TABLE III
N-(ω-PHTHALIMIDOALKYL)TRIALKYLAMMONIUM IODIDES
o-$C_4H_4(CO)_2N(CH_2)_nNR_1R_2R_3I$

n	Mp, °C	Yield, %		Formula[a]	Frog MPD,[b] mg/kg
		$NR_1R_2R_3 = N(CH_3)_3$			
2	293–295	54	C	$C_{13}H_{17}IN_2O_2$	>400
3	240	56	C	$C_{14}H_{19}IN_2O_2$	200
4	287–288	98	C	$C_{15}H_{21}IN_2O_2$	15
5	181–182.5[c]	90	C	$C_{16}H_{23}IN_2O_2$	15
6	214–215	90	C	$C_{17}H_{25}IN_2O_2$	20
7	160–161	95	C	$C_{18}H_{27}IN_2O_2$	20
8	173	86	C	$C_{19}H_{29}IN_2O_2$	20
9	119–121	87	C	$C_{20}H_{31}IN_2O_2$	10
10	172–173	92	C	$C_{21}H_{33}IN_2O_2$	20
11	153–153.5	91	C	$C_{22}H_{35}IN_2O_2$	40
		$NR_1R_2R_3 = NC_2H_5(CH_3)_2$			
4	268	88	A	$C_{16}H_{23}IN_2O$	50
6	118–120	79	A	$C_{18}H_{27}IN_2O$[d]	40
		$NR_1R_2R_3 = NCH_3(C_2H_5)_2$			
2	238–239	46	A	$C_{15}H_{21}IN_2O_2$[e]	300
3	237–238	46	A	$C_{16}H_{23}IN_2O_2$	100
4	280–281	80	A	$C_{17}H_{25}IN_2O_2$	30–40
6	127–128	60	A	$C_{19}H_{29}IN_2O_2$	20–30
8	93–94	53	A	$C_{21}H_{33}IN_2O_2$[f]	20
10	103–105	58	A	$C_{23}H_{37}IN_2O_2$	40
		$NR_1R_2R_3 = N(C_2H_5)_3$			
4	254–255	83	B	$C_{18}H_{27}IN_2O_2$	30
6	164–166	82	B	$C_{20}H_{31}IN_2O_2$	30
8	136–138	78	D	$C_{22}H_{35}IN_2O_2$	20
10	122–124	82	D	$C_{24}H_{39}IN_2O_2$	>50
		$NR_1R_2R_3 = N(C_2H_5)_2CH_2C_6H_5$			
4	192 dec	64	A	$C_{23}H_{29}IN_2O_2$[g]	30–40
5	165–165.5	94	A	$C_{24}H_{31}IN_2O_2$[g]	30–40
6	153	93	A	$C_{25}H_{33}IN_2O_2$[g]	80
		$NR_1R_2R_3 = NCH_3(CH_2C_6H_5)_2$			
4	95–98	88	B	$C_{29}H_{35}IN_2O_2$[h]	[i]
5	169–170	52	B	$C_{28}H_{31}IN_2O_2$	[i]
6	159–160	49	B	$C_{29}H_{33}IN_2O_2$	[j]
d-Tubocurarine chloride (DTC)					2

[a] All compounds showed a correct analysis for C, H, I except where noted. [b] MPD = minimum paralyzing dose (lymph-sac injection). [c] Sinters at 176°. Sample analyzed correctly only after melting and allowing to resolidify. Before melting the compound analyzed for the monohydrate (I: calcd, 30.2; found, 30.2). [d] C: calcd, 50.24; found, 50.65. [e] C: calcd, 46.40; found, 46.88. [f] H: calcd, 7.04; found, 6.62. [g] Analyzed for I only. [h] Calculated for monoethanolate. [i] No paralyzing action. [j] Too insoluble to test.

activities at comparable chain lengths. The dimethylethylammonium compounds possessed lower activity in the four- and six-carbon structures. The longer chain compounds were therefore not prepared. The same was true of the higher members of the diethylammonium compounds. Those compounds with two benzyl groups attached to the quaternary nitrogen showed no muscle-paralyzing activity in the frog. The six-carbon homolog was too water insoluble to be tested.

The most active compound of this series was N-(9-phthalimidononyl)trimethylammonium iodide which had approximately one-fifth the activity of *d*-tubocurarine in the frog. Several of these compounds demonstrated considerable ganglionic blocking action when tested on the nictitating membrane of the cat and varying degrees of depolarizing activity were obtained in anesthetized roosters.

