[CONTRIBUTION FROM THE RETINA FOUNDATION, DEPARTMENT OF OPHTHALMOLOGY OF THE MASSACHUSETTS EYE AND EAR INFIRMARY, THE PHYSICS RESEARCH DEPARTMENT, THE DEPARTMENT OF NEUROSURGERY OF THE MASSACHUSETTS GENERAL HOSPITAL AND THE HARVARD MEDICAL SCHOOL]

Boron-containing Heterocycles. I. Synthesis of Several Borimidazolines[1,2]

BY EMERY NYILAS AND A. H. SOLOWAY

RECEIVED NOVEMBER 25, 1958

A new class of boron-containing heterocycles is formed by the condensation of aromatic boronic acids with *o*-aromatic diamines. A mechanism for this reaction is presented. Support for this postulation is obtained by the isolation of an intermediate adduct and the use of the infrared and ultraviolet spectra.

Introduction.—The possibility of destroying selectively neoplastic cells in the brain by neutron-capture therapy is under active investigation[3-9] in this and other laboratories. However, this procedure as yet offers little promise for malignant tumors other than those of the brain.[10] The preparation of a boron-containing purine antimetabolite might extend this treatment to other neoplasms and offer a twofold attack. In the first instance, such a compound by its antimetabolic properties may competitively inhibit the growth of certain tumors. This aspect is supported by the discovery that some purine antagonists show definite activity against certain animal tumors.[11-13] Secondly, the incorporation of such molecules, containing B^{10}, into the nucleic acids of malignant cells would present a means for their destruction by thermal neutron irradiation. Thus, the metabolism of the tumor cell would itself serve in its eradication.

Our experiments were directed to the replacement of carbon 8 in the purines with a boron atom. In order to prepare some model compounds, aromatic *o*-diamines were condensed with alkyl- and arylboronic acids to form borimidazolines. For example, *o*-phenylenediamine reacts with phenylboronic acid in a homogeneous phase at elevated temperatures to produce a single compound in good yield. The reaction of boric acid with *o*-phenylenediamine, however, failed to yield a discrete isolable substance. This is not surprising in view of the fact that no monomers of the borazine type are known.[14]

These borimidazolines, in general, are stable compounds which may be recrystallized from non-polar solvents without alteration. Infrared spectra of the compounds showed the presence of a single peak in the region of 3500–3300 cm.$^{-1}$ corresponding to an imino function. There were no hydroxyl or primary amino groups present. The ultraviolet spectra of these substances exhibited two absorption maxima which were not present in the reactants or in the mixture of these materials. Finally, microanalytical data confirmed this class of compounds as being a new type of heterocycle, 2-substituted borimidazolines.

A previous attempt to prepare 2-phenylborobenzimidazoline utilizing different conditions was unsuccessful.[15] While this present investigation was being carried out, the synthesis of this new class of heterocycle was reported.[16,17]

Discussion.—The condensation reaction of the aromatic diamine with phenylboronic acid probably proceeds by the formation of an initial complex of the two reactants, which is very similar to complexes between the aromatic boronic acids and various amines.[18] The existence of such a complex and the suggested pathway of the reaction was indicated by the preparation of the adduct in aqueous methanol. The infrared spectrum of this low-melting complex still displays the presence of primary amino groups, as well as that of the hydroxyl groups of the boronic acid shown in Fig. 2A and Fig. 2B. Subsequently, when this adduct was melted, cyclization occurred with the formation of 2-phenylborobenzimidazoline whose spectrum is seen in Fig. 2C.

A characteristic broad band in the infrared spectra of many alkyl- and arylboronic acids occurs in the region of 1400–1300 cm.$^{-1}$. One peak of this band at about 1310 cm.$^{-1}$ is ascribed to the B–O stretching frequency[19] of the free boronic acid, but it is degenerated in the spectrum of the adduct and a new band appears in the 1125–1115 cm.$^{-1}$ region indicative of a B–N link.[19,20] Finally, both the peak for the B–O stretching frequency and the characteristic broad band of the free boronic acid disappear in the spectrum of the borimidazoline, but a small peak near 1110 cm.$^{-1}$ ascribable to a

---

(1) This research was supported by the United States Atomic Energy Commission under contract No. AT (30-1)-1093, by an Institutional Grant from the American Cancer Society, and by research grant (A-1110) from the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health, Public Health Service.

