

Fig. 5.

ported. While the earlier efforts to obtain this compound were not successful, it was found that the compound could be obtained in very low yields.

A solution of 0.8 g. of *p*-methoxynitrosobenzene in 10 ml. of glacial acetic acid was added slowly to a solution of 1.5 g. of *p*-ferrocenylaniline in 40 ml. of glacial acetic acid at room temperature. After standing at room temperature for 24 hours, the resulting dark brown suspension was poured into 100 ml. of water and filtered. The black precipitate so obtained was worked up for the desired compound, but only intractable materials were obtained. The filtrate from the original filtration, however, upon neutralization with NaOH yielded a black precipitate (1.2 g.) which was taken up in benzene and chromatographed on Florisil. After an initial yellow band, a second band (red) was collected and rechromatographed on Florisil. From the eluent was obtained 100 mg. of *p*-ferrocenyl-*p*'-methoxyazobenzene that was recrystallized from ethanol; m.p. 182–184° (uncor.); ultraviolet max. 362 mμ.

Anal. Calcd. for $C_{20}H_{20}ON_2Fe$: N, 7.07. Found: N, 7.12.

Determination of pK_a 's.—Solutions of the ferrocenylazobenzenes were prepared at 25° in aqueous solutions of sulfuric acid containing 20 vol. % ethanol in the same manner described by Jaffé^{6a}. The solutions were approximately 10^{-5} M in the ferrocenylazobenzenes and ranged in sulfuric acid wt. % from 15% to 75%. The absorbance of these solutions did not change on standing over a period of several hours. Stability tests were performed on a number of the ferrocenylazobenzenes over the entire range of sulfuric acid concentrations.

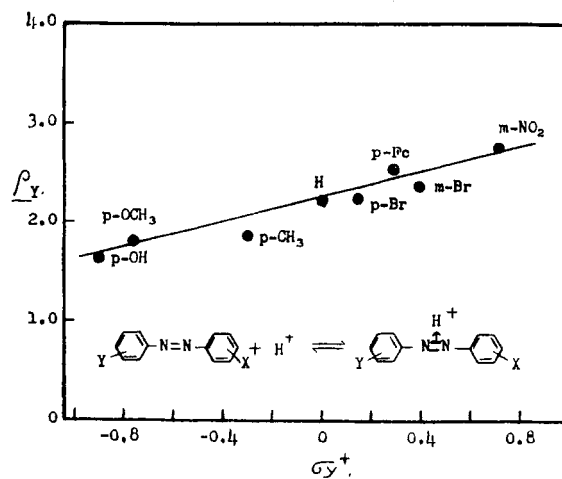


Fig. 6.

The spectra were obtained with a Cary model 14 instrument. The spectra were recorded over a range from 300 to 550 mμ. For each compound, ten arbitrary wave lengths were selected in the regions of maximum change for the determination of the pK_a 's. The pK_a 's were determined by the treatment described by Reilley and Smith.⁹ The procedure was checked by re-examining several of the compounds studied by Jaffé^{6d} and excellent agreement with Jaffé's values was found. For example, Jaffé found for azobenzene and *p*-nitroazobenzene -2.90 ± 0.02 and -4.70 ± 0.02 ; our values were -2.93 ± 0.05 and -4.70 ± 0.01 .

Recovery of *p*-Ferrocenyl-*p*'-bromoazobenzene.—A solution of *p*-ferrocenyl-*p*'-bromoazobenzene, typical of the solutions used in the pK_a measurements, was prepared from 0.22 mg. of the azo compound in 25 ml. of 50 wt. % H_2SO_4 containing 20 vol. % ethanol. This solution contained approximately half the azo compound converted into the protonated form. After dilution of the solution with 100 ml. of water, CCl_4 extraction failed to remove any of the azo compound from solution. However, after adjusting the pH to 6 with 6 N NaOH, 75% of the azo compound was extracted with two 10-ml. portions of CCl_4 . This estimate was made from the absorbance of the extract solution after dilution to 25 ml.

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[CONTRIBUTION FROM THE CENTRAL RESEARCH DIVISION AND PLASTICS AND RESINS RESEARCH UNIT, AMERICAN CYANAMID CO., STAMFORD, CONN.]

Synthesis of Boron Heterocycles from Biguanide

BY J. E. MILKS, G. W. KENNERLY AND J. H. POLEVY

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Biguanide has been found to react with aminoboranes and boron acids to give heterocyclic compounds containing tetra-valent, rather than trivalent, boron. Structures with an hydroxyl group on the boron atom were shown to hydrolyze reversibly, whereas a spiro compound and a compound with two phenyl groups on boron were unaffected by water. The heterocyclic system, which bears a positive and a negative charge, is related to the resonance stabilized biguanide conjugate acid.

