[CONTRIBUTION FROM THE AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

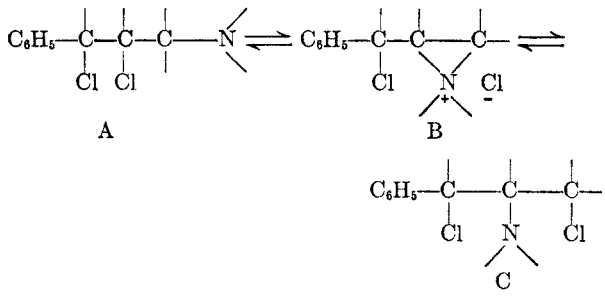
β,γ-Dihalopropylamines. II. 1-Amino-2,3-dichloro-3-phenylpropanes and Bis(β,γ-dichloropropyl)amines

RONALD A. MITSCH AND NORMAN H. CROMWELL

Received March 23, 1960

The hydrochlorides of 1-piperidino-, 1-dimethylamino-, 1-dibenzylamino-, 1-methylbenzylamino-, and 1-morpholino-2,3-dichloro-3-phenylpropane have been prepared by chlorine addition to the corresponding cinnamylamine hydrochlorides, obtained from the reaction of cinnamyl bromide with the corresponding secondary amine. These β,γ-dichloropropylamine hydrochlorides react very slowly with piperidine to produce triaminopropanes. The hydrochlorides of bis-*N*,*N*-(2,3-dichloro-3-phenylpropyl)-1-benzylamine and the 1-methylamine analogue were prepared by chlorination of the corresponding *N*,*N*-dicinnamylamines. *N*-(2,3-Dichloro-3-phenylpropyl)-*N*-(2,3-dichloropropyl)-1-benzylamine hydrochloride was also prepared by chlorination of *N*-allyl-*N*-benzylcinnamylamine hydrochloride. These compounds have been synthesized for pharmacological testing as antitumor agents, etc.

As a continuation of a general program concerned with the synthesis of potential anticancer agents, it seemed of interest to obtain for pharmacological testing a series of compounds having the functional group arrangement represented by the general formulas A and/or C.[1]



The relationship of the structural arrangements of A and C to that present in the nitrogen mustards is apparent. Compounds of type A and C might be expected to be converted to the potentially pharmacologically important[2,3] intermediate quaternary ethylenimmonium chloride (B) in neutral or basic media.

A possible method of synthesis for compounds of structure A and/or C involves the addition of chlorine to cinnamylamines. It has been shown from a series of melting point experiments that a compound of type C may rearrange to the isomeric type A on heating to its melting point.[1] The structures of type A seem to be thermodynamically more stable than those of type C.

The necessary cinnamylamines were prepared readily by the reaction of cinnamyl bromide with two equivalents of the respective secondary amine in ether or on refluxing in benzene solution. The conditions of reaction and the isolation techniques were varied somewhat in each case to obtain optimum yields of pure materials where possible. In this way the *N*-cinnamylpiperidine, morpholine, dimethylamine, methylbenzylamine, and dibenzylamine hydrochlorides were usually obtained in good yields.

N,*N*-Dimethylcinnamylamine hydrochloride had previously been prepared by Mannich and Chang,[4] and later by Braun and Kohler,[5] by heating cinnamyl bromide, and dimethylamine. *N*-Benzyl-*N*-cinnamylmethylamine hydrochloride had also been previously prepared from benzyl bromide and *N*-methylcinnamylamine by Blicke and Zienty,[6] who found this compound to possess weak antispasmodic activity.

Because of the hygroscopic nature of the hydrochloride salt of *N*,*N*-dibenzylcinnamylamine, this compound resisted purification and could not be isolated in the solid state, but remained as an oil. In the case of the less reactive cinnamyl chloride, a reaction temperature 50° higher was necessary to obtain a comparable yield of *N*-cinnamylpiperidine hydrochloride.

Chlorine was added to the cinnamylamine hydrochlorides in chloroform solution to produce the 1-amino-2,3-dichloro-3-phenylpropane hydrochlorides. In this way 1-piperidino, 1-dimethylamino, 1-morpholino, 1-dibenzylamino, and 1-methylbenzylamino-2,3-dichloro-3-phenylpropane hydrochlorides were obtained in good yields.

