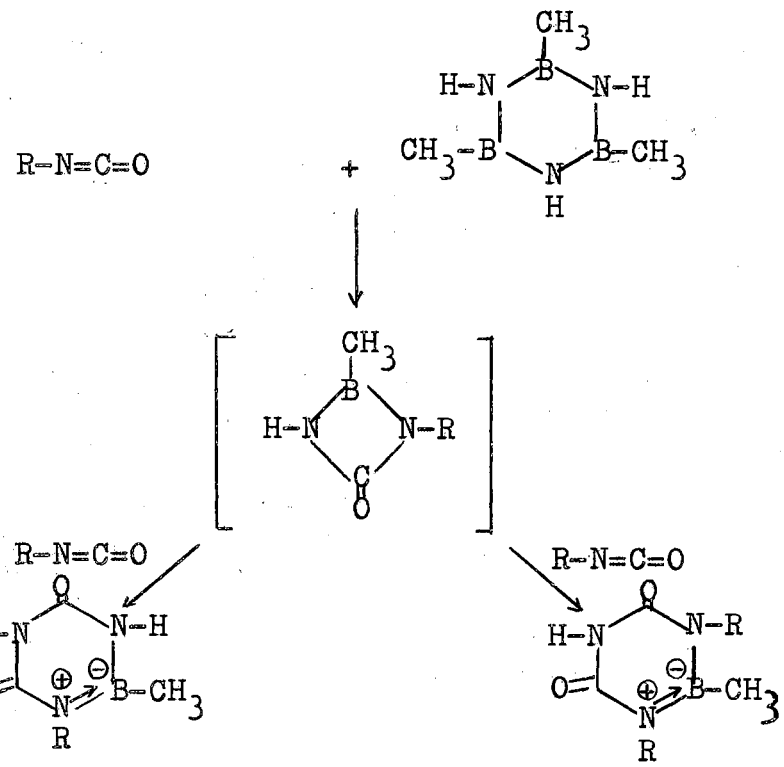
The reaction leading to the formation of the 2-bora-s-triazine ring system has not been studied previously and no mechanistic path has been proposed. One possible route to this compound involves formation of an isocyanate dimer, a uretidinedione, which could undergo cycloaddition with the borazine as follows:



The isocyanate dimers are well known compounds and are formed in the presence of a trialkylphosphine or tertiary amine catalyst.[33] If this mechanism is operative the desired ring system should be formed by addition of

uretidinedione to the borazine. Also only one product is possible from addition of borazine to the isocyanate dimer.

A second route to the compound involves the addition of the isocyanate to the borazine to give a cyclic four-membered ring intermediate that can add another isocyanate molecule to give the 2-bora-s-triazine ring system as follows:

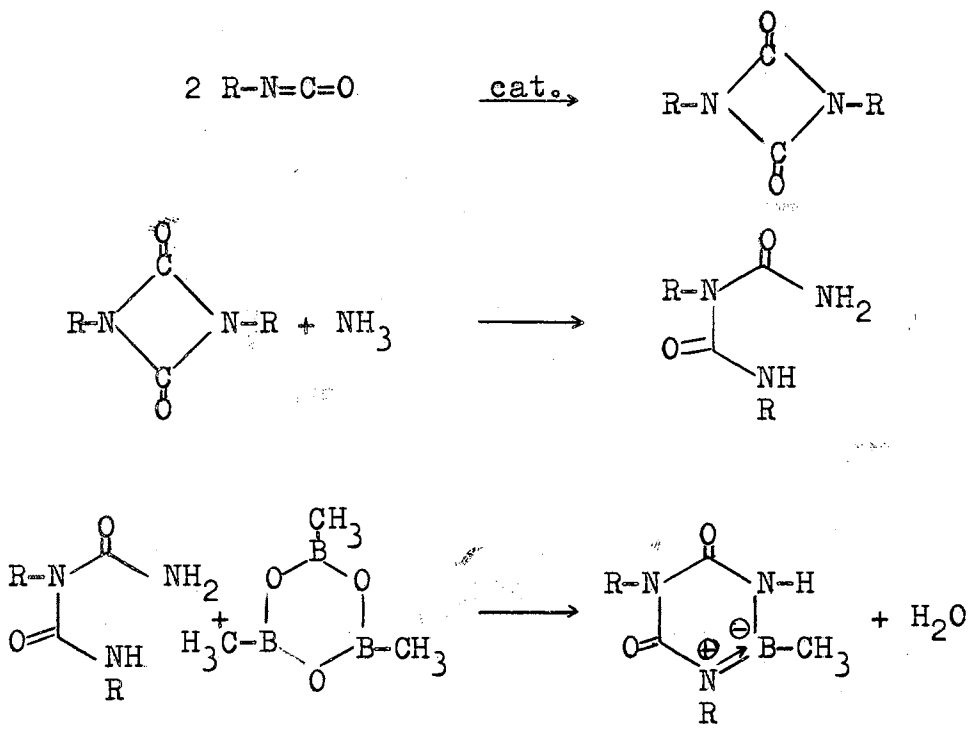


This mechanistic path is similar to the one proposed by Ulrich for the addition of isocyanates to carbon-nitrogen double bonds.[34]

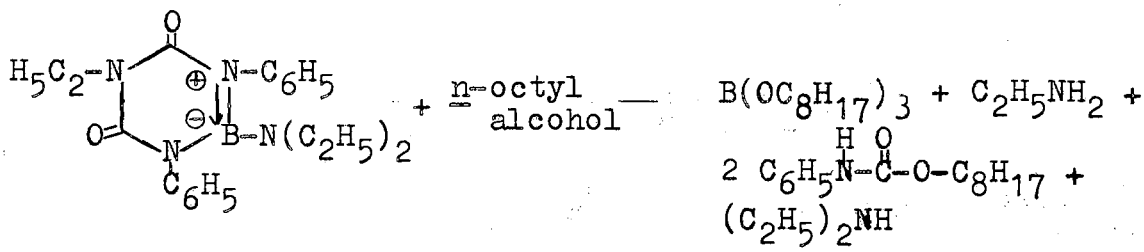
Four-membered cyclic compounds of the type $(RB-NH)_2$ are known.[35] Since the boron-nitrogen bonds in the borazines have double bond character it is not unlikely that this mechanism is operative, in which case, two

products are possible and the possibility for the formation of isomers exists.

If Boone's structure is correct, an independent synthetic route may be possible which would verify the structure. This route is given below.

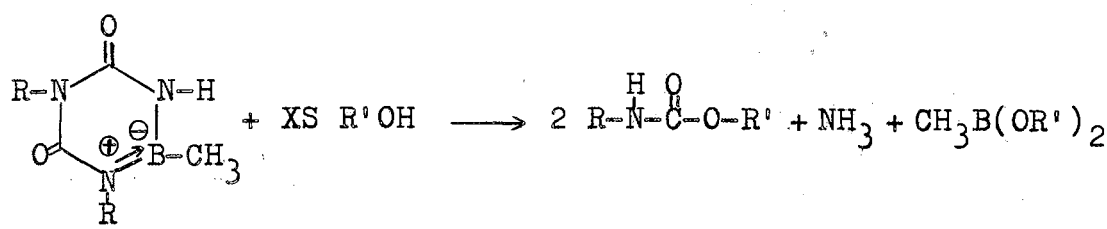


Added proof of structure could be obtained from a study of the solvolysis of the reaction products. Cragg and Lappert[29] have reported the synthesis of 2-(diethylamino)-1,3-diphenyl-5-ethyl-2-bora-(1H,3H,5H)-s-triazine-4,6-dione. The structure of the compound was assigned on the basis of degradation with n-octyl alcohol with subsequent identification of the solvolysis products. Their scheme is outlined below.

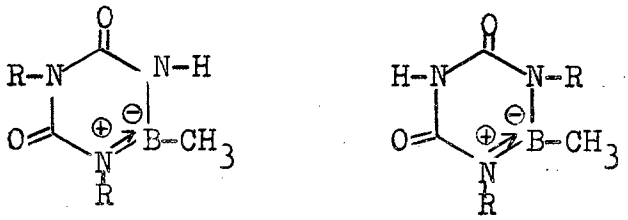


The fate of the boron atom of the 2-(diethylamino)-1,3-diphenyl-5-ethyl-2-bora-(1H,3H,5H)-s-triazine-4,6-dione would not be expected to be the same as that in the compounds we are working with. The exocyclic B-C bond is more stable to oxidation than the exocyclic B-N bond.

The reaction of 1,5-diphenyl-3-ethylbiuret with n-octyl alcohol to give n-octyl N-phenylcarbamate and ethylamine is straightforward and proceeds as expected. If solvolysis of the 2-methyl-1,5-diaryl-2-bora-(1H,3H,5H)-s-triazine-4,6-diones follows this route, it would react as in the equation below.



If solvolysis initially produces a 1,3-diarylbiuret as shown, further solvolysis may be analogous to that of 1,5-diphenyl-3-ethylbiuret. In this case, the products would be those shown. This, however, cannot be assumed and would not distinguish between the following isomers. Very little is known about the solvolysis of biurets with alcohols, so solvolysis of the 1,3-diarylbiurets may not

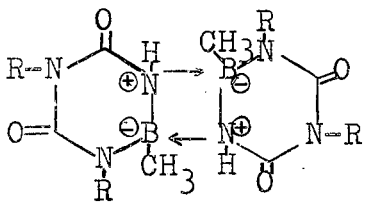


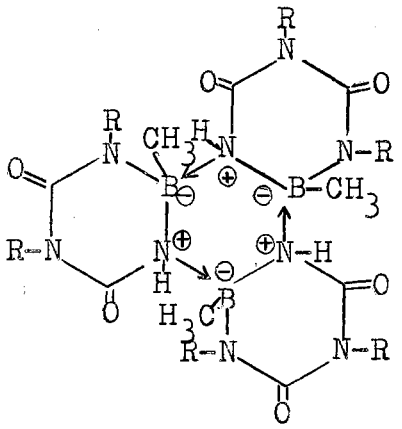
proceed in the manner as shown above.

Interpretation of spectral data for the 2-methyl-1,5-diaryl-2-bora-(1H,3H,5H)-s-triazine-4,6-diones is straightforward. Proton magnetic resonance spectra show an absorption for the aryl protons, for the aryl-methyl protons, for the boron-methyl protons, and for the proton on nitrogen. The absorption of the proton on nitrogen may be difficult to detect due to possible quadrupole broadening by the nitrogen-14 nucleus.[47] This broadening is pronounced in non-polar solvents. The N-H proton of B,B',B"-trimethylborazone in deuterochloroform is detectable only by integration. The presence of the N-H group could be detected by infrared spectroscopy. This will also disclose the presence of other functional groups.

Some boron heterocycles have a tendency to form dimers and trimers.[48] The possibility for this exists in the reaction of isocyanates and borazines. Possible polymers are given on the following page. If these are present, their presence is detectable from molecular weight determinations. The method used in this study is isopiestic and gives a number-average molecular weight, which is very sensitive to the presence of small- and large-molecular-weight impurities. Molecular weights in the range expected

for monomers will indicate the absence of any dimer or trimer.





CHAPTER IV

EXPERIMENTAL

Materials. Acetone (J. T. Baker). Reagent grade was further purified by refluxing through a Soxhlet extractor filled with 4A Molecular Sieves. This was then distilled and kept in a glass-stoppered Erlenmeyer flask, the top of which was fitted with a rubber septum to facilitate removal of acetone by a hypodermic syringe.

Acetone-d_6 (Diaprep). Lot # 671201 was used as received.

Ammonia (Matheson). A lecture bottle was used without further purification.

Ammonium Chloride (Fisher Scientific). Reagent grade was used without further purification.

Boron Trichloride (Matheson). C. P. grade was used without further purification.

n-Butyl Alcohol (Fisher Scientific). Reagent grade was used. It was stored over 4A Molecular Sieves and carefully decanted at the time of use.

t-Butyl Alcohol (Fisher Scientific). Reagent grade was used without further purification.

Bromoacetaldehyde Diethyl Acetal (Aldrich). White label grade was used without further purification.

Bromomethane (Eastman). White label grade was used without further purification.