Recent studies by Dewar and others¹ have shown that boron heterocycles with aromatic properties could be derived from normal aromatic compounds by replacing a pair of carbon atoms with a boron

and a nitrogen atom. Aromaticity in the heterocycles was demonstrated from ultraviolet data and from the unusual stability of the B–N bonds to hydrolysis as compared to simple aminoboranes. This stability was attributed to considerable

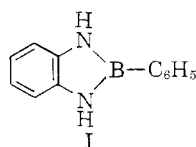
(1) (a) M. J. S. Dewar, V. P. Kubba and R. Pettitt, *J. Chem. Soc.*, 3073, 3076 (1958); (b) M. J. S. Dewar and R. Dietz, *ibid.*, 2728 (1959); (c) M. J. S. Dewar and V. P. Kubba, *Tetrahedron*, **7**, 213 (1959); (d) S. S. Chissick, M. J. S. Dewar and P. M. Maitlis, *Tetra-*

hedron Letters, No. **23**, 8 (1960); (e) P. M. Maitlis, *J. Chem. Soc.*, 425 (1961); (f) J. M. Davidson and C. M. French, *ibid.*, 191 (1960).

double bond character of the type $>\text{B}=\text{N}^{\oplus}<$. In view of these results it was of interest to synthesize and study the properties of the 1,2-dihydro-1,3,5,2-triazaborine ring which might be expected to resemble pyrimidines or s-triazines.

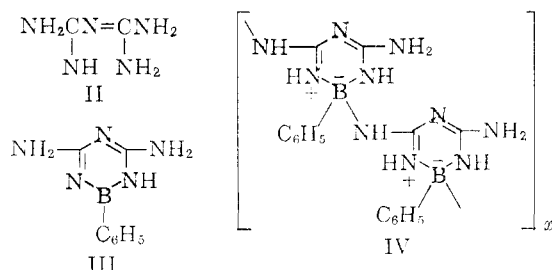


A reaction examined initially for forming heterocyclic rings with B-N bonds was the transamination of bis-(dimethylamino)-phenylborane with *o*-phenylenediamine. Dimethylamine was evolved on warming a benzene solution of the reactants and the product isolated was the known 2-phenylborobenzimidazoline (I).^{1b,2} Subsequently, it was found that transamination reactions of amino-boranes had been reported by Gerrard and co-



workers,³ and a detailed study of the reaction has been reported recently.^{4,5}

A reaction of biguanide (II) with bis-(dimethylamino)-phenylborane in hot pyridine gave dimethylamine and a solid which analyzed correctly for the expected heterocycle III. The compound, however, was insoluble in neutral organic solvents



other than dimethylformamide and was infusible below 400°. The fact that a polymeric structure (IV) was probably formed was suggested from the physical properties and from the observation that the infrared spectrum did not show a band in the region 1350–1500 cm.⁻¹ which could be attributed to nitrogen bonded to trivalent boron.⁶ Although coordination complexes of amines and amino boranes are unknown, the possibility of a coordinate bond to boron by chelation as shown is likely, particularly in view of the strong chelation of biguanide with metal ions.⁷

(2) R. L. Letsinger and S. B. Hamilton, *J. Am. Chem. Soc.*, **80**, 5411 (1958).

(3) W. Gerrard, M. F. Lappert and C. A. Pearce, *J. Chem. Soc.*, 381 (1957).

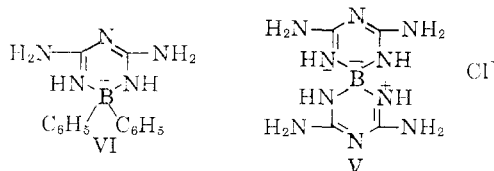
(4) D. W. Aubrey and M. F. Lappert, *Proc. Chem. Soc.*, 148 (1960).

(5) W. D. English, A. L. McCloskey and H. Steinberg, *J. Am. Chem. Soc.*, **83**, 2122 (1961).

(6) D. W. Aubrey, M. F. Lappert and H. Pysora, *J. Chem. Soc.*, 5239 (1960).

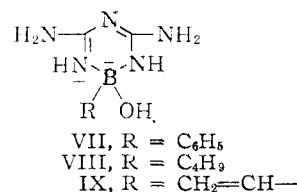
(7) C. F. P. Ray, *Chem. Revs.*, **61**, 313 (1961).

A transamination reaction of biguanide with tris-(dimethylamino)-borane similarly did not produce an isolable trivalent boron heterocycle but resulted in the formation of a spiro compound, isolated as the hydrochloride V, with two biguanide residues attached to boron. The nature of V was established by elemental analysis, by its molecular weight in water which accorded with that of a salt, and by the ultraviolet spectrum which showed a band at 219 mμ (ϵ 33,650) with an intensity approximately double that of the biguanidinium ion (λ_{max} 231, 15,200).

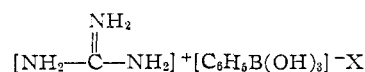


Synthesis of a monocyclic system with two phenyl groups on boron (VI) was accomplished by a transamination reaction of diethylaminodiphenylborane with biguanide. Like V, the infrared spectrum of VI did not show a band in the region 1350–1500 cm.⁻¹ for nitrogen bonded to trivalent boron, and, in addition, the boron magnetic resonance spectrum of VI in methanol was identical to that of sodium tetraphenylboronide in water⁸ (Table I), where boron is tetravalent.