The relatively low level of reactivity of the halogen atoms in the 1-amino-2,3-dichloro-3-phenylpropanes is indicated by the fact that the free bases can be isolated from their hydrochloride salts in the presence of sodium hydroxide, and also by the severity of the conditions required to obtain their

(1) N. H. Cromwell and A. Hassner, *J. Am. Chem. Soc.*, **77**, 1568 (1955).

(2) The vesicant properties of tris(β-chloroethyl)amine and methylbis-(β-chloroethyl)amine are well known, see: (a) K. Ward, *J. Am. Chem. Soc.*, **57**, 914 (1935); (b) O. Eisleb, *Ber.*, **74**, 1433 (1941); (c) K. A. Jensen and F. Lundquist, *Dansk. Tidsskr. Farm.*, **15**, 201 (1941). These compounds have been called "nitrogen mustards" because of their relationship structurally and biologically with mustard gas.

(3)(a) A. Gilman and F. S. Philips, *Science*, **103**, 409 (1946); (b) E. Boyland, *Brit. J. Pharmacol.*, **1**, 247 (1946).

(4) C. Mannich and Fu Tsong Chang, *Ber.*, **66B**, 419 (1933).

(5) J. von Braun and Z. Köhler, *Ber.*, **51**, 85 (1918).

(6) F. Blicke and F. B. Zienty, *J. Am. Chem. Soc.*, **61**, 775 (1939).

reaction with piperidine.[7] When 1-piperidino-2,3-dichloro-3-phenylpropane hydrochloride was refluxed for two days with five molar equivalents of piperidine in absolute ethanol, a low yield of the 1,2,3-tripiperidino-3-phenylpropane was obtained as shown by an ionic chlorine analysis of the isolated trihydrochloride salt.

To obtain another series of analogous materials for pharmacological testing, certain bis (β,γ-dichloropropyl)amine hydrochlorides were made by adding chlorine to the respective unsaturated amine. In general, methods for preparation of the unsaturated amine similar to those reported by previous workers, in which an aqueous medium was employed, failed to proceed satisfactorily.[8] Even in anhydrous ether the reaction products of cinnamyl bromide with the primary amine were often brown colored oils which resisted further purification and were consequently used as such in the chlorination reaction. In this manner the hydrochloride salt of *N,N*-dicinnamylmethylamine and the free base *N,N*-dicinnamylbenzlamine were prepared in fair yields.

N-Allyl-*N*-cinnamylbenzylamine hydrochloride was obtained by reacting cinnamyl bromide in ether solution with *N*-allylbenzylamine formed by the action of allyl bromide with benzylamine at room temperature. The hydrochloride salt of *N,N*-dicinnamylmethylamine had been previously prepared for antispasmodic studies by Blicke and Zienty.[6]

The preparation of the tetrachloro derivatives of the *N,N*-dicinnamyl- and *N*-allyl-*N*-cinnamylamines was a relatively simple procedure because the unsaturated amine hydrochloride salts were quite soluble in chloroform. Thus, by adding chlorine to the unsaturated amine hydrochloride dissolved in cold chloroform, the hydrochloride salts of bis(2,3-dichloro-3-phenylpropyl)-1-methylamine, bis(2,3-dichloro-3-phenylpropyl)-1-benzylamine, and *N*-(2,3-dichloropropyl)-*N*-(2,3-dichloro-3-phenylpropyl)-1-benzylamine were obtained.

When the oily material from the reaction of allyl bromide with benzylamine in refluxing benzene, which was assumed to be *N,N*-diallylbenzylamine hydrochloride, was chlorinated in chloroform, a material was isolated which possessed analytical percentages which could possibly be accounted for by the elimination of the benzyl group. Earlier reports state that dealkylation sometimes occurs with tertiary amines in carbon tetrachloride on adding bromine,[9] with the possibility of hydrolysis not being excluded.

Several of the β,γ-dichloroamines reported here either have been or are being tested in mice for anti-tumor activity by the Cancer Chemotherapy, National Service Center, National Institutes of Health, Bethesda, Maryland. They are also being tested for antihistaminic, anticonvulsant, adrenolytic and preganglionic blockade activity by Smith, Kline and French Laboratories, Philadelphia, Pennsylvania. The results of these tests will be reported elsewhere.

EXPERIMENTAL[10]

Cinnamyl bromide.[11] This material was prepared in 82–90% yields from cinnamyl alcohol and 48% hydrobromic acid by stirring at room temperature for 3 hr. Suitable purification was attained by separating and thoroughly mixing the greenish-oily layer with methanol, then discarding the methanol layer. Washing an ethereal solution of the bromide with water followed by drying and distillation gave a pure production, b.p. 91° (0.75 mm); n_D^{25} 1.6100.