Chlorobenzene (Fisher Scientific). Reagent grade was used without further purification.

Chloroform-d (Diaprep). Lot # 680701 was used as received.

Chloroform (Fisher Scientific). Spectroanalyzed grade was used without further purification.

Deuterium Oxide (Volk). Lot # 2212, 99.81 mole % was used.

Diethyl Ether (Fisher Scientific). Anhydrous diethyl ether was refluxed over lithium aluminum hydride distilled from it, and stored in a glass-stoppered flask until use.

Di-n-butyl Ether (Eastman). White label grade di-n-butyl ether was distilled from lithium aluminum hydride prior to use.

Diethyl Malonate (J. T. Baker). Reagent grade was distilled at reduced pressure prior to use.

1,4-Dioxane (J. T. Baker). Reagent grade was used after refluxing over sodium six hours and then distilling.

Ethyl Acetate (Fisher Scientific). Reagent grade was used without further purification.

Ethyl Alcohol (U. S. I.). Absolute Pure U.S.P.-N.F. grade was used without further purification.

Ethyl Bromoacetate (Matheson). White label grade was used without further purification.

n-Hexane (Fisher). Spectroanalyzed grade was used

without further purification.

Hydrogen bromide (Matheson). Gas in a lecture bottle was used without further purification.

Magnesium (Fisher Scientific). Grignard grade was used without further purification.

Methyl Alcohol (Fisher Scientific). Reagent grade was used without further purification.

Methyl Ethyl Ketone (Sargent). Technical grade was used without further purification.

Nitrogen (Linde). Lamp grade was used. The gas was dried by passing it through a trap of concentrated sulfuric acid, then through anhydrous calcium chloride.

Phenyl Isocyanate (Eastman). White label grade was used. It was distilled at reduced pressure prior to use.

Quinalizarin (Matheson, Coleman and Bell). White label grade was used without further purification.

Silica Gel HF-254 (E. Merck). Lot # F 2257 was used.

m-Toluidine (Eastman). White label was used without further purification.

o-Toluidine (Eastman). White label grade was used without further purification.

p-Toluidine (Aldrich). White label grade was used without further purification.

m-Tolyl Isocyanate (Eastman). White label grade was distilled at reduced pressure prior to use.

o-Tolyl Isocyanate (Eastman). White label grade was distilled at reduced pressure prior to use.

p-Tolyl Isocyanate (Eastman). White label grade was distilled at reduced pressure prior to use.

Tri-n-butylphosphine (Aldrich). White label grade was used without further purification.

Triethyl Borate (Aldrich). White label grade was used without further purification.

Trimethyl Borate (J. T. Baker). Baker grade was used without further purification.

Tetrahydrofuran (Fisher Scientific). Reagent grade was further purified by refluxing over lithium aluminum hydride, distilling from it and storing in glass-stoppered flasks in the cold until used.

Xylene (J. T. Baker). Reagent grade was further purified by refluxing over sodium, distilling from it, and storing over 4A Molecular Sieves.

Zinc (J. T. Baker). Powdered, reagent grade was used without further purification.

Instrumentation. Proton magnetic resonance spectra were obtained on a Varian Associates Model A-60 Analytical Nuclear Magnetic Resonance Spectrometer. In most cases the solvent used was deuterochloroform with the internal reference being methylene chloride which absorbs at 5.28 ppm vs tetramethylsilane.[59] Infrared spectra were obtained with a Beckman IR-5A spectrophotometer. Solution spectra were obtained using sodium chloride cell windows at a path length of 0.1 mm.

Molecular weight determinations were made using a

Coleman 115 Molecular Weight apparatus. Gas chromatographic analyses were done on an Aerograph Model A-90-P Gas Chromatograph equipped with a thermal conductivity detector. The column was a 11 ft. x $\frac{1}{4}$ in. copper column packed with 5% SE30 on 100/110 mesh Anachrom ABS. The carrier gas was helium at a flow rate of 95 ml. per minute. Mass spectra were obtained on a prototype LKB-9000 Mass Spectrometer-Gas Chromatograph at 70 eV. The mass spectra were obtained as the result of NSF Grant No. GB-7731 which supports the mass spectrometry research program at Oklahoma State University under the direction of Dr. G. R. Waller. Ultraviolet spectra were obtained using a Cary Model 14 Ultraviolet Spectrophotometer.

Determination of Elemental Analyses. Elemental analyses were determined by M-H-W Laboratories, P. O. Box 326, Garden City, Michigan. The analytical data reported for boron-containing compounds are the averages of duplicate determinations; the data reported for all other compounds are the result of single determinations.

Qualitative Determination for Boron. The quinalizarin test,[37] which is highly sensitive, reliable, and readily interpreted, was used exclusively as a test for boron.

A solution of quinalizarin in concentrated sulfuric acid (20 mg./l.) was prepared. The reagent has a red-violet color. The sample to be tested was dissolved in 1 ml. of concentrated sulfuric acid. Boron-containing compounds, in concentrated sulfuric acid, react to form the $(B{=}O)^{+}$ ion.

On addition of the quinalizarin solution to this a color change of red-violet to blue occurs. If boron is present the color change is immediate and the test is sensitive to 0.005 μg. of boric acid per milliliter.[37]

Attempted Preparation of 2-Diethoxyborylacetaldehyde Diethyl Acetal. Bromoacetaldehyde diethyl acetal, 19.70 g. (100 mmoles), in 30 ml. of anhydrous tetrahydrofuran was added dropwise from a 50-ml. pressure-equalizing dropping funnel to 2.50 g. (102 mmoles) of magnesium covered with 10 ml. of anhydrous tetrahydrofuran in a 100-ml. 3-necked flask equipped with a water-cooled condenser. The reaction began on slight warming and continued until all the acetal had been added. The Grignard solution was decanted from the excess magnesium into a 100-ml. pressure-equalizing dropping funnel. This Grignard solution was added dropwise to a solution of triethyl borate, 14.58 g. (100 mmoles), in 50 ml. of anhydrous tetrahydrofuran in a 200-ml. 3-necked flask. This addition was done at -70° and under a static atmosphere of nitrogen. No reaction appeared to occur. On warming the reaction mixture to -40° a white solid formed. The reaction mixture was poured onto 100 ml. of an ice-water mixture in a 500-ml. separatory funnel. The white solid was dissolved by 100 ml. of 1 N hydrochloric acid. The acidic aqueous solution was neutralized with solid sodium bicarbonate, washed with water, and dried over magnesium sulfate. Distillation of the ethereal solution yielded triethyl borate and a yellowish boron-containing

polymeric material that would not distill.

This reaction was repeated with saturated ammonium chloride solution, saturated sodium dihydrogen phosphate or 6 N hydrochloric acid solution in place of the 1 N hydrochloric acid solution. In all cases the result was the same.

Preparation of Di-n-butyl Ethyleneboronate. This material was obtained using the method of Matteson.[46] This preparation involved displacement of an ethoxy group from triethyl borate with vinylmagnesium bromide, transesterification to the butyl ester and isolation of this butyl ester by distillation at reduced pressure. The yield was 6.00 g. (33%); b.p. 45-47° (1.25 mm.); lit.[35] b.p. 30° (0.1 mm.).

Preparation of Di-n-butyl 2-Bromoethaneboronate. The method of Matteson and Liedtke[36] used in the preparation of this compound involved the free-radical addition of hydrogen bromide to the vinyl group of di-n-butyl ethyleneboronate.

The reaction was run in a 10-ml. pear-shaped 3-necked flask equipped with a reflux condenser with a calcium chloride drying tube and an inlet for hydrogen bromide. The boronate, 8.57 g. (47 mmoles), was placed in the flask and hydrogen bromide bubbled continuously through it. The mixture, held at 70° by a water bath, was irradiated for four hours with a 100-watt ultraviolet lamp. The mixture was then cooled and distilled at reduced pressure to yield 4.88 g. (39%) of the boronate; b.p. 63-68° (0.7 mm.); lit.[36] b.p. 48-50° (0.1 mm.).

Reaction of Di-n-butyl 2-Bromoethaneboronate and Acetaldehyde Diethyl Acetal 2-Magnesium Bromide. The boronate, 4.88 g. (18 mmoles), prepared in the previously described experiment was placed in a 50-ml. 3-necked flask with 5 ml. of tetrahydrofuran. The flask was equipped with a mechanical stirrer, a pressure equalizing dropping funnel and a water-cooled condenser fitted with a calcium chloride drying tube. The Grignard reagent, 13.6 ml. of a 1.25 M solution (17 mmoles), was added dropwise to the stirred solution of di-n-butyl 2-bromoethaneboronate. Gas evolution was immediate and after approximately 80% addition of the Grignard reagent a white solid formed, presumably magnesium bromide:etherate. After complete addition the mixture was filtered and the filtrate distilled. The filtrate yielded tetrahydrofuran and tri-n-butyl borate and an undistillable, amorphous boron-containing tar. This reaction was repeated with the same results each time.

Attempted Preparation of Ethyl 2-Diethoxyborylacetate. The procedure followed for this reaction was essentially the preparation of the Reformatsky reagent given in the Organic Synthesis.[32] The reactive intermediate, $BrZnCH_2CO_2C_2H_5$, is generated and reacts in situ. The reaction was run in a 150-ml. 3-necked flask equipped with a mechanical stirrer, water-cooled condenser with a calcium-chloride drying tube and a pressure-equalizing addition funnel. The ethyl bromoacetate, 16.7 g. (100 mmoles), and triethyl borate, 14.6 g. (100 mmoles), were placed in the

50-ml. addition funnel with 16 ml. of benzene and 5 ml. of ethyl ether. A small amount of this solution was added to 7.85 g. (120 mmoles) of powdered zinc. A reaction began and the remainder of the solution was added dropwise with stirring of the reaction mixture. Two layers formed as the addition neared completion, a dark lower layer and a yellow-green top layer. After addition was complete the mixture was stirred one hour.

The mixture was decomposed with 50 ml. of cold 10% sulfuric acid, and the separated benzene layer was extracted with two 6-ml. portions of 5% sulfuric acid, then two 6-ml. portions of water. The combined acid and water extracts were extracted with two 15-ml. portions of ether. The ether and benzene layers were combined and dried overnight over magnesium sulfate.

Distillation at atmospheric pressure of the dried extracts gave an ether fraction at 34-36°, an intermediate ether benzene fraction at 36-68°, and a benzene fraction at 68-78°. The pot residue was subjected to reduced pressure giving a fraction that distilled at 54° at 4 mm. This fraction gave a negative boron test and had an ester-like odor. Proton magnetic resonance and infrared spectra were identical with those for ethyl acetoacetate. A polymeric residue remaining in the pot gave a positive boron test.

Attempted Preparation of Diethyl 2-Diethoxyboryl-malonate from Diethyl Sodiomalonate and Triethyl Borate. Diethyl malonate, 16.0 g. (100 mmoles), and 50 ml. of

anhydrous ether were placed in a 200-ml. 3-necked flask equipped with a water-cooled condenser. Sodium hydride, 4.3 g. (100 mmoles), as a 55.6% suspension, was added in small portions. Hydrogen was evolved but the diethyl sodiomalonate that formed was insoluble in ether.

The procedure of Matteson and Cheng[17] for the preparation was next attempted. Diethyl sodiomalonate, (100 mmoles), was prepared from sodium t-butoxide and diethyl malonate in t-butyl alcohol. The sodium t-butoxide was prepared from 4.3 g. (100 mmoles) sodium hydride (as a 55.6% suspension) and 50 ml. of t-butyl alcohol. The t-butyl alcohol solution of diethyl sodiomalonate was added dropwise from a pressure-equalizing funnel to 14.6 g. (100 mmoles) of triethyl borate in a 200-ml. 3-necked flask equipped with a mechanical stirrer. The reaction was stirred overnight and worked up by addition of 25 ml. of water. The water layer was separated and extracted with three 25-ml. portions of ether. The ether layers were combined with the initial organic phase and dried over magnesium sulfate. Distillation of the organic phase gave ether, t-butyl alcohol, ethyl alcohol, and diethyl malonate.

