2.82 g (20% from **7**) of **9**, which was recrystallized from Et_2O and from MeAc-cyclohexane (mp 155–156°). *Anal.* ($C_{12}H_{14}O_2$) C, H.

cis- **and** *trans*-**3-Hydroxy-3-phenylcyclohexanol (10 and 11).**—A solution of $NaBH_4$ (0.30 g, 0.013 mole) in 50 ml of 95% EtOH was added in small portions to an EtOH solution of **9** (3.0 g, 0.016 mole) cooled in an ice bath. After stirring for 1 hr, several milliliters of glacial AcOH were added to destroy excess $NaBH_4$. The mixture was evaporated to 50 ml under N_2, diluted with H_2O, made basic with Na_2CO_3, and extracted with $CHCl_3$. The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to yield 2.84 g (95%) of the mixed isomers as a white solid. The two isomers were separated by column chromatography on silica gel; elution with C_6H_6 and C_6H_6–Et_2O afforded 1.39 g (45%) of the *cis* isomer **10** followed by 1.44 g (46%) of *trans* isomer **11**.

Isomer **10**, recrystallized from MeAc–C_6H_{12}, melted at 136.5–137°: nmr ($CDCl_3$) 1.16–2.50 (8 H, C_6H_{11}), 3.33–4.00 (2 H, OH), 4.00–4.36 (1 H, HCOH, $W_{1/2}$ = 11 Hz), 7.06–7.68 (5 H, aromatic). *Anal.* ($C_{12}H_{16}O_2$) C, H.

Isomer **11** recrystallized from MeAc–C_6H_{12} melted at 137.5–138°: nmr (C_2D_6SO) 0.92–2.20 (8 H, C_6H_{11}), 3.50–4.18 (1 H, HCOH, $W_{1/2}$ = 22 Hz), 4.18–4.90 (2 H, OH), 6.98–7.68 (5 H, aromatic). *Anal.* ($C_{12}H_{16}O_2$) C, H.

trans-**3-Hydroxy-3-phenylcyclohexyl** *p*-**Toluenesulfonate (12).**—Compound **11** (0.5 g, 0.0026 mole) was dissolved in 25 ml of dry C_5H_5N and cooled to 0°. *p*-Toluenesulfonyl chloride (0.57 g, 0.003 mole) was added and the solution was kept at 0° for 24 hr. After the solution was poured into 100 ml of ice–H_2O and acidified with HCl, 0.49 g of **12** was obtained by filtration. Recrystallization from MeAc-C_6H_{12} gave white crystals, mp 100–101°. The material decomposed rapidly on standing giving a dark green solid. Characterization of the white solid by ir and nmr spectroscopy gave the expected results.

3-Bromo-*trans*-**3-decalone (13).**[11]—A solution of Br_2 (65.5 g, 0.41 mole) in 100 ml of glacial AcOH was added with stirring to *trans*-2-decalone (60.0 g, 0.39 mole) in 900 ml of glacial AcOH. The reaction mixture was stirred for 45 min at 25° and partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ extracts were combined, washed repeatedly with H_2O, dilute Na_2CO_3, and again with H_2O. The solution was dried ($MgSO_4$) and evaporated under vacuum giving 92.3 g (100%) of **13** as a brown oil which was utilized in the next reaction without further purification.

trans-Δ^3-**2-Decalone (14).**[12]—A solution of bromo ketone **13** (45.1 g, 0.19 mole) in 50 ml of dry DMF was added to a stirred suspension of anhydrous LiBr (26.0 g, 0.30 mole) and Li_2CO_3 (34.5 g, 0.46 mole) in 200 ml of dry DMF at 120° under N_2. The mixture was stirred at 120–125° for 2 hr, cooled, poured into 700 ml of 25% AcOH, and extracted with several portions of $CHCl_3$. The combined extracts were washed with H_2O, dried ($MgSO_4$), and evaporated *in vacuo* to give a brown liquid which was distilled under N_2 to afford **14** (16.9 g, 58%, bp 66–71° (0.2 mm) as a relatively pure liquid. The product was further purified by preparative tlc on silica gel (hexane–Et_2O, 1:1) nmr ($CDCl_3$) 0.75–2.90 (12 H), 5.93 (1 H, doublet, J = 10 Hz with fine splitting, CH=CHC(=O)), 6.72 (1 H, doublet, J = 10 Hz, CH=CHC=O); uv λ_{max}^{EtOH} 228.5 mμ (ϵ 9170).