(2) Retina Foundation Paper #75.

(3) P. G. Kruger, *Proc. Natl. Acad. Sci. U. S.*, **26**, 181 (1940).

(4) P. G. Kruger, *Radiation Research*, **2**, 1 (1955).

(5) M. Javid, G. L. Brownell and W. H. Sweet, *J. Clin. Invest.*, **31**, 604 (1952).

(6) L. E. Farr, W. H. Sweet, J. S. Robertson, C. G. Foster, H. B. Locksley, D. L. Sutherland, M. L. Mendelsohn and E. E. Stickley, *Am. J. Roentgenol. Radium Therapy Nuclear Med.*, **71**, 279 (1954).

(7) W. H. Sweet and M. Javid, *J. Neurosurg.*, **9**, 200 (1952).

(8) P. A. Zahl, F. S. Cooper and J. R. Dunning, *Proc. Natl. Acad. Sci. U. S.*, **26**, 589 (1940).

(9) A. H. Soloway, *Science*, **128**, 1572 (1958).

(10) H. B. Locksley and W. H. Sweet, *Proc. Soc. Exp. Biol. Med.*, **86**, 56 (1954).

(11) H. E. Skipper, R. K. Robins and J. R. Thomson, *ibid.*, **89**, 594 (1955).

(12) H. E. Skipper, R. K. Robins, J. R. Thompson, C. C. Cheng, R. W. Brockman and F. M. Schabel, *Cancer Research*, **17**, 579 (1957).

(13) R. K. Robins and H. H. Lin, THIS JOURNAL, **79**, 490 (1957).

(14) P. F. Winternitz, "The Impact of Recent Developments in Boron Chemistry on Some Scientific and Engineering Problems," presented at the Meeting of the American Chemical Society, April, 1958.

(15) J. M. Sugihara and C. M. Bowman, THIS JOURNAL, **80**, 2443 (1958).

(16) M. J. S. Dewar, V. P. Kubba and R. Pettit, *J. Chem. Soc.*, 3076 (1958).

(17) R. L. Letsinger and S. B. Hamilton, THIS JOURNAL, **80**, 5435 (1958).

(18) D. L. Yabroff and G. E. K. Branch, *ibid.*, **55**, 1663 (1933).

(19) L. J. Bellamy, W. Gerrard, M. F. Lappert and R. L. Williams, *J. Chem. Soc.*, 2412 (1958).

(20) H. J. Becher, *Z. anorg. Chem.*, **271**, 243 (1953).

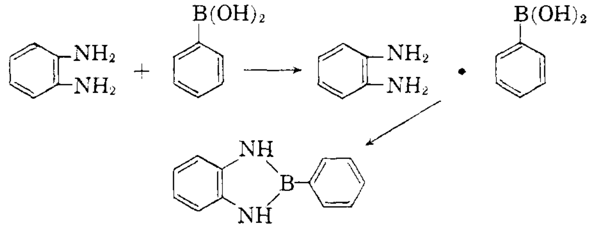


Fig. 1.

B–N *single bond linkage still remains.* A new peak appears at 1372 cm.$^{-1}$ which can be related to a B–N bond having double bond character as in the borazoles. This position of energy absorption is in good agreement with the findings of Becher and co-workers[20,21] who assigned the absorption frequency of the same bond at the 1378–1332 cm.$^{-1}$ region. The existence of a semi-polar B–N double bond is also supported by the ultraviolet spectra which will be discussed below.