N-Cinnamyldimethylamine hydrochloride. The preparation of this amine was accomplished by slowly adding 2 molar equivalents of anhydrous dimethylamine dissolved in ether to a cooled ethereal solution of cinnamyl bromide. The dimethylamine hydrobromide was removed by filtration after stirring overnight. The ether solution was washed with water, dried, and saturated with dry hydrogen chloride gas. The resulting colorless solid hydrochloride was removed and recrystallized from ethanol-ether in 82.5% yield, m.p. 189–191° (lit.,[12] m.p. 188°).

Anal. Calcd. for $C_{11}H_{16}NCl$: C, 66.82; H, 8.16; N, 7.08; Cl^-, 17.94. Found: C, 67.46; H, 8.03; N, 6.93; Cl^-, 18.38.[13]

1-Dimethylamino-2,3-dichloro-3-phenylpropane hydrochloride. A 3.0-g. sample of the recrystallized hydrochloride of *N*-cinnamyldimethylamine was dissolved in 100 ml. of dry chloroform and tank chlorine gas passed into the cooled solution over a period of 30 min. After standing at room temperature for 3 hr. partial evaporation of the solvent gave the colorless product, 3.25 g. (80% yield); recrystallized from ethanol-ether, m.p. 171–172.5°.

Anal. Calcd. for $C_{11}H_{16}NCl_3$: C, 49.18; H, 6.00; N, 5.22; Cl^-, 13.07. Found: C, 48.85; H, 6.16; N, 4.94; Cl^-, 12.96.

N-Cinnamylpiperidine hydrochloride. This material was prepared from cinnamyl bromide and 2 molar equivalents of piperidine in ether solution at room temperature. The reaction mixture was worked up in the usual manner to give 74–75% yields of the colorless hydrochloride salt, m.p. 207–209°; recrystallized from ethanol-ether, m.p. 207–208.5°.

Anal. Calcd. for $C_{14}H_{20}NCl$: C, 70.73; H, 8.48; N, 5.89; Cl^-, 14.91. Found: C, 70.78; H, 8.35; N, 5.81; Cl^-, 14.82.

The amine hydrochloride was also prepared from cinnamyl chloride (Eastman-3286) and 2 molar equivalents of piperidine, both in ether, (46.5% yield) by stirring at room temperature overnight, and in a 60% yield in refluxing benzene, m.p. 208.5–210°.

1-Piperidino-2,3-dichloro-3-phenylpropane hydrochloride. This dichloro compound was prepared by dissolving *N*-cinnamylpiperidine hydrochloride in chloroform and saturating with dry chlorine gas. The colorless hydrochloride salt was removed in an 85–95% yield by filtration after warming the chloroform solution and adding ether to induce crys-

(7) This property had been demonstrated with 1-amino-2,3-dichloropropanes, see Ref. 1.

(8) A. Parthiel and H. von Broich, *Ber.*, **30**, 618 (1897).

(9) H. Böhme and W. Krause, *Ber.*, **84**, 170 (1951).

(10) All melting points reported here are those obtained by heating the sample at the rate of 3° per min. unless otherwise stated.

(11) L. Claisen and E. Tietze, *Ber.*, **58**, 279 (1925).

(12) *Beilstein*, **12**, 1189.

(13) Direct Volhard titration was employed for the determination of ionic halogen.

tallization; recrystallized from ethanol-ether, m.p. 171–172.5°.

Anal. Calcd. for $C_{14}H_{20}NCl_3$: C, 54.48; H, 6.54; N, 4.54; Cl^-, 11.46. Found: C, 54.58; H, 6.55; N, 4.39; Cl^-, 11.51.

N-Benzyl-N-cinnamylmethylamine hydrochloride.[6] The hydrochloride salt of this amine was prepared in an analogous manner from cinnamyl bromide and 2 molar equivalents of *N*-benzylmethylamine in an ether solution at room temperature. The product was exceedingly hygroscopic and recrystallization from ethanol-ether resulted in a colorless solid in 38.2% yield, m.p. 142–144° (Lit.,[6] m.p. 141–142°).

Anal. Calcd. for $C_{17}H_{20}NCl$: C, 74.57; H, 7.36; N, 5.12; Cl^-, 12.95. Found: C, 74.11; H, 7.40; N, 5.33; Cl^-, 12.83.