Although the displacement of an hydroxyl group from boron by amines is generally difficult, the condensation of biguanide with phenylboronic acid to form VII in aqueous solution was surprisingly facile and essentially instantaneous. Compounds VIII and IX were prepared in a similar manner from butylboronic acid and vinylboronic acid, respectively. The polymer IV also afforded



VII on hydrolysis in aqueous dimethylformamide. In each of the compounds bearing the hydroxyl group, the charge on boron was the same as that in boron trifluoride etherate (Table I), and the elemental analysis, infrared spectrum and molecular weight agreed with the structure shown. Although a linear structure with a high electron density on boron through strong π -bonding with nitrogen is also conceivable, such a product is unlikely since with guanidine a condensation reaction with phenylboronic acid did not take place and only a



normal ionized salt (X) was isolated. The identity of X was established by the molecular weight in water and from elemental analysis.

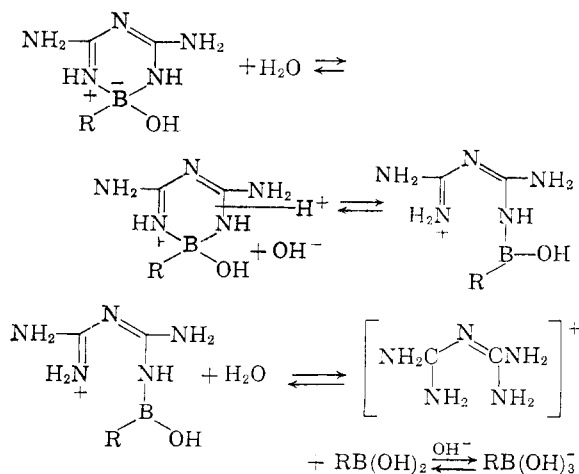
(8) T. P. Onak, H. Landesman, R. E. Williams and I. Shapiro, *J. Phys. Chem.*, **63**, 1533 (1959).

TABLE I
B'' N.M.R. CHEMICAL SHIFTS AND ULTRAVIOLET ABSORPTION SPECTRA OF SUBSTITUTED DIAZAAZONIABORINIDES

Compound	R	R'	Solvent	Chemical ^b shift	Solvent	λ_{\max} , m μ	ϵ
V			H ₂ O	219	33,650
Biguanide hydrochloride			H ₂ O	231	15,200
VI	C ₆ H ₅	C ₆ H ₅	MeOH	+8
			MeOH (HCl)	+15
VII	C ₆ H ₅	OH	MeOH	+6	H ₂ O	231	7,050
	C ₆ H ₅	OEt	EtOH	+2	EtOH	232	7,790
VIII	C ₄ H ₉	OH	MeOH	+1	H ₂ O	231	7,060
IX	C ₆ H ₅	OH	H ₂ O	231	7,160
XI ^a	OH	OH	MeOH	-2	H ₂ O	224	12,350
XII	OCH ₃	OCH ₃	MeOH	-2	MeOH	226	14,700

^a Measured as the monohydrate. ^b Relative to boron trifluoride etherate = 0.

By means of ultraviolet analysis, compounds VII, VIII and IX were found to hydrolyze reversibly. An initial solution of each of the compounds in water showed a single band at 231 m μ (ϵ 7000–8000) which slowly increased in intensity with time until an equilibrium was established. The addition of base retarded the change in absorption, but acid immediately caused an increase to that of the biguanidinium ion (λ 231, ϵ 15,200). The presence of the biguanidinium ion was also detected by forming the copper biguanide chelate with ammoniacal copper sulfate. Since the absorption at equilibrium *i.e.*, the formation of the biguanidinium ion, was reduced by adding the respective boronate anions (equivalent proportions of boronic acid and sodium hydroxide) to solutions of the heterocycles, this observation together with the effect of acid and base suggests that the mechanism of hydrolysis comprises an initial protonation of the ring to effect withdrawal of electrons from the B–N bond. Further attack by water on boron in the open structure



would then result in cleavage of the second B–N bond, and the position at equilibrium is subject to the concentration of the various species present.

As further evidence for the mechanism a comparison of the increase in absorption for solutions of VII (R = C₆H₅) and VIII (R = C₄H₉) contain-

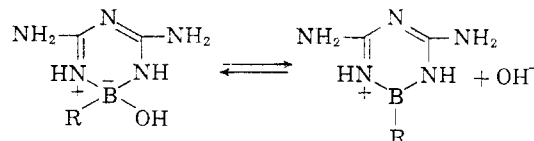
ing (1) the respective boronate anion (boronic acid and sodium hydroxide) and (2) sodium hydroxide alone showed that at equilibrium a smaller increase had occurred with 1 than 2 (Table II). A reverse