In Table I the series of compounds described above are listed with some of their analytical and physico-chemical data. Of special interest was the relative ease with which 4-nitro-*o*-phenylenediamine condensed with phenylboronic acid to yield 2-phenylboro-5-nitrobenzimidazoline. This is in contrast to the forcing conditions required for the condensation of the amine with aromatic carboxylic acids.[22]

Ultraviolet spectral data reveal that a relatively stable conjugated system is present in the compounds, especially in those with a 2-aryl substituent. In view of the boron–nitrogen double bond character, such a conjugated system is understandable. The borimidazoline type exhibits two main peaks in the ultraviolet spectra, one in the 230–245 mμ region and the other at 285–310 mμ. The nature of the substituent in the 2-position affects primarily the intensity of the absorbed energy and only to a lesser extent the wave length. For example, 2-propyl derivatives have much lower molecular extinction coefficients than their corresponding 2-aryl counterparts. Introduction, however, of substituents into position 5 gives rise to a considerable variation in the wave length of the absorption maxima. Electron-donating substituents produce a bathochromic shift in the absorption spectra, whereas electronegative groups result in a hypsochromic effect. This can be explained by the mesomeric action of groups in the 5-position upon the unshared pair of electrons of the nitrogen in the one position. Electron-releasing groups in the 5-position could result in an increase in the contribution of the B–N double bond character, whereas electron-withdrawing groups decrease the availability of this unshared pair for resonance interaction with the boron atom and the 2-aryl substituent.

Similar groups attached to the 2-phenyl ring have a much smaller effect on the spectra. If, as is assumed, polarization of the nitrogen unshared pair of electrons has a direct bearing on this absorption spectra, the effect of substituents on the 2-phenyl group would be sharply moderated by the electron-deficient boron atom in this resonance pathway.

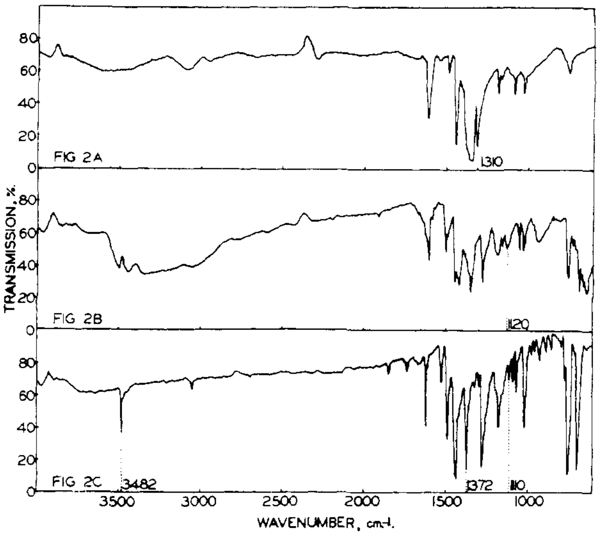


Fig. 2.

This boron heterocycle, as the borazoles, is quite stable to hydrolysis. 2-Phenylborimidazoline was recovered from a refluxing aqueous alcohol medium but on long standing, hydrolysis does occur as noted by spectral changes indicative of the cleavage of this compound.

Experimental

Materials.—The boronic acids were prepared in the usual manner.[23] The following aromatic diamines were obtained from commercial sources: *o*-phenylenediamine,[24] 3,4-diaminotoluene,[24] 4-chloro-*o*-phenylenediamine,[24] 4-nitro-*o*-phenylenediamine,[24] 2,3-diaminonaphthalene[25] and 3,4-diaminobenzoic acid.[25] 4-Methoxy-*o*-phenylenediamine was prepared by the reduction with tin and hydrochloric acid of 2-nitro-4-methoxyaniline.

General Method.—The compounds were prepared by two general procedures described below according to the solubility of the reactants. In general, the condensation reactions were performed in xylene or toluene which are suitable solvents for many of the acids and the diamines. However, where the reactants were insoluble, xylene was replaced by a xylene–Ansul Ether 141[26] (1:1) mixture or even the ether alone.

Reactions were performed on a 0.02 mole scale in approximately 100-ml. quantities of the solvents using equal mole amounts of the acid and the diamine. The crude products were then recrystallized from non-polar solvents such as benzene, toluene or cyclohexane.