Attempted Preparation of Diethyl 2-Diethoxyboryl-malonate from Diethyl Potassiomalonate and Triethyl Borate. This reaction was attempted using the same conditions as the previously discussed experiment. The potassium t-butoxide was prepared from t-butyl alcohol and potassium metal. The results were the same as in the previously

discussed experiment.

Attempted Preparation of Diethyl 2-Diethoxyboryl-malonate from Ethyl Ethoxymagnesiummalonate and Triethyl Borate. The reagent, ethyl ethoxymagnesiummalonate, was prepared according to the Organic Synthesis[38] preparation, except that it was prepared on a 100 mmole scale. The solid ethyl ethoxymagnesiummalonate was dissolved in 25 ml. of anhydrous ether and added through a pressure-equalizing dropping funnel to 14.6 g. (100 mmoles) triethyl borate in 25 ml. of anhydrous ether in a 200-ml. 3-necked flask equipped with a mechanical stirrer. The workup procedure was that of Matteson and Cheng[17] discussed earlier. No boron-containing compounds were obtained on workup.

Preparation of B,B',B"-Trichloroborazine. The synthetic procedure used was a modified version of the method of Laubengayer and Brown.[39] The reaction vessel in the reaction was a 2-liter 3-necked flask equipped with a mechanical stirrer, a Dewar-type dry-ice condenser fitted with a U-shaped phosphorus pentoxide drying tube, and an inlet for the boron trichloride gas. Finely ground ammonium chloride, 25.8 g. (480 mmoles), was added to the flask; 300 ml. of chlorobenzene were added and this mixture was stirred and heated to reflux. Boron trichloride was added directly from a lecture bottle through a two-feet long piece of Teflon® tubing. The gas was added at a slow enough rate that it did not pass through the condenser. If addition was too fast boron trichloride fumes could be

detected at the outlet of the drying tube. Addition was continued for eight hours at which time the liquid was cooled and poured off into a 500-ml. round bottomed flask and the solvent distilled at reduced pressure (55° at 60 mm). The solid that remained after the solvent was removed was sublimed at 40°. Sublimations were accomplished by evacuating the apparatus with sample in it and then closing off the apparatus at reduced pressure. The purified crystals were condensed on the Dry Ice cold finger in the apparatus and transferred under nitrogen in a polyethylene glove bag. The white crystals had a m.p. of 81-82° (sealed capillary); lit.[39] m.p. 83.9-84.5°.

The recovered chlorobenzene was returned to the reaction flask, more ammonium chloride was added and reaction started again. The cycle was repeated until 150 g. of the borazine were obtained. Yields were not calculated since the total amount of boron trichloride or ammonium chloride used was not known. The yield per cycle was approximately 20 g.

Preparation of B,B',B"-Trimethylborazine. This preparation was done according to the procedure described by Boone and Willcockson;[40] the scale was, however, one-fourth of theirs. The reaction vessel was a 3-necked flask equipped with a water-cooled condenser fixed with a phosphorus pentoxide U-shaped drying tube, a 250-ml. pressure-equalizing funnel and a mechanical stirrer. The B,B',B"-trichloroborazine, 46.0 g. (250 mmoles), was placed

in the flask with 120 ml. of anhydrous ether. The contents of the flask were cooled in 0° by an ice bath and held at this temperature throughout the reaction. This was followed by the addition with stirring of 341 ml. (a 200-ml., then a 141-ml. portion) of a 2.2 M ether solution of methylmagnesium bromide (750 mmoles). Addition required approximately three hours. The mixture was then left at room temperature for twenty hours with no stirring. The condenser was removed from the flask and the flask was fitted with a short, glass helices-packed column. A cold finger type distilling head was added; benzene was then added while ether was continuously distilled. (Caution! Byproducts of this reaction are pyrophoric boranes which distill with the first 100 ml. of ether. If this fraction is exposed to the air the boranes will ignite the ether.) When the temperature of the distillate reached 80° the distillation was stopped and the benzene slurry was filtered through a large Buchner funnel using a mat of glass wool to trap the solid. The solid was then washed with two 25-ml. portions of benzene and the filtrate was distilled at atmospheric pressure through an eighteen-inch spiral column to remove the benzene. The remaining mixture was distilled at reduced pressure to yield 9.45 g. (35%) of B,B',B"-trimethylborazine, b.p. 91.5° (245mm.); lit.[40] b.p. 95.2-95.8° (258 mm.); m.p. 30.5-31.5° (sealed capillary); lit.[40] m.p. 31.4-32.4°.

Preparation of 2-Methyl-1,5-diphenyl-2-bora-(1*H*,3*H*,5*H*)-*s*-triazine-4,6-dione. Phenyl isocyanate, 7.15 g. (60 mmoles), and B,B',B"-trimethylborazine, 1.35 g. (11 mmoles), were placed in a 30-ml. 1-necked pear-shaped flask equipped with a water-cooled condenser. Nitrogen was brought in through a line equipped with a T-joint and mercury pressure release valve. A small positive pressure of nitrogen was placed on the reaction and then the nitrogen was turned off. This insured that the reaction remained under nitrogen throughout its duration without fear of loss of material from the mixture by a nitrogen stream. The reaction mixture was then heated to 82° for 42 hours. Under these conditions no reaction was evident. It was then heated at gentle reflux for twelve hours. On cooling, the reaction mixture solidified to an amber glass. The condenser was then replaced with a vacuum-type micro distillation apparatus and this was evacuated to 0.5 mm. The mixture was slowly heated to remove the volatile materials. A small amount of volatile material was trapped in a Dry Ice trap. Attempts to purify the product further were futile. Therefore no melting points are recorded. Recrystallizations were attempted in an inert atmosphere box using a variety of anhydrous solvents, singly and in combination. Among the solvents tried was diethyl ether, di-*n*-butyl ether, toluene, benzene, *n*-hexane, and *n*-heptane. Analyses and spectra were obtained on the reaction mixture. A yield of 5.48 g. (66%) was obtained. Infrared ($CDCl_3$) 3401 (N-H),

3049 (Ar-H), 1706 (C=O), 1448 (B-N), 1233 $cm.^{-1}$ (C-N); proton magnetic resonance ($CDCl_3$)δ 0.25 (m, 3.3, B-C$\underline{H}_3$), and 7.45 ppm (m, 10.0, Ar-$\underline{H}$).

Anal. Molecular weight calculated for $C_{15}H_{14}N_3O_2B$: 279.12. Found: 276.14.

Preparation of 2-Methyl-1,5-di-m-tolyl-2-bora-(1H,3H,5H)-s-triazine-4,6-dione. This reaction was carried out using the same conditions as those for the reaction of phenyl isocyanate and B,B',B"-trimethylborazine. m-Tolyl isocyanate, 7.98 g. (60 mmoles), and B,B',B"-trimethylborazine, 1.35 g. (11 mmoles), were heated together as previously described. The product, 8.72 g. (94% yield), was an amber-colored glass. Infrared ($CDCl_3$) 3390 (N-H), 3030 (Ar-H), 1704 (C=O), 1426 (B-N), and 1203 $cm.^{-1}$ (C-N); proton magnetic resonance ($CDCl_3$)δ 0.25 (m, 2.6, B-C$\underline{H}_3$), 2.45 (s, 5.6, Ar-C$\underline{H}_3$), and 7.25 ppm (m, 8.0, Ar-$\underline{H}$).

Anal. (Table I) Calcd. for $C_{17}H_{18}N_3O_2B$: C, 66.47; H, 5.90; N, 13.68; B, 3.52. Found: C, 66.31; H, 5.91; N, 13.34; B, 3.14. Molecular weight calcd. for $C_{17}H_{18}N_3O_2B$; 307.17. Found: 295.54.

Preparation of 2-Methyl-1,5-di-o-tolyl-2-bora-(1H,3H,5H)-s-triazine-4,6-dione. The conditions used for this reaction were the same as those for the reaction of phenyl isocyanate and B,B',B"-trimethylborazine. o-Tolyl isocyanate, 7.98 g. (60 mmoles), and B,B',B"-trimethylborazine, 1.35 g. (11 mmoles), were heated as previously described. The product, 8.42 g. (91% yield), was an amber-colored glass.

Infrared ($CDCl_3$) 3378 (N-H), 3012 (Ar-H), 1689 C=O), 1426 (B-N), and 1276 cm^{-1} (C-N); proton magnetic resonance ($CDCl_3$) δ 0.17 (m, 2.6, B-CH_3), 2.40 (m, 5.6, Ar-CH_3), and 7.37 ppm (m, 8.0, Ar-H).

Anal. (Table I) Calcd. for $C_{17}H_{18}N_3O_2B$: C, 66.47; H, 5.90; N, 13.68; B, 3.52. Found: C, 66.34; H, 5.88; N, 13.20; B, 3.26. Molecular weight calcd. for $C_{17}H_{18}N_3O_2B$: 307.17. Found: 303.51.

Preparation of 2-Methyl-1,5-di-p-tolyl-2-bora-(1H,3H,5H)-s-triazine-4,6-dione. This reaction was performed using the same conditions as those in the previous three examples. p-Tolyl isocyanate, 7.98 g. (60 mmoles), and B,B'-B"-trimethylborazine, 1.35 g. (11 mmoles), were heated as previously described. The product, 8.25 g. (89% yield) was an amber-colored glass. Infrared (Figure 1) ($CDCl_3$) 3401 (N-H), 3021 (Ar-H), 1695 (C=O), 1408 (B-N), 1233 (C-N); proton magnetic resonance (Figure 2) ($CDCl_3$) δ 0.24 (s, 2.4, B-CH_3), 2.57 (s, 6.0, Ar-CH_3), and 7.37 ppm (m, 8.0, Ar-H).

Anal. (Table I) Calcd. for $C_{17}H_{18}N_3O_2B$: C, 66.47; H, 5.90; N, 13.68; B, 3.52. Found: C, 66.34; H, 5.88; N, 13.20; B, 3.26. Molecular weight calcd. for $C_{17}H_{18}N_3O_2B$: 307.17. Found: 312.17.

Preparation of 1,3-Diphenyl-2,4-uretidinedione. The preparation of 1,3-diphenyl-2,4-uretidinedione was performed according to the procedure of Raiford and Freyermuth.[41] Phenyl isocyanate, 10 g. (84 mmoles), was placed in a 50-ml. glass-stoppered Erlenmeyer flask. Three to four drops of tri-n-butylphosphine were added; crystals formed

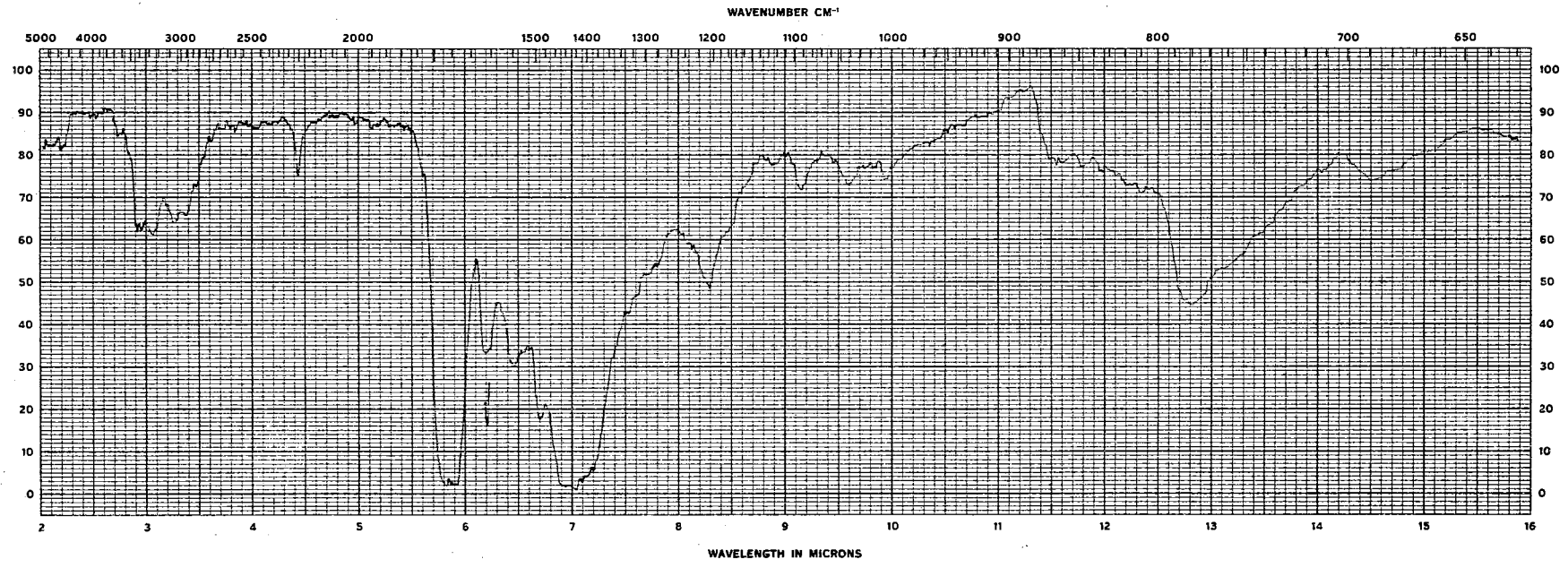


Figure 1. Infrared Spectrum of 2-Methyl-1,5-di-p-tolyl-(1H,3H,5H)-s-triazine-4,6-dione from p-Tolyl Isocyanate and B,B',B''-Trimethylborazine