TABLE II
HYDROLYSIS STUDIES OF DIAZAAZONIABORINIDES

Compound	R	Init. concn., mM	OH ⁻ concn., mM	Boron acid concn., mM	A_{231}	Hydroly- sis, %
VII	C ₆ H ₅	1.32			1.47	34
		1.31	4.0		1.15	21
		1.31	4.0 (3.0) ^a	3.1	1.11	17
VIII	C ₄ H ₉	7.60			6.12	12
		1.52			1.48	33
		1.52	0.49		1.39	25
IX	CH ₂ =CH	1.52	0.49 (0.13) ^a	0.49	1.35	23
		1.77			1.92	43
		3.99			5.54 ^b	79
XI	OH	1.00	5.0		1.22 ^b	51
		1.00	5.0 (0.19) ^a	5.0	1.08 ^b	29

^a Calculated hydroxide ion concentration after neutralization of the boron acids. The K_a values of the acids were obtained from the literature.⁹ ^b ϵ_{231} for XII was 9,050.

effect of reactants would have resulted had the change in absorption been caused by the dissociation of the hydroxyl group from boron.

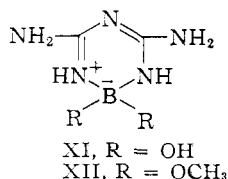


On dissolution of compound VII in alcohol, esterification gave the cyclic ethyl ester. Unlike diethyl phenylboronate, hydrolysis of the B–O bond did not occur under atmospheric conditions, although an immediate hydrolysis took place on addition of water. In alcohol no solvolysis of the B–N bond to form the biguanidinium ion was observed from the ultraviolet spectrum.

(9) D. L. Yabroff, G. E. K. Branch and B. Bettman, *J. Am. Chem. Soc.*, **56**, 1850 (1934).

From spectral studies compounds V and VI were found to be stable to hydrolysis. Upon addition of hydrochloric acid to a methanolic solution of VI the electron density at boron increased appreciably according to the boron magnetic resonance spectrum. This result, while not expected, suggests however that cleavage of the B-N bonds did not occur since hydrolysis requires the concomitant formation of diphenylborinic acid and the biguanidinium ion and thus a lower electron density with a trivalent boron compound.⁸

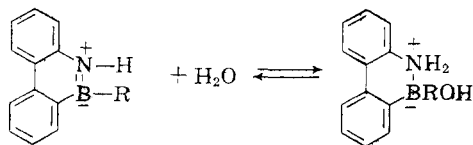
With compound V the ultraviolet spectrum showed a band at 219 m μ which shifted in acid solution to 216 m μ and was unchanged after 48 hours; on neutralization with base the band returned immediately to 219 m μ . Had hydrolysis taken place, a shift of the band to 231 m μ would have occurred as a consequence of an irreversible cleavage of the B-N bonds to boric acid and the biguanidinium ion. Under a variety of conditions a synthesis of the spiro structure could not be effected by the reverse reaction of biguanide with boric acid or trimethyl borate. With boric acid a monohydrate of XI was isolated and was shown by ultraviolet analysis to hydrolyze reversibly. In aqueous solution the compound showed a single peak, shifted from the expected position at 231 to 224 m μ , and at equilibrium the position of the band was intermediate of the two depending on the concentration. Water of hydration was strongly bound in the crystal lattice of the solid and was lost on heating to 150°. The anhydro form was unstable to moisture, however, and reverted to the monohydrate in air. Trimethyl borate and biguanide gave the



ester XII which hydrolyzed slowly in air to the hydrate of XI but was stable to cleavage of the B-N bonds in methanol according to the ultraviolet spectrum.

Conclusions

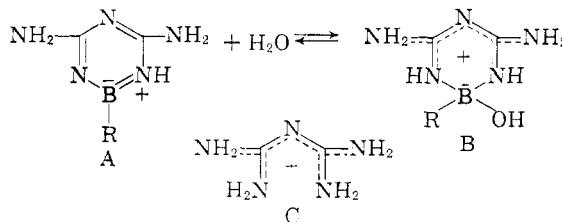
A fundamental difference between the behavior of the heterocycles obtained in the present work and those of Dewar is evident from the data presented. Derivatives of 10,9-borazarophenanthrene show phenanthrene-like aromaticity¹² which is lost on addition reactions across the $>\bar{B}=\bar{N}<$ dipolar bond.¹⁰ While addition of water to the latter was indicated from deuterium exchange of the imino



hydrogen, the equilibrium is far to the left. In contrast, little if any reduction in charge delocali-

(10) M. J. S. Dewar and P. M. Maitlis, *J. Am. Chem. Soc.*, **83**, 187 (1961).

zation occurs on addition of water across the $>\bar{B}=\bar{N}<$ bond of A to form B. This delocalization,



which is not permitted in the borazarophenanthrene-water adduct, apparently stabilizes B to a greater extent than A since compounds of type B and not type A were always isolated. A similar distribution of charge readily explains the extreme stability of the conjugate acid of biguanide (C) and of guanidine.¹¹

The stability of the borinide rings to solvolysis is undoubtedly influenced by electron release or withdrawal by substituents on boron and the consequent effect on the ease of dissociation of the B-N bond. The positively charged rings in the spiro structure V and the phenyl groups in VI were found to provide stability; hyperconjugative electron release from oxygen to boron should weaken bonding from nitrogen to boron and as outlined earlier bond cleavage occurred with an hydroxyl group on boron. Correlations of the B-O stretching frequency for boric acid and its esters, and phenylboronic acid and its esters, have been interpreted as indicating a greater hyperconjugative electron release from oxygen to boron in the acids.⁶ On this basis the stability of the B-N bonds in XII and the ethyl ester of VII to alcoholysis is understandable.