Experimental Section[5]

N-(ω-Bromoalkyl)phthalimides.—The N-(ω-bromoalkyl)phthalimides were prepared from potassium phthalimide and α,ω-dibromoalkanes by a previously reported method.[2]

N-(ω-Iodoalkyl)phthalimides.—A solution of anhydrous NaI (10.6 g, 0.071 mole) and the appropriate N-(ω-bromoalkyl)-phthalimide (0.01 mole) in 100 ml of dry Me_2CO was heated under reflux for 8 hr. Me_2CO was removed under reduced pressure and the residue was triturated with H_2O (50 ml). The solid remaining was filtered and recrystallized from EtOH.

N-(ω-Phthalimidoalkyl)dialkylamines.—A solution of 0.01 mole of the appropriate N-(ω-bromoalkyl)phthalimide and 0.04 mole of a secondary amine in 30 ml of C_6H_6 was heated on a steam bath for several hours. C_6H_6 and excess amine were removed under reduced pressure and the residue was dissolved in Et_2O. The solution was filtered to remove any amine hydrobromide, decolorized with charcoal, and dried. The dry Et_2O solution was used directly to prepare quaternary salts or treated with HCl gas to obtain the hydrochloride. The precipitated hydrochloride was collected, washed (Et_2O), and recrystallized (EtOH).

N-(ω-Phthalimidoalkyl)trialkylammonium Iodides.—The monoquaternary N-(ω-phthalimidoalkyl)trialkylammonium iodides were prepared by one of the following ways.

Method A.—A dry Et_2O solution of the N-(ω-phthalimidoalkyl)-dialkylamine was treated with a three- or fourfold excess of the appropriate alkyl iodide and allowed to stand overnight at room temperature. The precipitated quaternary salt was removed by filtration and the filtrate was allowed to stand until no more product was formed. The quaternary salts were recrystallized from either absolute EtOH or *i*-PrOH.

Method B.—The N-(ω-phthalimidoalkyl)dialkylamine (0.01 mole) and 10 ml of the RI were refluxed on a steam bath for 2–3 hr. The reaction flask was cooled and Et_2O was added to completely precipitate the quaternary salt. The salt was filtered, washed (Et_2O), dried, and recrystallized as in A.

Method C.—A solution of N-(ω-iodoalkyl)phthalimide (0.004 mole) in 50 ml of anhydrous Et_2O was saturated with Me_3N at 0° in a pressure bottle and allowed to stand at 30° for 72 hr. The precipitate was filtered from the reaction mixture, washed (Et_2O), and recrystallized as in A.

Method D.—The appropriate N-(ω-iodoalkyl)phthalimide (0.006 mole) and 10 ml of Et_3N were heated on a steam bath for 3 hr. During the course of the reaction the quaternary salt precipitated from solution. The flask was cooled and dry Et_2O was added to complete precipitation. The salt was filtered, washed (Et_2O), dried, and recrystallized as in A.

(5) C and H analyses are by Du-Good Chemical Laboratory, St. Louis, Mo., and Clark Microanalytical Laboratory, Urbana, Ill. Ionic halogen was determined potentiometrically in this laboratory. All melting points are corrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

Some Organoboron Compounds Containing a Bis(2-chloroethyl)amino Group Joined to Boron[1]

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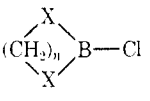
Boron, having two 2s and one 2p electrons, forms trivalent compounds that do not have a complete shell of valence electrons. These electron-deficient compounds, which are isoelectronic with carbonium ions, can coordinate with electron-donor molecules. Trivalent boron compounds having O, N, or related ele-

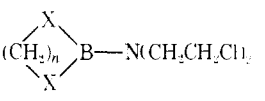
(1) This investigation was supported by Contracts PH43-64-51 and SA-43-ph-1740 with Chemotherapy, National Cancer Institute, National Institutes of Health, and by the C. F. Kettering Foundation.

ments bonded to B can compensate internally through back-coordination with lone-pair electrons.[2] These inherent characteristics of boron compounds suggested that boron derivatives in which a bis(2-chloroethyl)amino group is bonded directly to B would provide deactivated nitrogen mustard derivatives. The nitrogen mustard group should thereby be stabilized and latentiated; however, a potentially counterbalancing property is the fact that such derivatives might be prematurely hydrolyzed. A large number of publications[3] by Soloway and by others have dealt with the potential use of organoboron compounds in cancer therapy and, more particularly, with the possible exploitation of the nuclear properties of the ^{10}B isotope in chemoradiotherapy. In addition, Soloway and coworkers[4] have synthesized two nitrogen mustard derivatives of boron hydrides (a carborane and a carbonyl derivative) in which the mustard group is attached to carbon.