The semicarbazone of **14** was prepared in EtOH and recrystallized from EtOH–H_2O and EtOH–EtOAc, mp 204–207°. *Anal.* ($C_{11}H_{17}N_3O$) C, H, N.

4(e)-Dimethylamino-2(e)-phenyl-2(a)-hydroxy-*trans*-**decalin (16).**—To a stirred solution of Me_2NH (225 ml) in 100 ml of Et_2O was added a solution of **14** (10.0 g, 0.066 mole) in 50 ml of Et_2O at 0–5°. After addition, the reaction was stirred for 6 hr at 0°. Excess Me_2NH and Et_2O were evaporated under N_2 giving crude 4(e)-dimethylamino-*trans*-2-decalone (**15**) as a brown oil.

A solution of **15** (0.066 mole) in 50 ml of anhydrous Et_2O was added dropwise to a cold, stirred suspension of C_6H_5Li (0.26 mole) in 50 ml of Et_2O. After addition, the mixture was stirred overnight at 25°. The reaction flask was cooled and 50 ml of H_2O was added dropwise. The Et_2O layer was separated, dried ($MgSO_4$), and evaporated under vacuum to afford 18 g of viscous liquid which was chromatographed on neutral alumina (activity grade II). Nonpolar components were eluted with Skellysolve B–C_6H_6. Elution with C_6H_6–EtOAc afforded 7.76 g (43% from **14**) of **16** as a brown glass.

The methiodide of **16** was prepared in C_6H_6 and recrystallized from MeOH–EtOAc, mp 165–166°. *Anal.* ($C_{19}H_{30}INO$) C, H, N.

4(e)-Dimethylamino-2(e)-phenyl-2(a)-propionoxy-*trans*-**decalin (2).**—An Et_2O solution of **15** (0.04 mole) was added dropwise with stirring to a cooled suspension of freshly prepared C_6H_5Li (0.08 mole) in 50 ml of Et_2O. The ice bath was removed after addition and the mixture was stirred for 2 hr at 25°. The reaction was again cooled and $(EtCO)_2O$ (26.0 g, 0.20 mole) in 50 ml of Et_2O was added. After stirring 6 hr at 25°, the reaction was cooled and treated with 10% Na_2CO_3 solution. The Et_2O layer was separated and 10% NaOH was added to the H_2O layer which was further extracted with CH_2Cl_2. Organic extracts were combined, washed with H_2O, dried (Na_2SO_4), and evaporated *in vacuo*. The dark liquid residue was chromatographed on a column of neutral alumina (activity grade II). Nonpolar components were eluted with Skellysolve B–C_6H_6. Elution with C_6H_6–EtOAc afforded 1.45 g (20% from **15**) of **2** as a thick oil. *Anal.* ($C_{21}H_{31}NO_2$) C, H, N.

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Insect Chemosterilants. VIII. Boron Compounds[1a]

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Benzeneboronic acid and seven of its homologs containing electron-withdrawing substituents were moderately effective chemosterilants of house flies, *Musca domestica* L. The sterilizing activity of 39 cyclic condensation products of benzeneboronic acids with *o*-aminophenol, pyrocatechol, or other aromatic compounds was often higher than that of the parent boronic acid.

The reproductive capacity of insects can be reduced or eliminated by various types of chemical compounds.[2] Chemosterilants containing boron have been described only recently[3,4] and the full scope of their activity has not been explored. Because species specificity is a distinguishing feature of most chemosterilants that are not alkylating agents, structure–activity correlations cannot be applied generally to other than the test species. This paper describes the sterilizing activity of certain boron compounds in house flies, *Musca domestica* L., but some of these compounds were also tested in

(1) (a) Previous paper in the series: A. B. DeMilo and A. B. Bořkovec. *J. Med. Chem.*, **11**, 961 (1968).

(2) A. B. Bořkovec, "Insect Chemosterilants," Interscience Publishers, New York, N.Y., 1966.

(3) A. B. Bořkovec and J. A. Settepani, U. S. Patent 3,463,851 (1969).