1-(N)-Benzylmethylamino-2,3-dichloro-3-phenylpropane hydrochloride. The dichloro derivative was made by dissolving *N*-benzyl-*N*-cinnamylmethylamine hydrochloride in chloroform and saturating the cooled solution with dry chlorine gas. Evaporation of the solvent gave an 84.6% yield of a colorless oil which was very difficult to purify. After trying a variety of solvents a colorless solid in 47.6% yield was finally obtained from *n*-butyl alcohol-ether after cooling for 1 month; m.p. 122–124°.

Anal. Calcd. for $C_{17}H_{20}NCl_3$: C, 59.23; H, 5.85; Cl, 30.86. Found: C, 59.47; H, 5.89; Cl, 30.79.

N-Cinnamyldibenzylamine hydrochloride. The crude hydrochloride of this amine was prepared by dissolving dibenzylamine (19.7 g.) and cinnamyl bromide (9.8 g.) in 150 ml. of dry benzene and refluxing for 4 hr. The dibenzylamine hydrobromide was removed by filtration, after which the benzene solution was washed with water, dried, and saturated with dry hydrogen chloride gas. The hygroscopic hydrochloride resisted purification and was therefore used as such in the following chlorination reaction.

1-(N)-Dibenzylamino-2,3-dichloro-3-phenylpropane hydrochloride. A cooled, chloroform solution of *N*-cinnamyldibenzylamine was saturated with dry chlorine gas. Evaporation of the solvent resulted in 12.2 g. of a viscous brown colored oil, recrystallized successively from *n*-butyl alcohol-ether and ethanol-ether; 4.1 g. (31.8% yield), m.p. 93–95°.

Anal. Calcd. for $C_{23}H_{24}NCl_3$: C, 65.65; H, 5.75; N, 3.33. Found: C, 65.51; H, 6.10; N, 3.34.

N-Cinnamylmorpholine hydrochloride. The procedure used was identical with that for *N*-cinnamylpiperidine hydrochloride, using cinnamyl bromide and morpholine. The hydrochloride salt was a colorless solid obtained in 78.4% yield, m.p. 209–210.5°.

Anal. Calcd. for $C_{13}H_{18}NClO$: C, 65.12; H, 7.57; N, 5.84. Found: C, 65.18; H, 7.60; N, 5.86.

1-Morpholino-2,3-dichloro-3-phenylpropane hydrochloride. Purified *N*-cinnamylmorpholine hydrochloride was dissolved in chloroform, saturated with chlorine, and ether added to crystallize the colorless solid in 99% yield, m.p. 163.5–165°.

Anal. Calcd. for $C_{13}H_{18}NCl_3O$: C, 50.26; H, 5.84; Cl, 34.24. Found: C, 50.05; H, 5.88; Cl, 34.54.

N-Allylbenzylamine hydrochloride. This amine was obtained while attempting to prepare *N,N*-diallylbenzylamine hydrochloride by treating allyl bromide (0.2 mole) with benzylamine (0.3 mole) in ether solution and stirring at room temperature for 3 days. The benzylamine hydrobromide was filtered and the ether extract washed with water, dried, and saturated with hydrogen chloride gas to give a 47.5% yield of a cream colored solid, recrystallized from ethanol-ether, m.p. 143.5–144°.

Anal. Calcd. for $C_{10}H_{14}NCl$: C, 65.37; H, 7.67; N, 7.63. Found: C, 65.64; H, 7.36; N, 7.44.

N-Allyl-N-cinnamylbenzylamine hydrochloride. A 2.3-g. sample of *N*-allylbenzylamine hydrochloride was dissolved in 10% sodium carbonate and extracted with ether. The ether filtrate was dried and to it was slowly added 1.23 g. of cinnamyl bromide. The mixture was warmed to reflux and stirred overnight. Filtration of the amine hydrobromide indicated 71% reaction. The ether filtrate was washed with water, dried, and saturated with dry hydrogen chloride gas to give 68.7% yield of a hygroscopic colorless solid which resisted purification and was used as such in the chlorination reaction.

N-(2,3-Dichloro-3-phenylpropyl)-N-(2,3-dichloropropyl)-1-benzylamine hydrochloride. The crude oily hydrochloride of *N*-allyl-*N*-cinnamylbenzylamine from the above reaction was dissolved in chloroform, cooled, and saturated with chlorine gas. Adding ether precipitated 1.2 g. of a colorless solid, m.p. 139.5–141.5°.