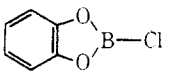
Several bis(2-chloroethyl)amino derivatives in which the N atom is bonded directly to B have now been prepared and evaluated for antineoplastic activity. 2-[Bis(2-chloroethyl)amino]-1,3,2-dioxaborolane (IIa), 2-[bis(2-chloroethyl)amino]-1,3,2-dioxaborinane (IIb), the analogous dithiaborolane (IIc), and dithiaborinane (IId) have been prepared from bis(2-chloroethyl)amine free base and the appropriate chloroborolanes and -borinanes. The required 2-chloro-1,3,2-diheteroborolanes (Ia, Ic) and 2-chloro-1,3,2-diheteroborinanes (Ib, Id) were prepared by the literature procedures[5-9] and were characterized by elemental analyses or by conversion to diethylamino derivatives (IIIa–d). Both the dioxaborolane (IIa) and the dioxaborinane (IIb) were viscous liquids that could be purified by vaporization at very low pressures; the S analogs (IIc, IId) were crystalline solids. An attempt to prepare 2-[bis(2-chloroethyl)amino]-1,3,2-benzodioxaborole from IV and 2 equiv of bis(2-chloroethyl)amine gave, instead, [bis(2-chloroethyl)amino]bis(*o*-hydroxyphenoxy)borane (V). The product was the same when equivalent amounts of IV, bis(2-chloroethyl)amine, and triethylamine were used. These results were surprising because elemental and nmr analyses indicated that IV was pure, the ring system is reported[10] to be quite stable, and other dialkylamino-1,3,2-benzodioxaboroles have been prepared.[10,11] An acyclic derivative, tris-[bis(2-chloroethyl)amino]borane (VI), was also prepared for biological evaluation.



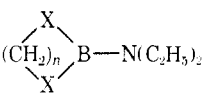
	n	X
Ia	2	O
b	3	O
c	2	S
d	3	S
e	2	NCH_3
f	3	NCH_3



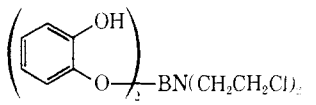
	n	X
IIa	2	O
b	3	O
c	2	S
d	3	S



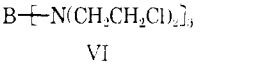
IV



	n	X
IIIa	2	O
b	3	O
c	2	S
d	3	S
e	2	NCH_3
f	3	NCH_3



V



VI

Attempts to obtain 2-[bis(2-chloroethyl)amino]-1,3-dimethyl-1,3,2-diazaboracycloalkanes from 2-chloro-1,3-dimethyl-1,3,2-diazaborolane (Ie) and -borinane[12] (If) were not successful under a variety of conditions, even though the analogous 2-diethylamino derivatives (IIIe, IIIf) were readily obtained. A possible explanation of the difference is that the bis(2-chloroethyl)amino derivatives may have suffered degradation during attempts to isolate them by vaporization at low pressures. The liquid chlorodiazaborinane (If) deposited a solid that appeared to be a dimer or a product resulting from further coordination (Experimental Section).

Antitumor Evaluation.[13,14] Bis(2-chloroethyl)amine might be formed *in vivo* from compounds containing the $(-X)_2BN(CH_2CH_2Cl)_2$ moiety by direct hydrolysis of the B–N bond or, stepwise, by initial hydrolysis of the B–X bonds. Alternatively, such compounds may function as moderated alkylating agents (1) without undergoing hydrolysis, (2) after partial hydrolysis (cleavage of one or both B–X bonds), or (3) after metabolic alteration.

Because of the possibility of rapid hydrolysis in aqueous media *in vitro*, IIa–d were administered to test animals in sesame oil (SO) as well as in aqueous media. In addition, the SO and aqueous suspensions were injected within 15 min of the time that the compounds first came into contact with the suspending media, and the aqueous suspensions of V and VI were injected within 5 min.