(4) J. A. Settepani, M. M. Crystal, and A. B. Bořkovec, *J. Econ. Entomol.*, **62**, 375 (1969).

TABLE I
STERILIZING ACTIVITY OF BORIC ACID AND OF BENZENEBORONIC ACIDS IN HOUSE FLIES
$RB(OH)_2$

No.	R	Ionization constant[a] $K_a \times 10^9$	Graded act.[b]	Source[c]
1	OH	0.653	++	A
2	C_6H_5	1.37	+++	A
3	$4\text{-}CH_3OC_6H_4$	0.482	+	B, C
4	$4\text{-}ClC_6H_4$		+++	B, D
5	$2\text{-}NO_2C_6H_4$	3	*d*	E
6	$3\text{-}NO_2C_6H_4$	50.0	++++	F
7	$4\text{-}NO_2C_6H_4$	70.7	+++	G
8	$2\text{-}CH_3\text{-}3,5\text{-}(NO_2)_2C_6H_2$	125	++++	B, H
9	$4\text{-}CH_3\text{-}3,5\text{-}(NO_2)_2C_6H_2$		++	I

[a] See ref 5. [b] Activity scale: 0, no sterility at 1% treatment level; +, partial sterility at 1% treatment level; ++, no pupae at 1% treatment level; +++, no pupae at 0.25–0.5% treatment level; ++++, no pupae at 0.05–0.1% treatment level. [c] A, commercial; B, Midwest Research Institute; C, mp 206–208°, F. R. Bean and J. R. Johnson, *J. Am. Chem. Soc.*, **54**, 4415 (1932), reported mp 208.5–209.5°; D, mp 225–258°, lit.[c] mp 261–262.5°; E, mp 130–134°, W. Seaman and J. R. Johnson, *J. Am. Chem. Soc.*, **53**, 711 (1931), reported mp 138.7–139.2°; F, mp 275–276°, lit. [c] mp 275–276.5°; G, mp 300–304° dec, lit.[c] 305° dec; H, mp 215–223°, K. Torssell, *Arkiv Kemi*, **10**, 513 (1957), reported for the acid mp 205° and for the anhydride mp 255°; I, see Experimental Section. [d] Toxic at 0.25–1.0% treatment levels, inactive at lower levels.

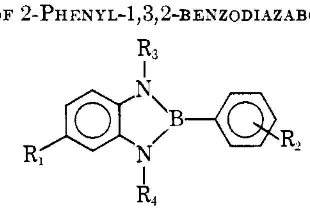
mentioned in this paper did not effectively sterilize these latter two species.

Boric acid and selected boron compounds containing at least one C–B bond were tested as chemosterilants in the diet of adult house flies. The data on sterilizing activity are summarized in Tables I–III. Numerous other related boron compounds were inactive and are not listed. The properties of new compounds synthesized in the course of our work are shown in Table IV.

Results and Discussion

Most of the benzeneboronic acids shown in Table I affect the growth of plant roots, and Torssell, *et al.*,[5] attempted correlating this activity with various physicochemical properties of the acids. Dissociation constants (K_a) of the acids were not directly related to activity but their complexing ability with polyols was correlated with growth-promoting effects. Similar correlation of the effects of boron compounds on the growth rate of the diatom, *Cylindrotheca fusiformis*, and other organisms was reported by Neales.[6] There is no apparent relationship between the biological activity in these organisms and the sterilizing effects in the house fly but the more active sterilants (**6**, **8** in Table I) were much stronger acids than the least active ones (**1**, **3**).