Procedure A.—The reactants in 0.02-mole amounts were dissolved with gentle heating in 100 ml. of xylene. The flask was attached to a distillation set up and over a period of two hours, half of the solvent was distilled at atmospheric pressure. In order to ensure complete reaction by the removal of any residual water formed in the reaction mixture, a volume of xylene equal to the quantity distilled was added. The distillation then was continued until the solution was concentrated to a final volume of 25 to 30 ml. A slow crystallization of the reaction mixture was then permitted. The solution was chilled, filtered, washed with petroleum ether and dried. Recrystallization was effected from a small volume of toluene.

Procedure B.—The reaction was carried out as in procedure A except the reactants were dissolved in the required amount of either a xylene–Ansul Ether 141 (1:1) mixture or Ansul Ether 141 alone. When the volume had been reduced to 25 to 30 ml., atmospheric distillation was discon-

---

(21) H. J. Becher, *Z. anorg. Chem.*, **289**, 262 (1957).

(22) D. W. Hein, R. J. Alheim and J. J. Leavitt, THIS JOURNAL, **79**, 427 (1957).

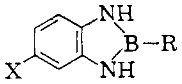
(23) A. H. Soloway, THIS JOURNAL, **81**, in press (1959).

(24) Eastman Organic Chemicals, Rochester 3, N. Y.

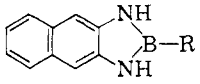
(25) K and K Laboratories, Inc., Jamaica 33, N. Y.

(26) Trade name for diethylene glycol dimethyl ether, b.p. 160–162°, product of the Ansul Chem. Co., Marinette, Wisc.

TABLE I



I–XII



XIII

No.	Substituents R	X	M.p., °C.[a]	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Ultraviolet absorption λ_{max}, mμ	Ultraviolet absorption $\epsilon_{max} \times 10^{-4}$	Ultraviolet absorption λ_{max}, mμ	Ultraviolet absorption $\epsilon_{max} \times 10^{-4}$	Yield,[b] %	Procedure[c]
I	*n*-Propyl	H	92–94	$C_9H_{13}N_2B$	17.51	17.62	232	0.543	284	0.553	53	A
II	*n*-Propyl	Methyl	99–101	$C_{10}H_{15}N_2B$	16.10	16.02	233	0.550	290	0.659	72	A
III	Phenyl	H	212–214	$C_{12}H_{11}N_2B$	14.44	14.15	245	0.865	296	1.74	91	A
IV	*p*-Methoxyphenyl	H	242–243	$C_{13}H_{13}ON_2B$	12.50	12.40	248	1.73	295	2.38	85	A
V	*p*-Chlorophenyl	H	219–221	$C_{12}H_{10}N_2BCl$	12.26	12.28	249	0.952	298	1.95	92	A
VI	*m*-Nitrophenyl	H	218–219	$C_{12}H_{10}O_2N_3B$	17.58	17.24	256	1.28	297	1.68	84	B
VII	*p*-Carboxyphenyl	H	281–282	$C_{13}H_{11}O_2N_2B$	11.77	11.50	235	2.18	289	0.377	79	B
VIII	Phenyl	Methyl	224–225	$C_{13}H_{13}N_2B$	13.47	13.31	248	0.897	302	1.86	89	A
IX	Phenyl	Methoxy	138–140	$C_{13}H_{13}ON_2B$	12.50	12.39	249	0.818	308	1.77	59	A
X	Phenyl	Chloro	183–184	$C_{12}H_{10}N_2BCl$	12.26	12.20	245	1.40	301	2.09	79	A
XI	Phenyl	Nitro	203–204	$C_{12}H_{10}O_2N_3B$	17.58	17.33	236	1.49	267	2.19	53	B
XII	Phenyl	Carboxy	209–210	$C_{13}H_{11}O_2N_2B$	11.77	11.68	222	2.70	308	1.41	95	B
XIII	Phenyl	......	327–328	$C_{16}H_{13}N_2B$	11.48	11.40	245	5.33	377	1.63	95	B

[a] Melting points are uncorrected and were determined in capillary tubes immersed initially in an unheated bath. [b] Recrystallized material. [c] This refers to the methods of preparation described in the Experimental part.

tinued and the mixture was evaporated to dryness *in vacuo*. The residue was suspended in 5 to 10 ml. of cold toluene, filtered, washed with petroleum ether and dried. The amorphous residue then was recrystallized from toluene.