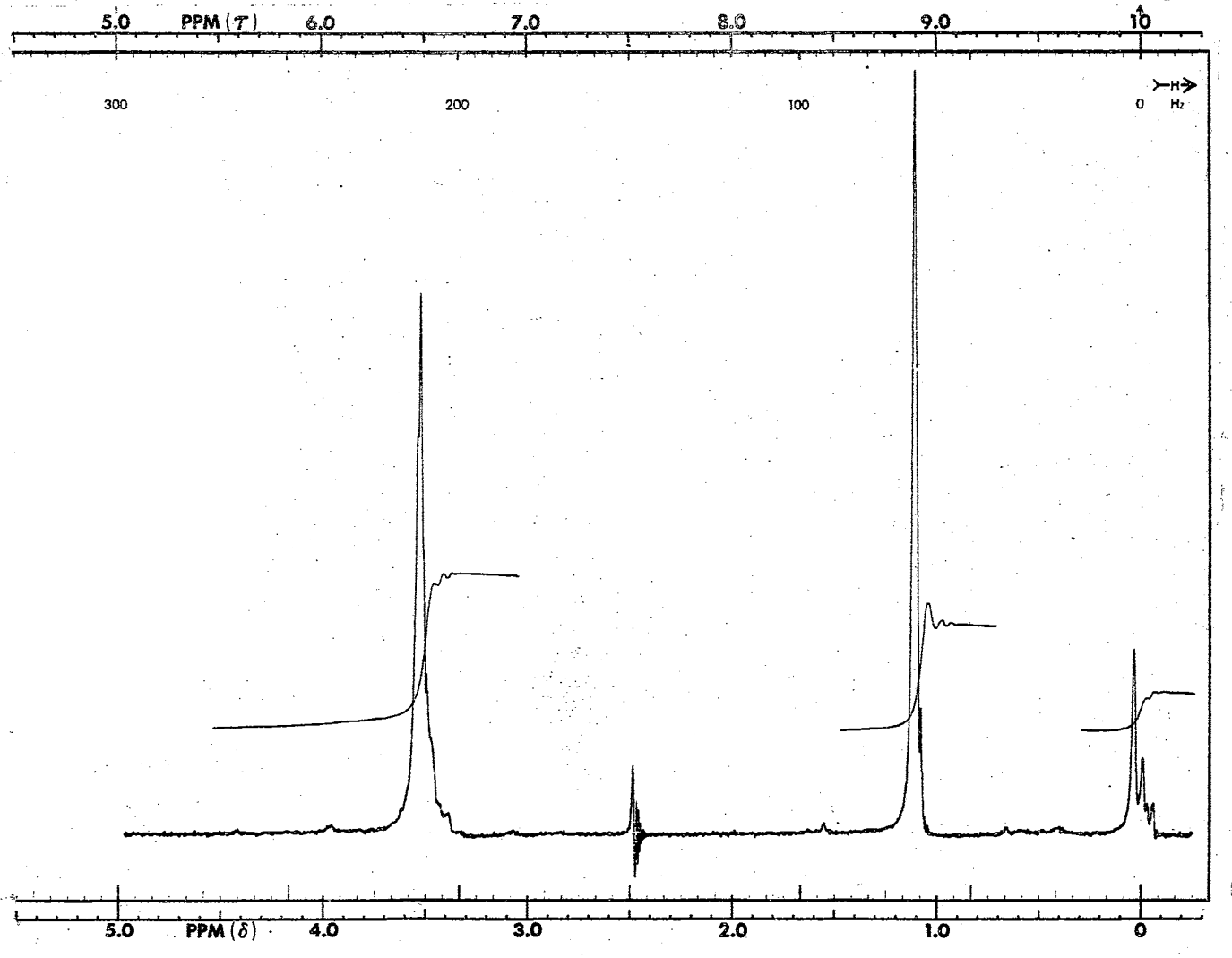


Figure 2. Proton Magnetic Resonance Spectrum of 2-Methyl-1,5-di-p-tolyl-(1H,3H,5H)-s-triazine-4,6-dione

immediately and after two to three minutes the liquid had completely solidified. After two hours at room temperature the solid was placed in a Buchner-type funnel and washed with 5 ml. of ether. The product was then recrystallized from benzene and 8.70 g. (87% yield) of the dimer was obtained; m.p. 181-182°; lit.[41] m.p. 175°.

Preparation of 1,3-Di-m-tolyl-2,4-uretidinetione. The procedure of Raiford and Freyermuth[41] was followed as described in the previous experiment. The yield of 1,3-di-m-tolyl-2,4-uretidinedione from 10 g. (75 mmoles) of m-tolyl isocyanate was 9.4 g. (94%); m.p. 167-168° (di-n-butyl ether), lit.[41] m.p. 159-160°.

Preparation of 1,3-Di-p-tolyl-2,4-uretidinedione. The procedure of Raiford and Freyermuth[41] was followed with tri-n-butylphosphine as catalyst. The yield of the uretidinedione from 10 g (75 mmoles), of p-tolyl isocyanate was 9.7 g. (97%); m.p. 195-195.5° (di-n-butyl ether), lit.[41] m.p. 185°.

Attempted Preparation of 1,3-Di-o-tolyl-2,4-uretidinedione. o-Tolyl isocyanate, 10 g. (75 mmoles), was placed in a 50-ml. glass-stoppered flask with 3-5 drops of tri-n-butylphosphine as catalyst. No visible evidence of reaction could be detected; no crystals were formed and after two weeks an oil was obtained. Trituration of the oil with 10 ml. of n-hexane gave a solid. The solid was recrystallized from a n-hexane:n-butyl ether mixture. The crystals obtained melted over a very broad range (121-135°)

and repeated recrystallizations did not improve the melting point. Thin-layer chromatography on Eastman Chromagram sheets, type K 301R, using a n-hexane:ethyl acetate (10:2) mixture for development showed two compounds.

Preparation of 1,3-Diphenylbiuret. 1,3-Diphenylbiuret was prepared using a modification of the procedure of Raiford and Freyermuth.[41] The dimer of phenyl isocyanate, 2.38 g. (10 mmoles), in 25 ml. of a saturated solution of ammonia in absolute ethyl alcohol (large excess) were stirred together in a glass-stoppered 50-ml. Erlenmeyer flask. The progress of the reaction was followed by thin-layer chromatography on Eastman Chromagram strips developed with chloroform. After 4-5 minutes the reaction had gone to completion. (Caution must be exercised because in the presence of the excess ammonia further addition of ammonia will occur to give side products. If the reaction is left for 48 hours, analytically pure sym-diphenylurea precipitates.) After the reaction was completed the excess ammonia and ethyl alcohol were evaporated in vacuum. The white solid that remained was recrystallized from ethyl acetate to yield 2.10 g. (83%), m.p. 176°, lit.[42] m.p. 165°.

Preparation of 1,3-Di-m-tolylbiuret. The procedure used in this preparation was that of Raiford and Freyermuth[41] discussed previously. The dimer of m-tolyl isocyanate, 2.66 g. (10 mmoles), was placed in a 50-ml. glass-stoppered Erlenmeyer flask with 10 ml. of absolute ethyl alcohol and 10 ml. of a saturated solution of ammonia in absolute ethyl

alcohol. This was stirred approximately 5 minutes; thin-layer chromatography showed no starting material remaining at this time and the solvent and ammonia were removed by vacuum. The solid that remained was recrystallized from methyl ethyl ketone:n-hexane (40:60). The yield was 2.22 g. (78%), m.p. 115-116; infrared (KBr) 3436 (N-H), 3311 (N-H), 3040 (Ar-H), 1712 (C=O), 1664 (amide I), and 1613 (amide II); proton magnetic resonance ($CDCl_3$) δ 2.27 and 2.32 (s, s, 6.2, Ar-CH_3), 5.63 (s, 2.1, -NH_2), 7.02 (m, 8.9, Ar-H), and 10.48 ppm (s, 1, N-H). The singlets at δ 5.63 and 10.48 ppm would not exchange with deuterium oxide alone, but on addition of deuterium chloride/deuterium oxide, exchange occurred readily with appearance of a new peak at δ 6.08 ppm. This compound has not been described in the literature.

Anal. (Table II) Calcd. $C_{16}H_{17}N_3O_2$: C, 67.38; H, 6.05; N, 14.83. Found: C, 68.55; H, 6.40; N, 15.05. Molecular weight calcd. for $C_{16}H_{17}N_3O_2$: 283.34. Found: 276.17.

Preparation of 1,3-Di-p-tolylbiuret. The procedure as previously described for the preparation of 1,3-di-m-tolylbiuret was used to obtain this compound. 1,3-Di-p-tolyl-2,4-uretidinedione, 2.66 g. (10 mmoles), 10 ml. of absolute ethyl alcohol, and 10 ml. of a saturated ammonia in ethyl alcohol solution were added together in a 50-ml. glass-stoppered Erlenmeyer flask. The mixture was stirred approximately 5 minutes at which time thin-layer chromatography showed none of the starting material.

Evaporation of solvent and ammonia in vacuum left a white solid which was recrystallized from ethyl acetate. The yield was 2.08 g. (74%), m.p. 185-186°; infrared (Figure 3) (KBr) 3509 (N-H), 3401 (N-H), 3125 (Ar-H), 1712 (C=O), 1681 (amide I), 1597 (amide II); proton magnetic resonance (Figure 4) ($CDCl_3$) δ 2.43 and 2.35 (s, s, 5.9, Ar-$C\underline{H}_3$), 5.77 (s. 1.7, -$N\underline{H}_2$), 7.28 (m, 8.1, Ar-$\underline{H}$) and 10.33 ppm (s, 1.0, N-$\underline{H}$). The singlets at δ 5.77 and 10.33 ppm were not exchangable with deuterium oxide alone but on addition of deuterium chloride/deuterium oxide, exchange occurred. This compound is not described in the chemical literature.

Anal. Calcd. for $C_{16}H_{17}N_3O_2$: C, 67.38; H, 6.05; N, 14.83. Found: C, 68.34; H, 6.13; N, 14.97. Molecular weight calcd. for $C_{16}H_{17}N_3O_2$: 283.34. Found: 286.95.