Experimental

Bis-(dimethylamino)-phenylborane.—Phenylboron dichloride¹² (59.4 g., 0.374 mole) in 25 ml. of benzene was added over 1 hour with stirring to 1.80 moles (120 ml. at Dry Ice-acetone temperature) of dimethylamine in 450 ml. of benzene cooled in an ice-bath. Insoluble dimethylamine hydrochloride was collected on a filter and the benzene solution was distilled first at atmospheric pressure and then under reduced pressure to give 51.0 g. (78%) of bis-(dimethylamino)-phenylborane, b.p. 92° (7 mm.). *Anal.* Calcd. for C₁₀H₁₇N₂B: C, 68.2; H, 9.67; N, 15.9; B, 6.14. Found: C, 67.8; H, 9.76; N, 15.8; B, 6.49.

Tris-(dimethylamino)-borane was prepared as above from 0.51 moles (42 ml. at Dry Ice temperature) of boron trichloride and 3.35 moles (222 ml.) of dimethylamine; yield 40.0 g. (55%), b.p. 147–148° (lit.¹³ 147.5°).

Diethylaminodiphenylborane.—Tris-(diethylamino)-borane (54.6 g., 0.25 mole) prepared as described in the literature⁵ was cooled to 0° and treated with 60 g. (0.51 mole) of boron trichloride. After standing overnight, the mixture was distilled under reduced pressure to yield 87.0 g. (78%) of diethylaminoboron dichloride.¹⁴ A portion (46.0 g., 0.30 mole) in 200 ml. of ether was treated dropwise phenylmagnesium bromide (0.66 mole of magnesium, 0.66 mole of bromobenzene) in ether at such a rate that the solution refluxed gently. The solution was heated for 1.5 hours, treated with 135 ml. (1.32 mole) of diethylamine to precip-

(11) G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1955, p. 358.

(12) D. R. Nielsen and W. E. McEwen, *J. Am. Chem. Soc.*, **79**, 3081 (1957).

(13) E. Wiberg and K. Schuster, *Z. anorg. Chem.*, **213**, 77 (1933).

(14) R. C. Osthoff and C. A. Brown, *J. Am. Chem. Soc.*, **74**, 2375 (1952).

itate the magnesium salts and heated again for 3 hours. The product was isolated by distillation under reduced pressure in 58% yield (41.4 g.), b.p. 156° (6 mm.).

Anal. Calcd. for $C_{16}H_{20}NB$: C, 81.0; H, 8.44; N, 5.90; B, 4.56. Found: C, 80.16; H, 8.46; N, 5.83; B, 4.99.

Biguanide.—Anhydrous biguanide sulfate was prepared by heating the dihydrate at 110° for 8 hours. To 13.5 g. (0.334 mole) of sodium hydroxide in 400 ml. of dry methyl alcohol was added 50.0 g. (0.167 mole) of the salt. The mixture was stirred at room temperature for 2 hours and then refluxed for 45 minutes. The insoluble sodium sulfate was collected, washed with methanol and the combined methanol solution was concentrated to a small volume under reduced pressure. The crystalline product which separated was isolated in 81% yield, m.p. 142° (lit.¹⁵ 142°).

2-Phenylborobenzimidazole (I).—To a suspension of 2.88 g. (0.027 mole) of *o*-phenylenediamine in 40 ml. of benzene was added 4.7 g. (0.027 mole) of bis-(dimethylamino)-phenylborane in 20 ml. of benzene and the mixture was heated to reflux for 1.5 hours. After cooling, the solution deposited 3.4 g. (65%) of I, m.p. 209–210°, which after one recrystallization from benzene gave pure I, m.p. 214–215°. Additional material, 1.7 g., was obtained by evaporating the mother liquors to a small volume.

Anal. Calcd. for $C_{12}H_{11}N_2B$: C, 74.3; H, 5.67; N, 14.4; B, 5.57. Found: C, 74.57; H, 6.00; N, 13.9; B, 5.10.