Adduct of *o*-Phenylenediamine and Phenylboronic Acid.—In 25 ml. of 90% methanol was added 2.44 g. of phenylboronic acid and 2.16 g. of *o*-phenylenediamines. The solution was warmed at 60° for one hour and then concentrated *in vacuo*, to near dryness without warming above 60°. The solution was filtered, washed with a small volume of water and dried; a yield of 1.9 g., m.p. 70–72°, was obtained. At its melting point, the product resolidified and melted at 206–207°. This is the 2-phenylborobenzimidazoline, characterized by infrared spectra.

Infrared Spectra.—One mg. of twice-recrystallized substances was made up with 150 mg. of anhydrous potassium bromide[27] to a disk in the usual manner. All spectra were taken with a Perkin–Elmer model 21 recording spectrophotometer.

Ultraviolet Spectra.—The absorption spectra of twice-recrystallized materials were determined in freshly-prepared methanolic solutions, approximately 10^{-4} molar. All spectra were recorded with a Beckman DK-2 automatic spectrophotometer.

Acknowledgments.—The authors are very grateful to Drs. William H. Sweet, Gordon L. Brownell and E. A. Balazs for their great interest and encouragement in this work. It is a pleasure to acknowledge the technical assistance of Mr. Paul Szabady. We wish to thank Miss Mary Ellen Collins and Mr. E. T. Kaiser for their coöperation in obtaining the infrared spectra.

BOSTON 14, MASS.

---

(27) Harshaw Chem. Co., Cleveland 6, Ohio.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

The Mechanism of the Reaction of Some Dialkyl and Diaryl Mercury Compounds with Hydrogen Chloride

BY RAYMOND E. DESSY, G. F. REYNOLDS[1] AND JIN-YOUNG KIM

RECEIVED AUGUST 12, 1958

The rates of reaction of diphenyl-, dimethyl-, diethyl-, di-*n*-propyl-, di-*i*-propyl-, divinyl- and dicyclopropylmercury with hydrogen chloride in dimethyl sulfoxide have been measured by a convenient conductometric method at various temperatures. The sequence of reactivities found is $(\Delta)_2$ Hg > $(H_2C{=}CH)_2$ Hg > $(C_6H_5)_2Hg$ >> Et_2Hg > *i*-Pr_2Hg > *n*-Pr_2Hg > Me_2Hg. The effect of addition of dioxane, water, various inorganic salts and acids, the results of experiments involving DCl and the observed second-order kinetics all point to a four-center mechanism involving attack by molecular HCl.

In 1935, Ingold[2] in his classical series on S_N reactions, proposed what he termed S_E reactions—electrophilic substitution at a carbon center. This class of reactions could be divided, as the S_N reactions, into two categories—S_E1 and S_E2. Without experimental evidence, Ingold predicted what sequence of reactivities might be expected from each reaction path. Since that time many investigations have been initiated which involve a study of S_E reactions. Most of these have involved the use of organomercury compounds as the substrate providing the nucleophilic carbon for various practical reasons.

Earlier qualitative work by Marvel[3] with the reaction

$$R{-}Hg{-}R + HCl \longrightarrow RHgCl + R{-}H \qquad (1)$$

indicated the sequence of reactivity to be *t*-Bu > *s*-Bu > *n*-Bu. No attempt at a rate or kinetic investigation was made.

In 1932, Kharasch[4] published the results of an

---

(1) Procter and Gamble Research Fellow 1957–1958.

(2) E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 244 (1935).

(3) C. S. Marvel and H. O. Calvery, THIS JOURNAL, **45**, 820 (1923).

(4) M. S. Kharasch and A. L. Flenner, *ibid.*, **54**, 675 (1932).