Preparation of Methaneboronic Anhydride-Pyridine Complex. This material was obtained by the method of Matteson.[43] The reaction vessel was a 3-liter 3-necked flask equipped with a mechanical stirrer and a one-liter pressure-equalizing addition funnel. Trimethyl borate, 104 g. (1 mole), was placed in the flask with 500 ml. of anhydrous ether and this was cooled to -55° with a Dry Ice-ethyl alcohol bath. To this was added with stirring 770 ml. of a 1.2 M solution of methylmagnesium bromide. After addition was complete the mixture was allowed to warm up to 0° and then it was acidified with 340 ml. of 3 N hydrochloric acid solution saturated with sodium chloride. The

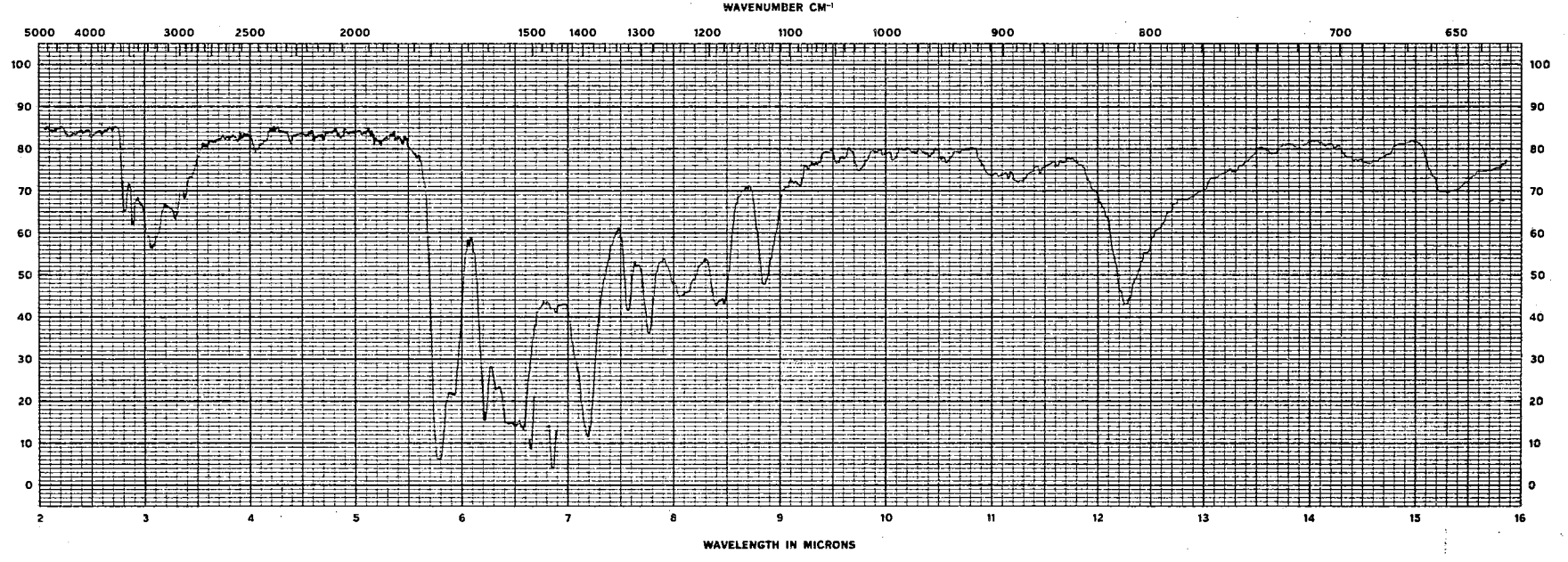


Figure 3. Infrared Spectrum of 1,3-Di-p-tolybiuret

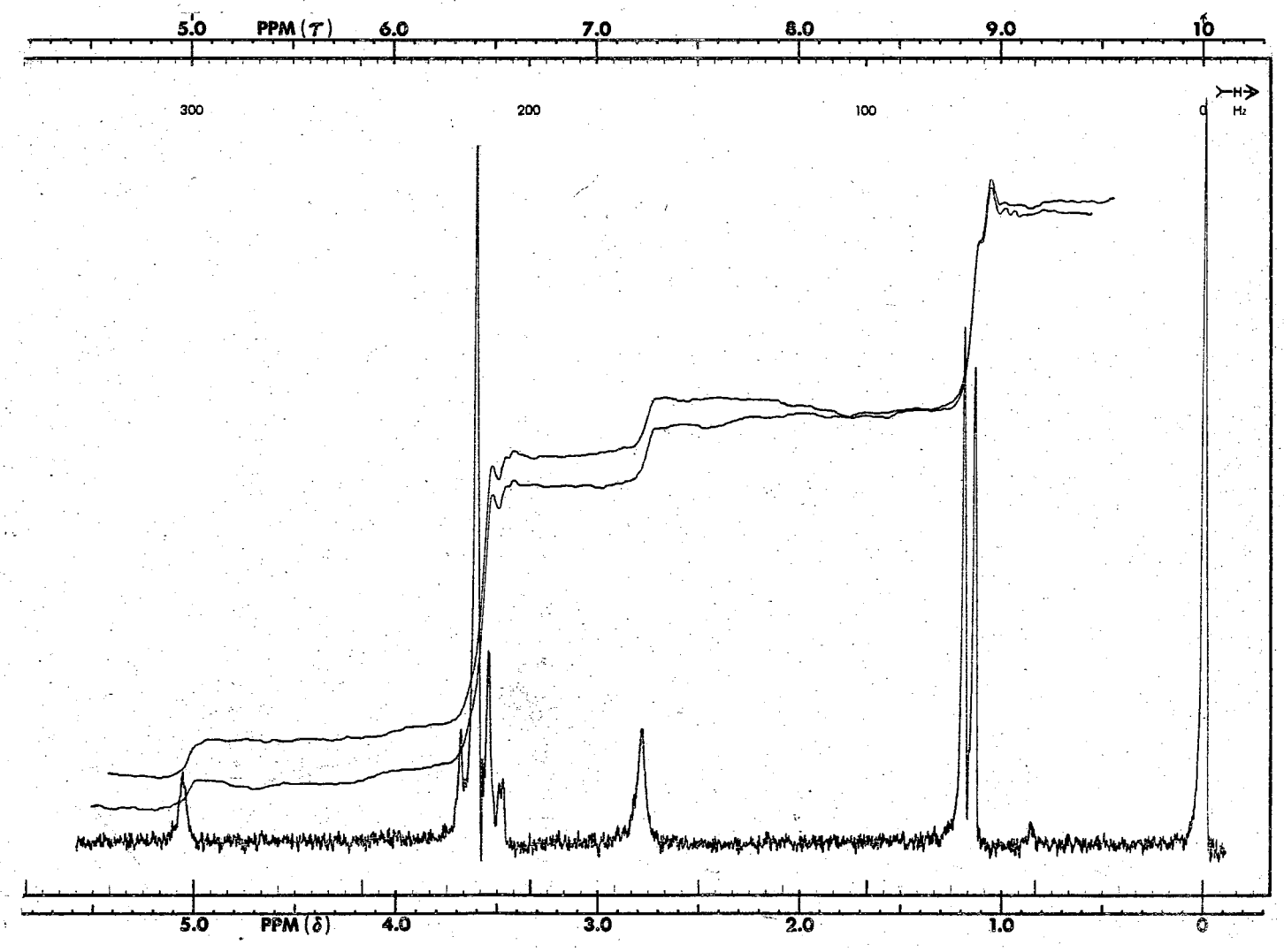


Figure 4. Proton Magnetic Resonance Spectrum of 1,3-Di-p-tolylbiuret

reaction mixture was then extracted with three 100-ml. portions of n-butyl alcohol. This organic phase was washed with 58 ml. of a saturated solution of sodium chloride, extracted twice more with solutions of 7.7 g. of sodium hydroxide in 15 ml. of water, and extracted with 58 ml. of water.

These basic extracts were combined and concentrated to a frothy mass by evaporating the water at 60-70° at 20 mm. To this was added 154 ml. of pyridine, 19 ml. of water, and a solution of pyridine bisulfate made from 31 ml. of pyridine and 42.5 ml. of concentrated sulfuric acid. This mixture was refluxed two hours, cooled and filtered to remove sodium sulfate. The sodium sulfate was washed with 125 ml. of benzene and this filtrate was distilled. The water and benzene azeotroped off first; then pyridine distilled. After the pyridine was removed the residue was distilled at reduced pressure to yield the methaneboronic anhydride-pyridine complex. The yield of the compound was 44. g. (72%), b.p. 137-137.5° (695 mm.); lit.[43] b.p. 139-143° (700 mm.).

The Reaction of 1,3-Diphenylbiuret and Methaneboronic Anhydride-Pyridine Complex. The reaction vessel for this reaction was a 65-ml. pear-shaped flask equipped with an efficient condenser and a Dean-Stark trap. The reaction was run under a static atmosphere of nitrogen as discussed previously. The biuret, 7.65 g. (30 mmoles), anhydride complex, 2.25 g. (11 mmoles), and 50 ml. of xylene were

refluxed for 18 hours. Water was observed as a cloudy distillate which azeotroped over into the trap with xylene. The xylene, water, and pyridine were removed from the trap and more xylene was removed until it had all distilled into the trap. The pot residue was then heated to > 150° under vacuum. A white crystalline solid formed around the top of the flask; an amber glass remained in the bottom of the flask. This product gave a positive boron test and its infrared spectrum was identical with the product of the reaction of phenyl isocyanate and borazine. Infrared ($CDCl_3$) 3401 (N-H), 3257, 3049 (Ar-H), 1706 (C=O), 1443 (B-N), and 1233 (C-N) cm^{-1}. The yield was 3.36 g. (35%).

The Reaction of 1,3-Di-p-tolylbiuret and Methaneboronic Anhydride-Pyridine Complex. This preparation was performed as in the previously described experiment except that the quantities were scaled down. The biuret, 2.83 g. (10 mm.), anhydride complex, 0.68 g. (3.3 mm.), and 50 ml. xylene were refluxed 18 hours. The reaction product, isolated as previously described, gave a positive boron test and its infrared spectrum was identical with the product from p-tolyl isocyanate and B,B',B"-trimethylborazine. The yield was 1.20 g. (34%). Infrared (Figure 5) ($CDCl_3$) 3401 (N-H), 3021 (Ar-H), 2924, 1695 (C=O), 1439 (B-N) and 1233 (C-N) cm^{-1}.

The Reaction of 1,3-Di-m-tolylbiuret and Methaneboronic Anhydride-Pyridine Complex. The biuret, 2.83 g. (10 mmoles), anhydride complex, 0.68 g. (3.3 mmoles), and 50 ml. of

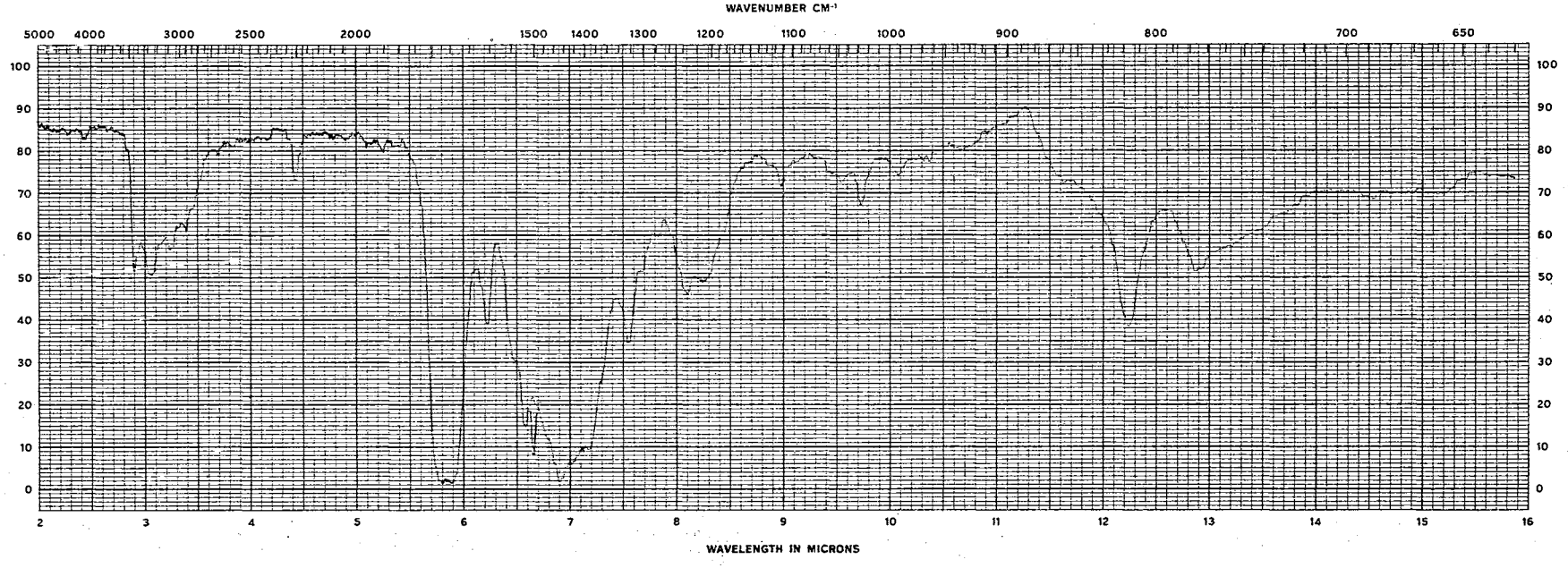


Figure 5. Infrared Spectrum of 2-Methyl-1,5-di-p-tolyl-(1H,3H,5H)-s-triazine-4,6-dione from 1,3-Di-p-tolylbiuret and Methaneboronic Anhydride

xylene were reacted and the product isolated as previously described. The product gave a positive boron test and its infrared spectrum was identical with that of the product of the m-tolyl isocyanate and B,B',B"-trimethylborazine reaction. The yield was 0.94 g. (27%). Infrared ($CDCl_3$) 3344 (N-H), 3021 (Ar-H), 2932, 1689 (C=O), 1428 (B-N), and 1205 (C-N) cm^{-1}.