Anal. Calcd. for $C_{19}H_{22}NCl_5$: C, 51.67; H, 5.02; Cl, 40.14. Found: C, 51.53; H, 4.69; Cl, 39.95.

N,N-Dicinnamylbenzylamine. Stirring 2 molar equivalents of cinnamyl bromide and three molar equivalents of benzylamine in ether for 40 hr. at room temperature precipitated 99% of the expected by-product. The ether solution was washed with water, dried and evaporated to give a 66% yield of a light orange colored oil, which was mixed with petroleum ether (b.p. 60–70°) and cooled to give a colorless solid, m.p. 62–64°; recrystallized from methanol, m.p. 64–65°; hydrochloride, m.p. 211–214°.

Anal. Calcd. for $C_{25}H_{25}N$: C, 88.45; H, 7.42; N, 4.13. Found: C, 88.40; H, 7.31; N, 4.18.

Bis-N,N-(2,3-dichloro-3-phenylpropyl)-1-benzylamine hydrochloride. A cooled solution of *N,N*-dicinnamylbenzylamine hydrochloride in chloroform was saturated with chlorine gas. Partial evaporation of the solvent resulted in a yellow solid which was recrystallized from ethanol-ether to give an 87.2% yield of a colorless solid, m.p. 165–166°.

Anal. Calcd. for $C_{25}H_{26}NCl_5$: C, 57.99; H, 5.06; Cl, 34.24. Found: C, 58.15; H, 5.52; Cl, 34.04.

N,N-Dicinnamylmethylamine hydrochloride. A gummy hygroscopic material which was used in the following chlorination reaction was obtained when 0.15 mole of a standard monomethylamine-ether solution and 0.1 mole of cinnamyl bromide in ether were allowed to stir 12 hr. at room temperature. Working up by the usual procedure and saturating with hydrogen chloride gas developed the product.

Bis-N,N-(2,3-dichloro-3-phenylpropyl)-1-methylamine hydrochloride. The crude amine hydrochloride was saturated with chlorine in chloroform and the addition of ether precipitated 3.6 g. (58%) of a colorless solid melting at 179–181°, after recrystallization from acetone-ether.

Anal. Calcd. for $C_{19}H_{22}NCl_5$: C, 51.67; H, 5.02; Cl, 40.14. Found: C, 51.24; H, 5.11; Cl, 39.93.

N,N-Diallylbenzylamine hydrochloride. To a solution of allyl bromide (0.2 mole) in refluxing benzene was slowly added benzylamine (0.3 mole). After filtration the benzene filtrate was washed, dried, and saturated with hydrogen chloride gas, resulting in a dark brown oily hydrochloride (yield 55%) which was used as such in the subsequent chlorination reaction.

Bis-N,N-(2,3-dichloropropyl)amine hydrochloride. The crude dark brown colored unsaturated amine hydrochloride from the previous experiment was chlorinated in the usual manner, except that the temperature was raised to 16°. Standing overnight, followed by evaporation, gave 17.1 g. of a light tan colored oil. Recrystallization from ethanol-ether resulted in 3.5 g. of a colorless solid, m.p. 178–179°.

Anal. Calcd. for $C_{13}H_{16}NCl_5$: C, 42.71; H, 4.96; $C_6H_{12}NCl_5$; C, 26.16; H, 4.39; Found: C, 26.24; H, 4.26.

1,2,3-Tri(N-piperidino)-1-phenylpropane trihydrochloride. To a solution of 27.6 g. of redistilled piperidine in 300 ml. of absolute ethanol was slowly added 20.0 g. of 3-phenyl-2,3-dichloro-1-piperidinopropane hydrochloride. The mixture was heated at reflux under nitrogen for 2 days. Evaporation of the ethanol solvent and addition of dry ether resulted in the by-product, piperidine hydrochloride. Filtration followed by drying of the ether filtrate and saturation with dry hydrogen chloride gas gave a light tan colored solid. This was shaken in water and the insoluble residue removed by filtration, after which 10% sodium carbonate solution was added to liberate the free amine. The precipitated oil was extracted with ether and saturated with hydrogen chloride gas, yield-

ing a light yellow colored salt, m.p. 188–192° after losing gas from 150–170°.

An ionic chlorine analysis indicates this material to be the trihydrochloride salt.

Anal. Calcd. for $C_{23}H_{42}N_3Cl_3$; Cl^-, 22.70. Found: Cl^-, 22.33.