Transamination of Bis-(dimethylamino)-phenylborane with Biguanide.—To 5.40 g. (0.0535 mole) of biguanide suspended in 75 ml. of dry pyridine was added 9.45 g. (0.0534 mole) of bis-(dimethylamino)-phenylborane. The mixture was heated nearly to reflux for 1 hour under dry nitrogen after which the evolution of dimethylamine could not be detected with moist litmus paper. The evolved gas collected in 0.5 *N* hydrochloric acid corresponded to 89% of theory for the displacement of two dimethylamino groups. The insoluble product IV, poly-[(4-amino-1,2,3-trihydro-2-phenyl-3,5,1,2-diazaazoniaborinid-2,6-amer)-*alt*-azamer] was collected and dried under high vacuum at 110°, m.p. > 400°, yield 7.0 g. (70%).

Anal. Calcd. for $C_8H_{10}N_3B$: C, 51.4; H, 5.35; N, 37.5; B, 5.78. Found: C, 51.2; H, 5.81; N, 37.2; B, 5.71.

Reaction of Biguanide with Tris-(dimethylamino)-borane.—A solution of 18.45 ml. of tris-(dimethylamino)-borane (0.099 mole) in 25 ml. of dry pyridine was added dropwise to a stirred solution of 20 g. (0.20 mole) of biguanide in 400 ml. of hot pyridine. An insoluble precipitate formed immediately which did not appear to change on extended heating. After heating at reflux for 2 hours, the mixture was cooled and the solid was collected and washed with benzene; yield 21.7 g., m.p. > 400°.

A portion of the transamination product, 19.7 g., was slurried in 20 ml. of water, heat was evolved and after a few minutes the mixture solidified. The solid was collected and washed with acetonitrile; yield 23.5 g., m.p. > 400°. Acidification of 20.5 g. of the latter suspended in 200 ml. of water with 217 ml. of 0.5 *N* hydrochloric acid gave a solution of pH 5.50. Evaporation of the solution under reduced pressure to 140 ml. resulted in the precipitation of 5.23 g. of 2,4,8,10-tetraamino-1,7-dihydro-3,5,9,11-tetraaza-1,7-diazonia-6-boridasp[ro]undeca-1,3,7,9-tetraenechloride (V), m.p. > 400°, which corresponded to 28% of the biguanide employed in the reaction.

Anal. Calcd. for $C_4H_{12}N_{10}BCl$: C, 19.5; H, 4.88; N, 56.9; B, 4.39; Cl, 14.4; mol. wt., 123; formula wt., 246. Found: C, 18.9; H, 4.71; N, 55.5; B, 5.33; Cl, 14.6; mol. wt. (in water), 113.

4,6-Diamino-1,2,3-trihydro-2,2-diphenyl-3,5,1,2-diazaazoniaborinide (VI).—A solution of 4.82 g. (0.048 mole) of biguanide and 1.31 g. (0.048 mole) of diethylaminodiphenylborane in 100 ml. of pyridine was refluxed for 1 hour, and evaporated to dryness. The residue was dissolved in 40 ml. of methyl alcohol and treated with excess water to precipitate 11.47 g. of X (90%), m.p. 265–266° dec.

Anal. Calcd. for $C_{14}H_{16}N_8B$: C, 63.4; H, 6.03; N, 26.4; B, 4.07. Found: C, 63.39; H, 6.06; N, 26.7; B, 3.99.

4,6-Diamino-1,2,3-trihydro-2-hydroxy-2-phenyl-3,5,1,2-diazaazoniaborinide (VII).—A solution of 3.0 g. of phenyl-

boronic acid and 2.5 g. of biguanide in 30 ml. of hot water on cooling deposited 3.85 g. (76%) of VII. The compound decomposed at 226–230° to a solid which was infusible below 400°.

Anal. Calcd. for $C_8H_{12}N_5BO$: C, 46.9; H, 5.85; N, 34.1; B, 5.26; mol. wt., 222. Found: C, 46.7; H, 5.71; N, 34.1; B, 3.86; mol. wt. (in water), 205.

Compound VII was also isolated from the hydrolysis of 1.0 g. of IV by adding 0.5 ml. of water to a solution of IV in 6 ml. of dimethyl formamide; yield 0.5 g., m.p. 225–228° dec. The infrared spectrum after recrystallization from water was identical to the product prepared above. The mother liquor from the hydrolysis step deposited 0.43 g. of unchanged IV by dilution with acetonitrile.

Esterification of Compound VII.—A 1.0 g. sample was dissolved in 20 ml. of boiling ethyl alcohol. On cooling, 0.70 g. of 4,6-diamino-1,2,3-trihydro-2-ethoxy-2-phenyl-3,5,1,2-diazaazoniaborinide, a microcrystalline solid, precipitated; m.p. > 260°. An additional 0.30 g. was obtained when the solution was evaporated to dryness.

Anal. Calcd. for $C_{10}H_{16}N_5BO$: C, 51.5; H, 6.85; N, 30.0; B, 4.63. Found: C, 51.8; H, 7.17; N, 29.6; B, 4.83.

4,6-Diamino-1,2,3-trihydro-2-butyl-2-hydroxy-3,5,1,2-diazaazoniaborinide (VIII) was prepared by mixing 6.0 g. (0.05 mole) of *n*-butylboronic acid in 35 ml. of warm water with 5.0 g. (0.05 mole) of biguanide in 35 ml. of water. The crystalline product was collected, washed with water and acetonitrile; yield 5.78 g., (68%), m.p. 192–218° dec. and at 274–276° dec.