TABLE II
STERILIZING ACTIVITY OF 2-PHENYL-1,3,2-BENZODIAZABOROLES IN HOUSE FLIES



No.	R_1	R_2	R_3	R_4	Graded act.[a]	Source[b]
10	H	H	H	H	++	A
11	H	$4\text{-}OCH_3$	H	H	0	B, C
12	H	4-Cl	H	H	+++	B, D
13	H	$3\text{-}NO_2$	H	H	+++	E
14	OCH_3	H	H	H	+++	B, F
15	CH_3	H	H	H	+++	B, G
16	NO_2	H	H	H	+++	H
17	H	H	H	C_6H_5	+++	I
18	H	H	H	CH_3	+++	I
19	H	H	H	$4\text{-}CH_3OC_6H_4$	++	I
20	H	4-Cl	H	C_6H_5	+++	I
21	H	$3\text{-}NO_2$	H	CH_3	+++	I
22	H	$3\text{-}NO_2$	CH_3	CH_3	++	I
23	H	$3\text{-}NO_2$	H	$4\text{-}CH_3OC_6H_4$	+++	I
24	H	$2\text{-}CH_3\text{-}3,5\text{-}(NO_2)_2$	H	$4\text{-}CH_3OC_6H_4$	++++	I
25	OCH_3	$2\text{-}CH_3\text{-}3,5\text{-}(NO_2)_2$	H	CH_3	+++	I

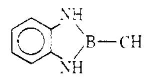
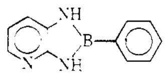
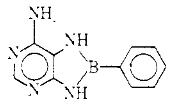
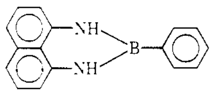
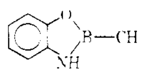
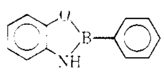
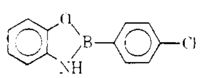
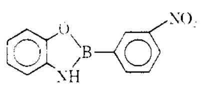
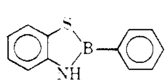
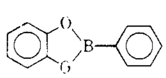
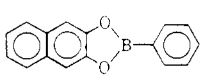
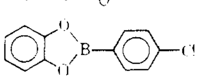
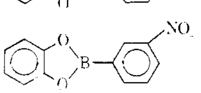
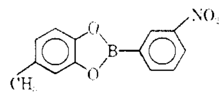
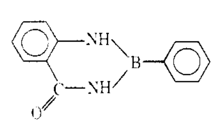
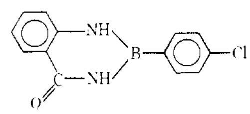
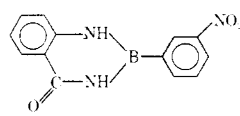
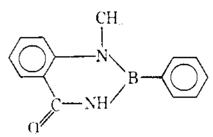
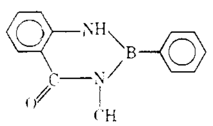
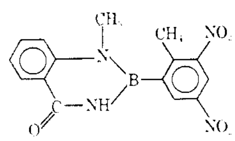
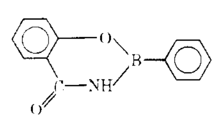
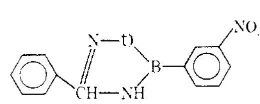
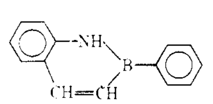
[a] See Table I, footnote *b*. [b] A, commercial; B, Midwest Research Institute; C, mp 257–260°, E. Nyilas and A. H. Soloway, *J. Am. Chem. Soc.*, **81**, 2681 (1959), reported mp 242–243°; D, mp 223–226°, lit. [c] mp 219–221°; E, mp 209–211°, lit. [c] mp 203–204°; F, mp 139–141°, lit. [c] mp 138–140°; G, mp 228–231°, lit. [c] mp 224–225°; H, mp 202–203°, lit. [c] 203–204°; I, see Experimental Section.

other species of insects: screw-worm flies, *Cochliomyia hominivorax* (Coquerel), Mexican fruit flies, *Anastrepha ludens* (Loew), and the boll weevil, *Anthonomus grandis* Boheman. Some comparison between the activity of boron compounds in house flies and in screw-worm flies was possible but the susceptibility of Mexican fruit flies and boll weevils was largely limited to toxicity. Nontoxic levels of boron compounds

The sterilizing activity of 2-phenyl-1,3,2-benzodiazaboroles is shown in Table II. Since activities in all tables are reported on a weight basis, it is apparent that the molar activities of most of the diazaboroles are

(5) K. Torssell, J. H. McClendon, and G. F. Somers, *Acta Chem. Scand.*, **12**, 1373 (1958).
(6) T. F. Neales, *Aust. J. Biol. Sci.*, **20**, 67 (1967).