Acknowledgment. The work described here was supported in part by Research Grant CY 2931 from the National Cancer Institute, U. S. Public Health Service.

LINCOLN, NEB.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, UNIVERSITY OF CHICAGO]

New Heteroaromatic Compounds. VII. Chloro and Bromo Derivatives of 10-Hydroxy-10,9-borazarophenanthrene

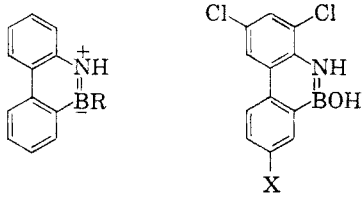
MICHAEL J. S. DEWAR AND VED P. KUBBA

Received March 14, 1960

Chlorination or bromination of 10-hydroxy-10,9-borazarophenanthrene gave the 6,8-dichloro or dibromo derivatives. Further chlorination of 6,8-dichloro-10-hydroxy-10,9-borazarophenanthrene gave the 2,6,8-trichloro derivative. Syntheses of the ethers from 2- and 6-chloro-10-hydroxy-10,9-borazarophenanthrene are described.

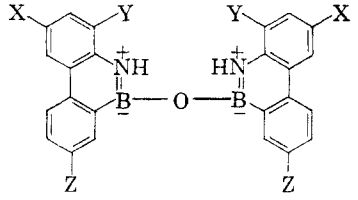
In a previous paper[1] we reported the nitration and chlorination of 10-methyl-10,9-borazarophenanthrene (Ia) and the nitration of 10-hydroxy-10-9-borazarophenanthrene (Ib). We have now examined the chlorination and bromination of Ib.

Chlorination of Ib with two moles of chlorine at room temperature gave, in good yield, a dichloro derivative which was shown to be 6,8-dichloro-10-hydroxy-10,9-borazarophenanthrene (IIa) by degradation to 3,5-dichloro-2-aminodiphenyl with cold concentrated sulfuric acid.[1]



Ia. R = Me
Ib. R = OH

IIa. X = H
IIb. X = Cl



IIIa. X = Y = H, Z = Cl
IIIb. X = Cl, Y = Z = H
IIIc. X = Y = Z = Cl
IIId. X = Y = Br, Z = H

When the chlorination was repeated with one mole of chlorine, IIa remained the sole isolable product. All attempts to obtain monochloro derivatives failed, even when less than one mole of chlorine was used. Since we had hoped to obtain a mixture of monochloro derivatives we began work on the synthesis of possible isomers; 2- and 6-chloro-10-hydroxy-10,9-borazarophenanthrene were readily obtained by hydrolysis of the corresponding 10-chloro derivatives[1] and isolated as their anhydrides, IIIa and IIIb, respectively. Since no monochloro derivatives could be obtained from Ib and since the necessary starting material (2-amino-3-chlorodiphenyl) is inaccessible we did not synthesise the 8-chloro derivative.

Chlorination of Ib with three moles of chlorine at a higher temperature gave 2,6,8-trichloro-10-hydroxy-10,9-borazarophenanthrene (IIb) which on standing at room temperature lost water to form the corresponding ether (IIIc). The structure of IIIc was indicated by its synthesis from IIIa by chlorination.

Bromination of Ib with two moles of bromine in acetic acid gave 6,8-dibromo-10-hydroxy-10,9-borazarophenanthrene which was isolated as the corresponding ether (IIId). The structure of IIId was shown by degradation to 2-amino-3,5-dibromodiphenyl with concentrated sulfuric acid and by synthesis from 2-amino-3,5-dibromodiphenyl by the method previously described.[2] The ultraviolet absorption spectra of these compounds in 95% ethanol solution are indicated in Table I.

DISCUSSION

Theory suggests[1] that the 8-position in 10,9-borazarophenanthrene should be the most reactive towards electrophilic substitution, followed closely by the 6-position. This was shown to be the case for nitration of Ia and Ib while chlorination of Ia gave almost exclusively the 8-chloro derivative. Here we have shown that the 6- and 8-positions of Ib are also the most reactive for chlorination and bromination.

The effect of a $-E$ substituent (such as hydroxyl)

(1) M. J. S. Dewar and Ved P. Kubba, *Tetrahedron*, 7, 213 (1959).

(2) M. J. S. Dewar, V. P. Kubba, and R. Pettit, *J. Chem. Soc.*, 3073 (1958).