Solvolysis of 2-Methyl-1,5-diphenyl-2-bora-(1H,3H,5H)-s-triazine-4,6-dione. n-Butyl alcohol (20 ml.) and 2.79 g. (10 mmoles) of the boron compound were placed in a 1-necked, pear-shaped flask with a standard taper 10/30 opening for nitrogen. The flask was fitted with a water-cooled condenser with a calcium chloride drying tube. The reaction mixture was refluxed one hour under a stream of dry nitrogen and cooled to room temperature and the liquid removed under vacuum. The liquid was caught in a Dry Ice cold trap and the remaining solid was refluxed for 12 hours more with 20 ml. of n-butyl alcohol. After 12 hours the liquid was removed under vacuum as previously described and added to the first batch. The liquid gave a positive boron test and the solid gave a negative test. The liquid was distilled at atmospheric pressure through an 18-inch glass spiral column until approximately 5 ml. remained in the pot. The pot residue gave a positive boron test and vapor phase chromatographic analysis showed the boron compound to be di-n-butyl methaneboronate. Comparison with authentic samples using thin-layer chromatography showed the solid to

be a mixture of phenylurea, 1,3-diphenylbiuret, sym-diphenylurea, n-butyl N-phenylcarbamate, and an unidentified compound.

This unidentified compound was isolated by placing 200 mg. of the solid mixture in 0.5 ml. of acetone. Aliquot ml. portions of this solution were streaked on each of four plates prepared with silica gel for preparative thin-layer chromatography. Each plate was developed four times using n-hexane:ethyl acetate (10:2). The band to be isolated (second from the top of the plate) was scraped from each plate and placed in a fine fritted glass filter. The silica gel was washed with 3 10-ml. portions of absolute methyl alcohol. The methyl alcohol solution, on evaporation of the solvent under vacuum, yielded 28 mg. (14% w/w) of a white solid. Infrared ($CDCl_3$) 3412 (N-H), 3246 (N-H), 2958 (C-H), 1718 (C=O), 1315, 1226, 1104, 1082, 870 and 776 $cm.^{-1}$; proton magnetic resonance (28 mg./0.5 ml. $CDCl_3$) δ 0.97 and 1.57 (m, 7, $-CH_2-CH_2-CH_3$), 4.17 (t, 2, $O-CH_2-$), 7.27 (m, 4.8, Ar-H), and 9.90 ppm (s, 1.1, Ar-NH); mass spectrum (70 eV) m/e for P^+, $(P+1)^+$ and $(P+2)^+$, (rel. intensity); 236 (100), 237(14), and 238(3). For the parent ion, $P^+ = 236$, according to Beynon's[44] table a molecular formula of $C_{12}H_{16}N_2O_3$ will give a $(P+1)^+$ ion of relative intensity of 14.10 and a $(P+2)^+$ ion of relative intensity of 1.52 which is in good agreement with relative intensities obtained for this compound.

Solvolysis of 2-Methyl-1,5-di-o-tolyl-, -di-m-tolyl-, and -di-p-tolyl-2-bora-(1H,3H,5H)-s-triazine-4,6-diones with n-Butyl Alcohol. Each of these isomers was solvolyzed using the same procedure as for the diphenyl isomer. n-Butyl alcohol (20 ml.) and 3.07 g. (10 mmoles) of each isomer were refluxed together under a stream of dry nitrogen for one hour and the liquid removed by vacuum. The solid and 20 ml. of n-butyl alcohol were refluxed for 12 hours more. The liquid was then removed under vacuum and its volume reduced to 5 ml. by distillation as before. It gave a positive boron test and on vapor-phase chromatographic analysis the boron compound was shown to be di-n-butyl methaneboronate.

One hundred mg. of the solid residue was dissolved in 0.25 ml. of acetone and placed on thin-layer chromatography plates prepared for preparative separations. In each case 10 mg. (10% w/w) was obtained from the respective mixtures. The spectral data are summarized below.

ortho Isomer. Infrared ($CHCl_3$) 3401 (N-H), 3289 (N-H), 2932 (C-H), 1718 (C=O), 1486 and 1458 (C-H scissoring), and 1163 and 1100 $cm.^{-1}$ (sym. and asym. C-O-C). No mass or proton magnetic resonance spectrum was obtained for this isomer.

meta Isomer. M.p. 132; infrared ($CHCl_3$) 3412 (N-H), 3280 (N-H), 2950 (C-H), 1725 (C=O), 1471 (C-H scissoring), 1235 and 1103 $cm.^{-1}$ (sym. and asym. C-O-C); mass spectrum, m/e for P^+, $(P+1)^+$ and $(P+2)^+$ and (rel. intensity), 250 (100), 251 (16), and 252 (2). Beynon's[44]

table predicts, for these ions and relative intensities, a molecular formula of $C_{13}H_{18}N_2O_3$.

para Isomer. M.p. 123-129°, infrared ($CHCl_3$) 3412 (N-H), 3280 (N-H), 2942 (C-H), 1710 (C=O), 1471 (C-H scissoring), and 1239 and 1103 (sym. and asym. C-O-C), and 820 cm^{-1} (C-H bending); 70 eV mass spectrum (Figure 6) m/e for P^+, $(P+1)^+$ and $(P+2)^+$ and (rel. intensity), 250 (100), 251 (19.7) and 252 (2.7). Beynon's[44] table predicts a molecular formula of $C_{13}H_{18}N_2O_3$.

Solvolysis of 1,3-Diphenyl-, 1,3-Di-m-tolyl-, and 1,3-Di-p-tolylbiuret with n-Butyl Alcohol. Each biuret was solvolyzed using the same conditions as those used in solvolysis of the boron compounds. In a typical experiment, 10 mmoles of biuret and 20 ml. of n-butyl alcohol were refluxed for 13 hours under a stream of dry nitrogen. The ammonia could be detected at the drying tube opening, and in the case of the phenyl isomer the nitrogen was passed through 125 ml. of 0.1 N hydrochloric acid solution. Back titration of the excess hydrochloric acid with 0.1 N sodium hydroxide required 54.3 ml. Therefore, 7.1 mmoles of ammonia was produced by the reaction.

After refluxing 13 hours the mixture was cooled to room temperature and the volatile components removed under vacuum and trapped. Vapor-phase chromatography showed the liquid to be n-butyl alcohol. Thin-layer chromatographic analysis by comparison with authentic samples showed the mixture to be phenylurea, 1,3-diphenylbiuret, sym-diphenylurea

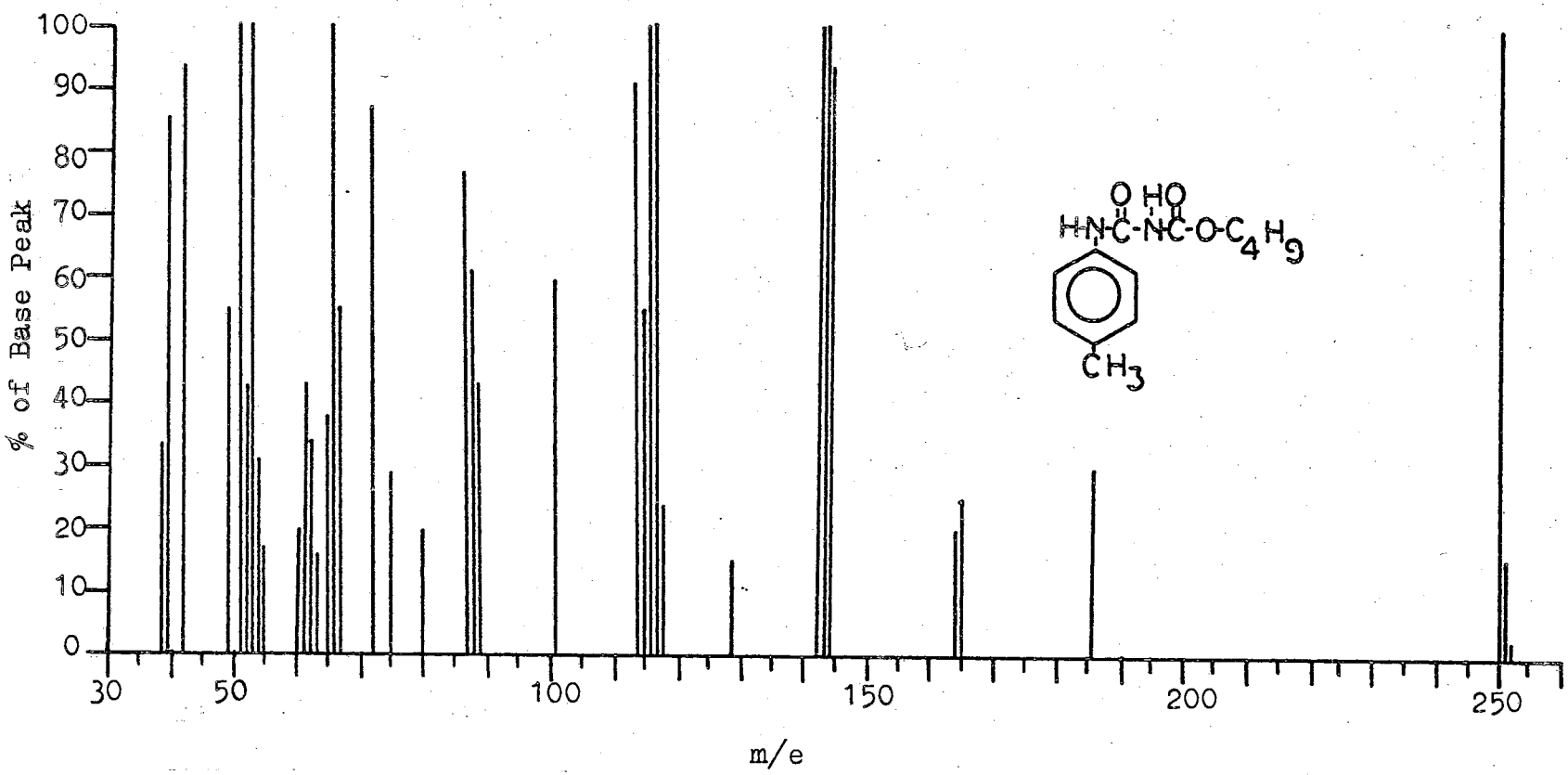


Figure 6. 70 eV Mass Spectrum of 1-Butyl-4-p-tolylallophanate

and n-butyl N-phenylcarbamate.

Solvolysis of 1,3-di-m-tolyl- and 1,3-di-p-tolylbiuret under these same conditions produced ammonia (not quantitatively determined) in both cases, m-tolylurea, sym-di-m-tolylurea, and n-butyl N-(o-tolyl)-carbamate and p-tolylurea, and n-butyl N-(p-tolyl)-carbamate, respectively. Both reaction mixtures contained unreacted biuret.