Table III
Sterilizing Activity of Cyclic Derivatives of Boronic Acids in House Flies

No.	Structure	Graded act.[a]	Source[b]
26		0	A, B
27		++	C
28		+++	D
29		0	E
30		0	A, F
31		+++	A, G
32		+++	D
33		++++	D
34		+++	A, H
35		+++	I
36		+++	J
37		+++	K
38		+++	L
39		+++	D
40		+	K
41		0	D
42		+++	D
43		+++	D
44		+	D
45		++++	D
46		+++	D
47		+++	D
48		0	A, N

[a] See Table I, footnote *b*. [b] A, Midwest Research Institute; B, mp 94–95°, D. Ulmschneider and J. Goubeau, *Chem. Ber.*, **90**, 2733 (1957), reported mp 94°; C, mp 223°, H. Zimmer, E. R. Andrews, and A. D. Sill, *Arzneim.-Forsch.*, **17**, 607 (1967), reported mp 221.5–222°; D, see Experimental Section; E, mp 91–92°, F. F. Caserio, J. J. Cavallo, and R. I. Wagner, *J. Org. Chem.*, **26**, 2157 (1961), reported mp 92.5–93.5°; F, mp 28–29°, lit. B mp 32–34°; G, mp 101–101.5°, M. J. S. Dewar, V. P. Kubba, and R. Pettit, *J. Chem. Soc.*, 3076 (1958), reported mp 105–106°; H, mp 150–151°, lit. G mp 154–156°; I, mp 108–109°, lit. G mp 109–110°; J, mp 219–220°, I. R. Hemming and D. G. Johnston, *J. Chem. Soc.*, 466 (1964), reported mp 225°; K, mp 149–150°, I. R. Hemming and D. G. Johnston, *ibid.*, 314 (1966), reported mp 150–151°; L, mp 173–174°, lit. K mp 179°; M, mp 213–214°, S. S. Chissick, M. J. S. Dewar, and R. Dietz, *J. Chem. Soc.*, 2728 (1959), reported mp 137.5–139°.

greater than those of the corresponding benzeneboronic acids.

2-Phenyl-1,3,2-benzodiazaborole and its derivatives hydrolyze in aqueous media to benzeneboronic acids and the rate of hydrolysis is affected, in a predictable way, by substituents on the benzene rings and N atoms (R_1–R_4 in Table II). Thus, when R_2 is electron withdrawing, nucleophilic attack on B should be facilitated, and the rate of hydrolysis should increase. We have confirmed the hydrolysis-enhancing effect of NO_2 by measuring spectrophotometrically the rates of hydrolysis of **10** and **13** in aqueous EtOH. The nitro derivative **13** hydrolyzed approximately twice as fast as the unsubstituted compound **10**.

In general, diazaboroles which were the most stable to hydrolysis exhibited the greatest enhancement of chemosterilizing activity over that of the corresponding benzeneboronic acids. It was not possible, however, to determine whether this greater reltive activity of the compounds in Table II is an inherent property of the diazaboroles themselves, or the result of a gradual release of active benzeneboronic acids by an *in vivo* hydrolysis. Furthermore, in view of the inherent inaccuracy of the oral screening method,[7] the differences in activity were not large enough to form a basis for structure–activity correlations.

(7) G. C. LaBrecque, R. L. Fye, A. B. DeMilo, and A. B. Bořkovec, *J. Econ. Entomol.*, **61**, 1621 (1968).

TABLE IV
PROPERTIES OF NEW COMPOUNDS

No.	Reaction time, hr	Recrystn solvent[a]	Yield, %	Mp, °C	Formula[b]
17	18	A	73	132–133	$C_{18}H_{15}BN_2$
18	2	B	68	78	$C_{13}H_{13}BN_2$
19	24	B	70	161–162	$C_{19}H_{17}BN_2$
20	21	B	90	124–125	$C_{18}H_{14}BClN_2$
21	3	B	71	125	$C_{13}H_{12}BN_3O_2$
22	1	B	68	105	$C_{14}H_{14}BN_3O_2$
23	20	B	91	175–176	$C_{19}H_{16}BN_3O_3$
24	24	C	60	198	$C_{20}H_{17}BN_4O_5$
25	2	C	62	179	$C_{15}H_{17}BN_4O_5$
28	3	B	74	310–312	$C_{10}H_{10}BN_5$
32	1	C	73	139–140	$C_{12}H_9BClNO$
33	2	C	71	175–176	$C_{12}H_9BN_2O_3$
39	2	C	74	170	$C_{13}H_{10}BNO_4$
41	2	D	93	>300	$C_{13}H_{10}BClN_2O$
42	2	D	81	>300	$C_{13}H_{10}BN_3O_3$
43	2	C	79	177–178	$C_{14}H_{13}BN_2O$
44	2	C	54	190–191	$C_{14}H_{13}BN_2O$
45	2	C	82	230	$C_{15}H_{13}BN_4O_5$
46	2	C	71	205–206	$C_{13}H_{10}BNO_2$
47	2	C	53	221–224	$C_{13}H_{10}BN_3O_3$