Anal. Calcd. for $C_8H_{16}N_5BO$: C, 39.0; H, 8.65; N, 37.9; B, 5.85; mol. wt., 188. Found: C, 38.6; H, 8.67; N, 37.5; B, 5.95; mol. wt. (in water), 184.

4,6-Diamino-1,2,3-trihydro-2-hydroxy-2-vinyl-3,5,1,2-diazaazoniaborinide (IX).—On mixing 7.0 g. (0.07 mole) of biguanide and 12.89 g. (0.07 mole) of di-*n*-butyl vinylboronate¹⁶ in 15 ml. of water no precipitate formed. Slow addition of acetonitrile gave a brownish gum which was removed by decanting the mother liquor. The first crop of crystals (1.20 g.) was collected after 250 ml. of acetonitrile had been added. A second crop (3.24 g.) was collected after a total of 550 ml. of acetonitrile had been added; yield 41%, m.p. 178–180° dec.

Anal. Calcd. for $C_4H_{10}N_5BO$: C, 31.0; H, 6.45; N, 45.1; B, 6.97. Found: C, 30.9; H, 6.52; N, 47.3; B, 6.94.

4,6-Diamino-1,2,3-trihydro-2,2-dihydroxy-3,5,1,2-diazaazoniaborinide (XI).—The monohydrate of compound XI precipitated in 88% yield when a hot solution of 3.0 g. of biguanide and 1.83 g. of boric acid was cooled to room temperature.

Anal. Calcd. for $C_2H_{10}N_5BO_3$: C, 14.75; H, 6.14; N, 43.0; B, 6.64; mol. wt., 163. Found: C, 15.18; H, 6.44; N, 43.70; B, 6.9; mol. wt. (in water), 153.

On heating 1.0 g. of the hydrate in 25 ml. of dodecane at 163° a molecule of water was evolved rapidly, and the anhydro form was collected by filtration.

Anal. Calcd. for $C_2H_8N_5BO_2$: C, 16.6; H, 5.52; N, 48.4; B, 7.46. Found: C, 16.5; H, 5.73; N, 48.1; B, 7.31.

In air, recombination with water was complete after 72 hours.

4,6-Diamino-1,2,3-trihydro-2,2-dimethoxy-3,5,1,2-diazaazoniaborinide (XII).—A warm solution of 2.7 g. of biguanide and 2.8 ml. of trimethyl borate in 20 ml. of methyl alcohol on cooling to room temperature gave 3.2 g. (75%) of compound XI.

Anal. Calcd. for $C_4H_{12}N_5BO_2$: C, 27.7; H, 6.94. Found: C, 26.6; H, 7.78.

Hydrolysis of the ester to the hydrate of XI slowly occurred in air and was complete according to the infrared spectrum after 24 hours.

Guanidinium Trihydroxyphenylborate (X).—A solution of 4.78 g. of guanidine hydrochloride in 25 ml. of water was neutralized with 2.0 g. of sodium hydroxide. The solution was mixed with 5.20 g. (0.05 mole) of phenylboronic anhydride in 35 ml. of hot water and cooled. The crystalline product, 4.30 g., was collected, washed with 50% aqueous

(15) K. H. Slotta and R. Tschesche, *Ber.*, **62B**, 1396 (1929).

(16) Kindly supplied by Mr. R. Kugel.

acetonitrile and then acetonitrile. An additional 3.19 g. was obtained when the combined liquors were evaporated to about 20 ml. under reduced pressure. The ultraviolet spectrum of a solution of the salt in water was the same as an alkaline solution of phenylboronic acid.

Anal. Calcd. for $C_7H_{14}N_3BO_3$: C, 42.2; H, 7.04; N, 21.1; B, 5.43; formula wt., 199; mol. wt., 99. Found: C, 42.6; H, 7.11; N, 21.3; B, 5.64; mol. wt. (in water), 92.

B^{11} N.m.r. Chemical Shifts.—The nuclear magnetic resonance spectra were obtained using a Varian high resolution nuclear magnetic resonance spectrometer. The chemical shifts in Table I are relative to boron trifluoride etherate as zero reference. Because of the breadth of the resonance lines and the consequent uncertainty in fixing the exact position of the bands, the effect of the substituents on the chemical shielding of boron could not be delineated with assurance.

Ultraviolet Absorption Measurements.—The ultraviolet absorption studies were performed with a Cary automatic recording spectrophotometer, Model 11. The spectra of compounds VII, VIII, IX and XI (Table I) were obtained

with alkaline solutions in order to retard changes in the spectra due from hydrolysis.