Preparation of Di-n-butyl Methaneboronate. This material was obtained by a modified preparation of Matteson.[43] Methaneboronic anhydride-pyridine complex, 4.08 g. (20 mmoles), 30 ml. of n-butyl alcohol, and 25 ml. of benzene were refluxed 3 days under an 18-inch column equipped with a Dean-Stark trap to catch the water produced by the reaction.

After three days the reaction mixture was distilled at reduced pressure to yield 2.25 g. (44%); b.p. 96° (52 mm.); proton magnetic resonance (neat) δ 0.15 (s, 3, B-CH_3), 0.95 and 1.46 (m, m, 15.6, -$CH_2CH_2CH_2$), and 3.76 ppm (t, 4.4, O-CH_2-). This compound is also new.

Reaction of 1,3-Diphenyl-2,4-uretidinedione and B,B',B''-Trimethylborazine. 1,3-Diphenyl-2,4-uretidinedione, 3.75 g. (15 mmoles), B,B',B''-trimethylborazine, 0.61 g. (5 mmoles), and 40 ml. of benzene were refluxed together under a static nitrogen atmosphere for 24 hours. The volatile components were removed under vacuum and B,B',B''-trimethylborazine, 0.50 g. (82%), was recovered unreacted.

Attempted Preparation of 1,3-Diphenylbiuret from sym-Diphenylurea and Carbamyl Chloride. Because the 1,3-di-o-tolyl-2,4-uretidinedione could not be prepared, the biuret could not be obtained by the route of Raiford and Freyermuth.[41] It was, therefore, felt that the biuret could be obtained by addition of carbamyl chloride to the sym-di-o-tolylurea. The reaction was first attempted with sym-diphenylurea and carbamyl chloride. If this had been successful, it would have been attempted with sym-di-o-tolylurea and carbamyl chloride.

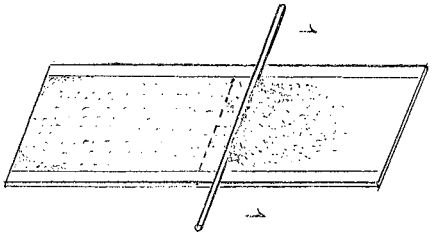
Carbamyl chloride was prepared using the procedure and the reaction apparatus that was described by Slocombe and his coworkers.[45] sym-Diphenylurea, 2.14 g. (10 mmoles), was added to a 50-ml. 3-necked flask with 25 ml. of tetrahydrofuran. The generated carbamyl chloride condensed and dropped into the solution and when approximately 1.5 ml. had dropped into solution, generation was stopped and the flask was removed. A magnetic stirring bar was added, the flask was stoppered, and the mixture was stirred 24 hours. Water was added to decompose the excess carbamyl chloride and the mixture was extracted with ether. The ether solution was dried over magnesium sulfate and the solvent evaporated. Thin-layer chromatography showed no evidence of 1,3-diphenylbiuret so the synthesis of 1,3-di-o-tolylbiuret was not attempted.

Preparation of Thin-Layer Chromatography Plates for Preparative Use. For preparative separations, 20 x 20 cm.

plates were used. Preparation involved cleaning the plates and then uniformly applying the silica gel at the desired thickness (~1 mm.).

The plates were cleaned with an abrasive cleanser and rinsed at least 5 times under a running stream of distilled water. If the plates were not clean in places, water would bead up on these areas and plates were further cleaned until water adhered to the entire surface of the plates. The plates were dried in the air and stored until use.

The plates were coated by the technique of Lees and de Muria.[54] Two plates were coated at a time. On opposite edges of each plate was placed a double layer of masking tape; these plates were then placed together. The silica gel (10 g.) and 20 ml. of distilled water were placed in a 30-ml. screw cap bottle. This was thoroughly mixed and the slurry poured onto the plates. A 30-cm. long glass rod was used to spread the slurry evenly over the plates and the excess was pushed off the end of the plates.



Several plates were done this way before the technique gave good results. The plates were air-dried 30 minutes, the tape removed and the plates activated at 110° for 2 hours.

Determination of Molecular Weights. Molecular weights were obtained using a Coleman 115 Molecular Weight Apparatus. The molecular weight of a sample is determined from the difference in vapor pressure of a solvent and that of a solution of the compound in that solvent. A typical determination is described in the following experiment for obtaining the molecular weight of 2-methyl-1,5-di-o-tolyl-2-bora-(1H,3H,5H)-s-triazine-4,6-dione. A sample (5.190 mg.) was weighed on a micro balance. This sample was dissolved in acetone in a 5-ml. volumetric flask and a portion of this solution was placed in the sample chamber of the instrument. From a predetermined calibration curve (using acetone solutions of benzil) the molarity of the solution was found to be 3.42×10^{-3}. Since the concentration of the solution in mg./ml. was known, the molecular weight can be determined from the following relationship.

$$1 \text{ mmole} = \frac{5.190 \text{ mg.}/5 \text{ ml.}}{3.42 \times 10^{-3} \text{ mmoles/ml.}}$$

It is calculated to be 303.51.

CHAPTER V

RESULTS AND DISCUSSION

Synthesis of four compounds with the 2-bora-s-triazine ring system was accomplished by the reaction of siocyanates with B,B',B''-trimethylborazine.[28] The structures of the compounds were corroborated by 1) elemental analysis and molecular weight data, 2) proton magnetic resonance and infrared data, 3) solvolysis of the boron compounds, and 4) synthesis by an independent route.

Analytical Data. The results of the elemental analyses are summarized in Table I. The data for carbon, hydrogen, and nitrogen are in excellent agreement with the values calculated for these compounds. The elemental composition found for boron is slightly low but the results agree fairly closely with theoretical values. Any hydrolysis that would occur in handling would cause a low percent composition for boron. Analytical data were not obtained for the phenyl isomer since Boone[28] reports these data in his patent. Boone reports no other data to substantiate the structure of this compound.

The molecular weights determined for the compounds are within experimental error of the theoretical values. The value for the m-tolyl isomer, 295.54, is low as compared to

TABLE I

ANALYTICAL AND SPECTRAL DATA FOR THE 2-METHYL-1,5-DIARYL-2-BORA-(1H,3H,5H)-s-TRIAZINE-4,6-DIONES

Aryl Group	Molecular Weight		Elemental Analysis		Spectral Data	
	Calcd.	Found	Calcd., %	Found, %	Infrared, $cm.^{-1}$	Proton Magnetic Resonance ppm vs TMS (rel. intensity)
C_6H_5-	279.12	276.14	----	----	3401, 3257, 3049, 1706, 1448, 1233.	0.25 (3.3) 7.45 (10.0)
o-$CH_3C_6H_4-$	307.17	303.51	C, 66.47 H, 5.90 N, 13.68 B, 3.52	C, 66.34 H, 5.88 N, 13.20 B, 3.26	3378, 3226, 3012, 1689, 1426, 1267.	0.17 (2.6) 2.40 (5.6) 7.37 (8.0)
m-$CH_3C_6H_4-$	307.17	295.54	C, 66.47 H, 5.90 N, 13.68 B, 3.52	C, 66.34 H, 5.91 N, 13.34 B, 3.14	3390, 3280, 3030, 2932, 1704, 1426, 1203.	0.25 (2.6) 2.45 (5.6) 7.25 (8.0)
p-$CH_3C_6H_4-$	307.17	312.17	C, 66.47 H, 5.90 N, 13.68 B, 3.52	C, 66.49 H, 5.78 N, 13.39 B, 3.28	3401, 3021, 2924, 1695, 1408, 1233.	0.24 (2.4) 2.57 (6.0) 7.37 (8.0)

the calculated value of 307.17; however, the difference of 3.7% is not unacceptable. The good agreement in the observed and calculated values rules out the possibility of dimer or trimer formation in the reaction or in solution. A small percentage of polymer formation would be detected by the technique used to obtain the molecular weights.

Spectral Data. The infrared spectra of these compounds show the presence of the important functional groups. All show a N-H stretching absorption in the region of 3400 cm^{-1}. This is characteristic of a free N-H group.[55] A poorly resolved and weak absorption in the region of 3280 $cm.^{-1}$ may be the hydrogen-bonded N-H absorption.[55] All these compounds show absorption in the region of 3000 $cm.^{-1}$ resulting from aromatic C-H stretching.[55] The carbonyl absorption is present as a very broad and strong band centered in the 1700 $cm.^{-1}$ region.[55] The position of the B-N band is highly dependent upon the double-bond character of the B-N group and usually appears in the region of 1520-1380 $cm.^{-1}$ for aminoboranes and borazines.[56,57] All spectra show absorptions in the region of 1400-1450 $cm.^{-1}$ which may be due to the B-N group. Other absorptions found are listed in Table I.

Proton magnetic resonance spectra show absorptions for the aromatic protons, the aryl-methyl protons when present, and the methyl protons on the boron atom.

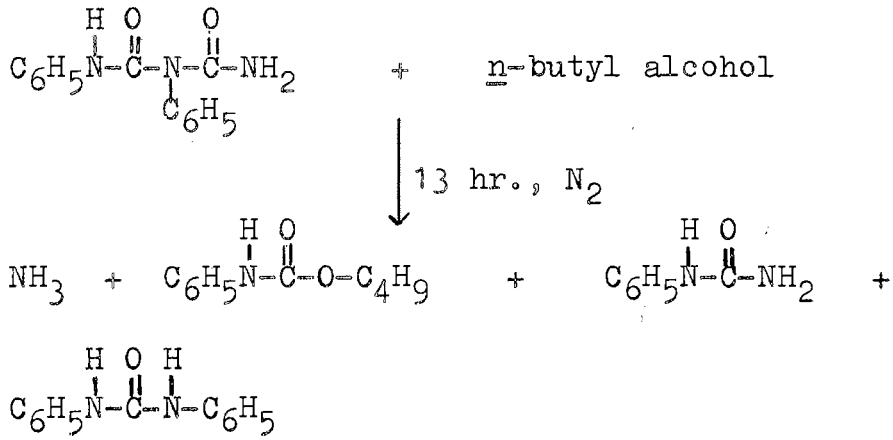
The $B-CH_3$ absorption appears at very high field of δ 0.2 ppm. These absorptions are not sharp but are slightly

broadened and in the cases of the ortho and meta isomers appear to have multiplet character. No spin-spin couplings occur between boron and the methyl protons so the multiplet character may be due to restricted rotation about the B-C bond to give an A_2B type spectrum or it may be due to the presence of an isomer. Pople, Schneider and Bernstein[58] predict that restricted rotation about the central bond of a molecule of the type, CH_3-CRRS, where R and S are large groups and $R \neq S$, will result in a second order A_2B spectrum for the methyl group. This is unlikely for these compounds since heating the sample did not alter their spectra. An isomeric impurity is more plausible. Such impurity would not be detected by elemental analysis or molecular-weight determinations.

The N-H proton could not be detected in any of the spectra even though its presence is confirmed by the infrared data. At first this was very confusing but it soon became apparent after looking at the proton magnetic resonance spectrum of n-butyl N-phenylcarbamate and examining the work of Bloodworth and Davies[47] why this was so. The N-H proton of some carbamates could not be detected in deuterochloroform due to the broadening effect of the nitrogen-14 nucleus.

Solvolysis Data. Cragg and Lappert[29] reported that the solvolysis of 2-(diethylamino)-1,3-diphenyl-5-ethyl-2-bora-(1H,3H,5H)-s-triazine-4,6-dione first formed a biuret; the biuret was further solvolyzed to give an amine

and two moles of alkyl N-arylcarbamate. With this compound as a model, it was expected that solvolysis of the 2-methyl-1,5-diary-2-bora-(1H,3H,5H)-s-triazine-4,6-diones would initially form a 1,3-diarylbiuret, which would further react to give ammonia and two moles of an alkyl N-aryl-carbamate. Solvolysis of 1,3-diphenylbiuret with n-butyl alcohol did not proceed as expected but gave the products as shown below. The reaction product also contained a small



amount of unreacted biuret. The compounds were identified by thin-layer chromatography by comparison with known compounds. The boron compounds did not give products consistent with the intermediate being a 1,3-diarylbiuret. From each of the solvolysis mixtures was isolated a compound that proved to be 1-butyl-4-arylallophanate. The structures of these isolated compounds were assigned from the spectral data given in Table II.