[a] A, benzene–pentane; B, toluene–pentane; C, toluene; D, acetone. [b] Satisfactory microanalyses of C, H, B, and N were obtained for all compounds except **28**, for which no analysis is reported.

Other cyclic derivatives of boronic acids (Table III) likewise exhibited somewhat greater activity than the corresponding free acids. Unfortunately, the increase was never substantial and none of the 48 compounds in Tables I–III maintained its activity at dose levels below 0.05% in the diet.

A direct quantitative comparison between the susceptibility of house flies and screw-worm flies[4] to orally administered boron chemosterilants was not possible because of the different feeding habits of the two species. Although boronic acids **2**, **4**, and **6** were toxic to screw-worm flies at concentrations that were effective and nontoxic in house flies, the lack of activity of the relatively nontoxic diazaboroles **12**, **14**, and **16** in the screw-worm fly indicated that the fertility of this insect is not greatly affected by boronic acids. On the other hand, the screw-worm fly is more susceptible than the house fly to the sterilizing effects of boric acid or ompounds that yield boric acid on hydrolysis. In comparison to other chemosterilants,[2] the boron compounds mentioned here are only moderately effective but they constitute a new category of insect sterilants. Detailed investigations of their physiological effects in insects may show the way to new structural types with higher sterilizing activity.

Experimental Section[8]

3,5-Dinitro-*p*-tolueneboronic Acid (9).—*p*-Tolueneboronic acid (5.0 g, 0.037 mole) was added in small portions to a stirred mixture of fuming HNO_3 (12 ml) and concentrated H_2SO_4 (18 ml). The temperature was maintained below −20° during the addition, and between −10 and −20° for 1 hr thereafter. Crude acid, mp 295–300°, was then precipitated by pouring the reaction mixture onto ice and was isolated by filtration. A pure sample, 3.8 g (48%), was obtained by recrystallization from water. Because the acid gradually lost water on standing, it was converted to its anhydride by warming at 100° (0.6 mm) for 6 hr; mp >300°. Recrystallization of the anhydride from CH_2Cl_2 provided a pure sample. *Anal.* ($C_{21}H_{15}B_3N_6O_{15}$) C, H, N, B.

Cyclic Derivatives of Benzeneboronic Acids.—The title compounds were prepared by refluxing a mixture of the benzeneboronic acid and the required amine, amide, or hydroxy compound in toluene under a Dean–Stark water collector. After the calculated amount of H_2O had collected in the trap (1–24 hr), the reaction mixture was concentrated, if necessary, and chilled to precipitate the product. Details of the preparations and physical properties of new compounds are gathered in Table IV.

Hydrolysis Rate Study.—Two cyclic compounds, 2,3-dihydro-2-phenyl-1H-1,3,2-benzodiazaborole (**10**) and its 2-(*m*-nitrophenyl) analog **13**, were chosen for a comparative rate of hydrolysis study. Both compounds exhibited a maximum at 297 mμ in their uv spectra, and the rate of change in this absorption with time in 70% aqueous EtOH was measured. After correcting for the slight absorption of the hydrolysis products at 297 mμ,[9] the usual plot of log concentration *vs.* time provided psuedo rate constants of 3.1×10^{-5} sec^{-1} for **10** and 6.1×10^{-5} for **13**.

(8) Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Microanalyses were performed by Gailbraith Laboratories, Knoxville, Tenn. Analyses indicated by the symbols of elements were within ±0.4% of theoretical values. Uv spectra were recorded on a Beckman DK-2 spectrophotometer.

(9) H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962, p 556.