Solutions for hydrolysis studies were prepared by adding aqueous sodium hydroxide alone or together with an aqueous solution of the requisite boron acid to stock solutions of the cyclic borinides. The amount of biguanidinium ion, and hence the extent of hydrolysis, at equilibrium (Table II) was calculated from the equation

$$C_2 = (A_{231} - \epsilon_1 C_1) / (\epsilon_2 - \epsilon_1)$$

where C_1 represents the initial concentration of the heterocycle C_2 the concentration of biguanidinium ion, A_{231} the absorption in a 1-cm. cell, and ϵ_1 and ϵ_2 the molar extinction coefficient of the heterocycle of biguanidinium ion, respectively, at 231 m μ .

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The Protonation of Indoles: Position of Protonation

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The principal conjugate acid of an indole in strong aqueous acids is the 3-protonated isomer. This has been inferred from ultraviolet absorption spectra and confirmed by proton magnetic resonance measurements on a series of methylindoles. Deuterium exchange experiments show that exchange occurs generally at the 1- and 3-positions of the indole ring, and in some cases at the 2-position. Exchange at the 1- and 2-positions may occur by protonation of those positions. Some evidence for 1-protonation is provided by the infrared spectra of solid salts of indoles, which show the presence of 1- or 3-protonated species or both, depending on the indole, the acid and the method of isolation of the salt. In the conjugate acid of an indole, exchange in the 2-position takes place by protonation competitive with that at the 3-position, whereas exchange at the 1-position takes place by proton loss competitive with that at the 3-position. Diprotonation does not appear to be important in any of the exchange processes. The effects of methyl substituents in the hetero ring on the relative extents of 3- and 2-protonation are discussed.

The protonation of the indole nucleus has been of interest for many years from both theoretical and synthetic points of view. Although feebly basic, simple alkyl derivatives of indole form isolable salts with strong acids.¹ Moreover, a number of reactions of indoles are acid catalyzed. Dimerization and trimerization,² hydrogenation³ and attack by molecular oxygen³ fall in this group. The orientation and ease of reaction in electrophilic substitutions such as nitration will certainly be influenced by the extent of prior protonation.⁴

Two fundamental problems arise in a consideration of the protonation of the indole nucleus and its bearing on the reactions mentioned above. The first, which is the main subject of this paper,

is the position of protonation. The second question, which will be treated in more detail in a subsequent paper, concerns the basicity of indole relative to other well-known bases, and the effect of substituents on the basicity.^{5,6}

Every position of the hetero ring of indole has been suggested as the site of protonation.^{2,4a,7} Some evidence which bears on this point was provided by Koizumi, who studied the acid-catalyzed exchange of deuterium in D_2O for ring hydrogens of indole and a number of its methyl derivatives.^{7,8} With increasing concentration of acid, first the hydrogen on nitrogen and then both that hydrogen and the β -hydrogen underwent exchange. At still higher concentrations of acid ($> 0.8 N$ HCl) further exchange occurred.⁹ It

(1) (a) P. Wagner, *Ann.*, **242**, 388 (1887); (b) K. A. Hofmann, A. Metzler and K. Hobold, *Ber.*, **43**, 1082 (1910); (c) B. Oddo, *Gazz. chim. ital.*, **43** I, 385 (1913).

(2) (a) G. F. Smith, *Chemistry & Industry*, 1451 (1954); (b) W. E. Noland and C. F. Hammer, *J. Org. Chem.*, **25**, 1525 (1960); (c) R. L. Hinman and E. Shull, *ibid.*, **26**, 2339 (1961).

(3) R. L. Hinman and P. Frost, in "Plant Growth Regulation," R. L. Klein, Ed., Iowa State Univ. Press, Ames, Iowa, 1961, p. 205; also unpublished work from this Laboratory. It has recently been suggested that reduction of indoles in acidic media may take place by way of a protonated indole (A. R. Bader, R. J. Bridgwater and P. R. Freeman, *J. Am. Chem. Soc.*, **83**, 3319 (1961)). In the pyrrole series the catalytic effect of acids on oxidation and hydrogenation (A. Treibs and H. G. Kolm, *Ann.*, **606**, 166 (1957)) and on trimerization (H. A. Potts and G. F. Smith, *J. Chem. Soc.*, 4018 (1957)) has also been noted.

(4) (a) R. de Fazi, G. Berti and A. da Settimo, *Gazz. chim. ital.*, **89**, 2238 (1959); (b) W. E. Noland, Univ. of Minnesota, personal communication.

(5) R. L. Hinman and J. Lang, *Tetrahedron Letters*, **21**, 12 (1960).

(6) The basicities of a number of methylpyrroles and identification of the α -position as the site of protonation have recently been reported (R. J. Abraham, E. Bullock and S. S. Mitra, *Can. J. Chem.*, **37**, 1859 (1959)).

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(8) M. Koizumi and T. Titani, *Bull. Chem. Soc. Japan*, **13**, 307 (1938); M. Koizumi, *ibid.*, **14**, 453 (1939).

(9) Exchange of the α -hydrogen was suggested to explain the results at the higher acid concentrations. Although exchange at this position occurs in some cases (see below), it is not clear that this was proved by the early work, the results of which were obscured by the occurrence