The proton magnetic resonance spectrum of the compound from the phenyl isomer had four absorptions: a singlet at δ 9.90 ppm, a multiplet at δ 7.27 ppm, a triplet at δ 4.17 ppm (J = 6.3 cps), and multiplets at δ 1.57 and 0.95 ppm.

TABLE II

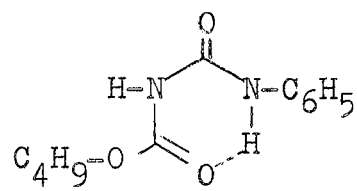
DATA FOR THE 1-BUTYL-4-ARYLALLOPHANATES

Aryl Group	Melting Points °C.	Proton Magnetic Resonance, ppm vs TMS (rel. intensities)	Mass Spectrum, m/e (rel. intensities)	Infrared, $cm.^{-1}$
C_6H_5-	120° (dec)	9.90 (s, 1.0) 7.27 (m, 4.4) 4.17 (t, 2.0, J=6.3 cps) 1.57 and 0.95 (m, m, 6.4)	$(P)^+$, 236 (100) $(P+1)^+$, 237 (14) $(P+2)^+$, 238 (3)	3412, 3246, 2958, 1718, 1315, 1226, 1104, 1082, 870, 776.
o-$CH_3C_6H_4-$				3401, 3289, 2932, 1718, 1486, 1458, 1163, 1100.
m-$CH_3C_6H_4-$	130-2°		$(P)^+$, 250 (100) $(P+1)^+$, 251 (16) $(P+2)^+$, 252 (2.1)	3412, 3280, 2950, 1725, 1471, 1235, 1103.
p-$CH_3C_6H_4-$	123-9°		$(P)^+$, 250 (100) $(P+1)^+$, 251 (19.7) $(P+2)^+$, 252 (2.7)	3412, 3280, 2942, 1710, 1471, 1239, 1103, 820.

The relative intensities were 1.1:4.8:2.0:7.0, respectively.

The mass spectrum of the phenyl isomer shows a P^+ ion of 236 of relative intensity 100, a $(P+1)^+$ ion of relative intensity 14 and a $(P+2)^+$ ion of relative intensity 3. Since the parent ion has an even molecular weight the molecular ion must contain an even number of nitrogen atoms. Beynon's[44] table of isotope abundances predicts a molecular formula of $C_{12}H_{16}N_2O_3$ will have P^+, $(P+1)^+$, and $(P+2)^+$ peaks of relative intensities 100, 14.10, and 1.52, respectively. This is in good agreement with the intensities found for the phenyl isomer.

1-Butyl-4-phenylallophanate has a structure that is compatable with these data. The proton at position 2 is not exchangeable in non-polar solvents and is not seen in the proton magnetic resonance spectrum. The molecule will associate in non-polar solvents as shown below.[47] This



gives rise to intramolecular hydrogen bonding between the carbonyl and the proton at position 4. Since this proton is exchanging faster than quadrupole broadening can occur the proton shows a sharp singlet.

The infrared spectral data substantiates the structure as being 1-butyl-4-phenylallophanate.

If the compound is 1-butyl-4-phenylallophanate the

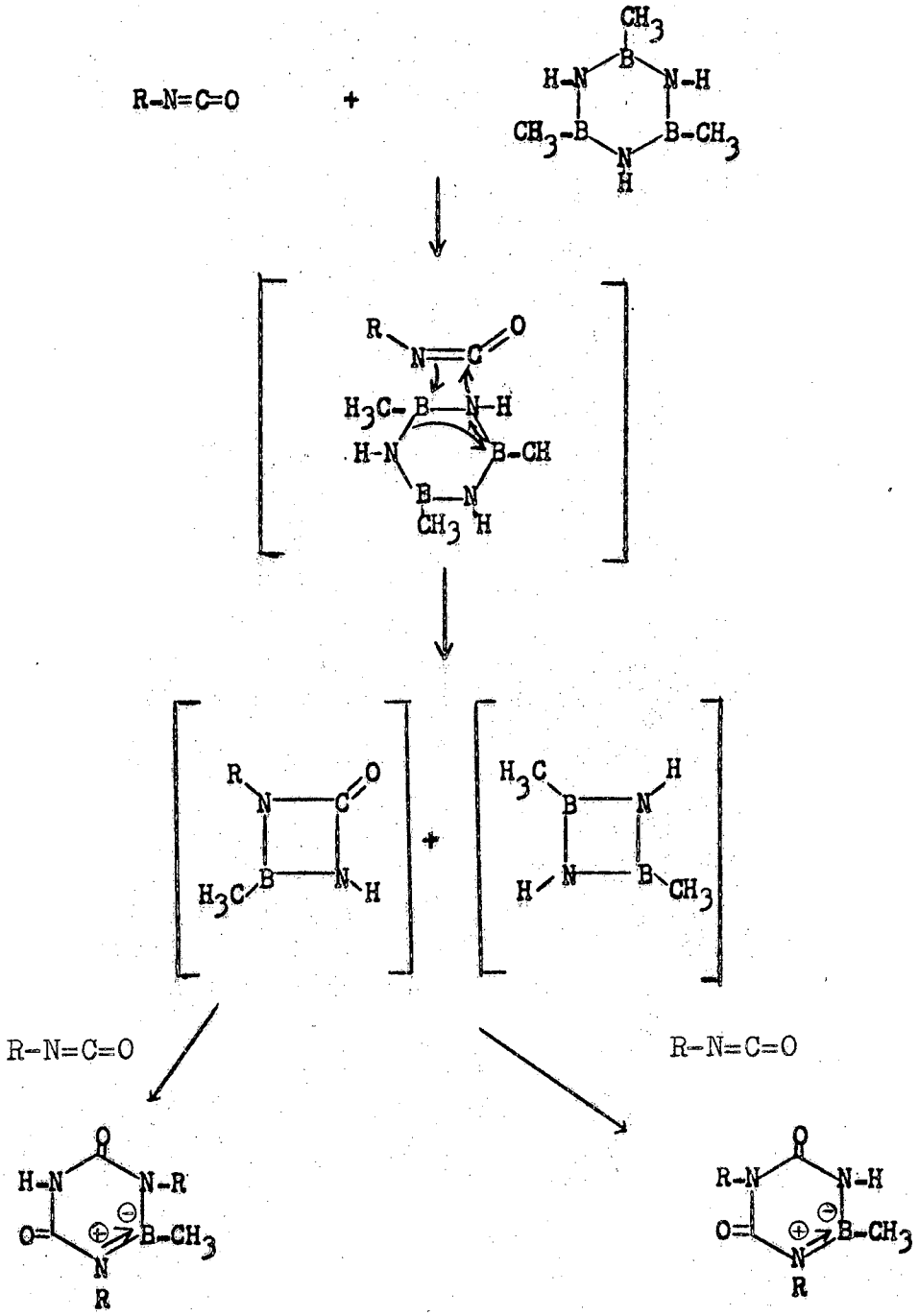
unidentified products from the solvolysis mixtures of the meta and para boron compounds should give parent ions of m/e = 250. This is found and from Beynon's[44] table a molecular formula of $C_{13}H_{18}N_2O_3$ is predicted. (No mass spectrum could be obtained from the ortho isomer because an infrared spectrum was obtained on the sample first and some decomposition occurred from this.) The infrared spectra of the ortho, meta, and para isomers agree with the structures as assigned.

That the three allophanates are present as solvolysis products of the boron compounds can be explained by the presence of 2-methyl-1,3-diaryl-2-bora-(1H,3H,5H)-s-triazine-4,6-diones as a product from the reaction of the isocyanates with B,B',B''-trimethylborazine.

A mechanism consistent with these findings is presented on page 67. This mechanism is similar to one proposed by Ulrich[34] for the addition of isocyanates to carbon-nitrogen bonds. It is reasonable to expect a similar mechanism to be operative here due to some similarity of boron-nitrogen and carbon-nitrogen bonds.

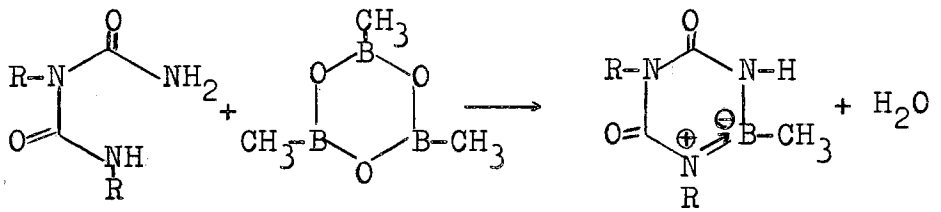
This mechanism explains the presence of the small amount of 1,5-diaryl isomer in the product. The requirement for the four-membered ring compound, $(BCH_3NH)_2$, can be justified. Compounds of this type are known and have been isolated.[35]

The reaction could not involve the formation of isocyanate dimers with the addition of the borazine to these


R-N=C=O
+
R-N=C=O
R-N=C=O

dimers to give the 2-bora-s-triazine ring system. This route will give only 2-methyl-1,3-diaryl-2-bora-(1H,3H,5H)-s-triazine-4,6-diones.

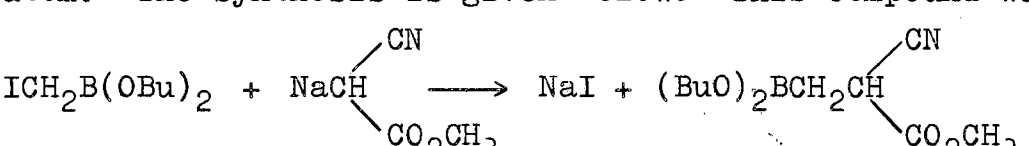
Synthesis by the independent route given below



substantiates the 2-methyl-1,5-diaryl-2-bora-(1H,3H,5H)-s-triazine-4,6-dione structure. Although this route will not give any of the 1,3-diaryl isomer, it is formed in such a small amount in the reaction of the isocyanates with B,B',B''-trimethylborazine that it would not be detected in the reaction product by infrared spectroscopy.

Several attempts were made to prepare a compound having 2-borapyrimidine ring system. However, the desired substituted boronic acid esters for cyclization with urea resisted preparation.

No boronates have been reported that contain a carbonyl group beta to the boron atom. Matteson and Cheng[17] have reported the synthesis of α-cyano-β-dibutoxyborylpropionate, a molecule which has a carbonyl group gamma to the boron atom. The synthesis is given below. This compound was



isolated by distillation so the proposed intermediates

should have been thermally stable. The syntheses must not have given the intermediates as proposed but polymeric material instead.

Stability of the 2-Methyl-1,5-diaryl-(1*H*,3*H*,5*H*)-*s*-triazine-4,6-diones. Two experiments were performed in attempt to determine the hydrolytic stability of these compounds. One involved ultraviolet spectroscopy and the other proton magnetic resonance.

An ultraviolet spectrum of the boron compound in dioxane was obtained, water was added, and a new spectrum was obtained to see if changes occurred. The two spectra were different, but the spectrum in water did not change after several minutes. The spectrum of the boron compound in dioxane showed an intense absorption at 218 nm. and a shoulder at 252 nm. with no other absorptions present. Addition of water caused a change in the intensities of these absorptions with no new peaks being introduced. The spectrum of 2-methyl-1,5-diphenyl-2-bora-(1*H*,3*H*,5*H*)-*s*-triazine-4,6-dione after water was added was identical with the spectrum of 1,3-diphenylbiuret. The changes in intensity could be the result of a conformational change or from hydrolysis. In either case no new chromophores are introduced.

The proton magnetic resonance spectrum of the compound in deuterated chloroform was obtained, water was added to the solution, and the spectrum determined again. In the case of the *p*-tolyl isomer on addition of water no change

occurred immediately. After 15 minutes peaks appeared at δ 10.20, 8.82, and 5.83 ppm. The peak at δ 10.20 and the one at δ 5.83 ppm are probably due to the -NH- and $-NH_2$ groups, respectively, of the biuret. The peak at δ 8.82 ppm may be due to the formation of $CH_3B(OH)_2$ and if this is so hydrolysis may be slow. After 16 hours these peaks had increased significantly in intensity.

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