Walker Carcinosarcoma 256.—Details of the testing procedures for intramuscular Walker carcinosarcoma 256 (IM W256) are given in the footnotes of Table I. In primary testing, IIa, IIb, IId, V, and VI inhibited

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(12) M. P. Brown, A. E. Dann, D. W. Hood, and H. B. Silver, *ibid.*, 1618 (1962).

(13) Abbreviations are defined in the footnotes of Table I.

(14) Biological testing was performed by the Chemotherapy Department of Southern Research Institute under Contract PH43-65-594 with Chemotherapy, National Cancer Institute, National Institutes of Health; *in vivo* testing was carried out under the supervision of Drs. F. M. Schabel, Jr., and W. R. Laster, Jr., and cell-culture tests were under the supervision of Dr. C. J. Dixon.

TABLE I

ORGANOBORON MUSTARDS *vs.* IM W256[a]

Compd	Route[b]	Vehicle[c]	Dose, mg/kg/day	Mortality, deaths/total	Av wt change, g, T/C	Av tumor wt, g, T/C	Tumor T/C ratio, %
IIa	Ip	CMC	200	6/6			
			100	1/6	−13/+17	0.9/8.3	10
			20	0/6	+17/+14	0.6/6.4	9
			10	0/6	+13/+14	6.4/6.4	100
	Sc	SO	200	5/6			
			100	0/6	−8/+17	0.8/8.3	9
			20	0/6	+12/+14	3.0/6.4	46
			10	0/6	+19/+14	5.1/6.4	79
			5	0/6	+16/+14	7.0/6.4	109
IIb	Ip	CMC	50	4/6			
			25	2/6	−9/+11	0.1/7.2	1
	Sc	SO	100	5/6			
			50	2/6	−11/+20	0.1/7.9	1
			50	1/6	−11/+11	0.0/7.2	0
IId	Ip	CMC	100	1/6	−12/+17	0.0/8.5	0
			20	0/6	+7/+14	0.3/6.4	4
			10	0/6	+16/+14	4.0/6.4	62
			5	0/6	+14/+14	5.0/6.4	78
	Sc	SO	100	2/6	−6/+17	0.0/8.5	0
			100	1/6	0/+19	0.5/9.0	5
			20	0/6	+14/+14	2.8/6.4	43
			10	0/6	+19/+14	5.3/6.4	82
			5	0/6	+7/+14	6.5/6.4	101
V	Ip	CMC + T80	200	7/7			
			100[d]	1/19	−5/+16	0.33/6.8	5
			50	0/7	0/+16	0.0/5.6	0
			25	0/7	+11/+16	2.7/5.6	48
VI	Ip	CMC + T80	100[e]	4/6			
			50[f]	3/13	−10/+17	0.44/7.7	6
			25	0/7	−9/+13	0.9/7.4	12
			12.5	0/7	+4/+13	3.9/7.4	52
			6.25	0/7	+7/+13	6.4/7.4	86

[a] Implantation on day 0; schedule of treatment: qd 3-6. Mortality and tumor weights determined on day 7. Average host-weight change = average host weight on day 7 minus average host weight on day 3; T = treated animals, C = control (untreated neoplasm-bearing) animals. [b] Ip = intraperitoneal; Sc = subcutaneous. [c] CMC = 0.4% carboxymethylcellulose in 0.85% aqueous NaCl, SO = sesame oil, T80 = Tween 80. [d] Average of three experiments; 12 rats without tumors on day 7. [e] Results at 200 mg/kg/day varied. During two tests, all animals survived and T/C ratios were 3 and 4%; in a third test, however, the mortality was 5/6. [f] Average of two experiments.

the growth of IM W256 (Table I); IIc was not tested against this tumor. Strong inhibition was generally accompanied by a large difference between the average weight change of the treated and the control rats, but an adverse effect on the growth of treated animals was not always observed, *e.g.*, IIa in CMC at 20 mg/kg/day. Also, IIa in some earlier tests against subcutaneously implanted W256 (treated qd 1–5) completely inhibited growth without adversely affecting host weight.

Leukemia L1210.[15]—All day 2 tests of IIa–d consisted of doses of 400, 200, 100, and 50 mg/kg given in both CMC and in SO to groups of four mice. Doses for chronic testing were selected on the basis of the toxicity data from the day 2 tests and were administered to groups of six mice. Each daily dose was administered in CMC and in SO (except for IIb). Day 2 tests of V and VI consisted of doses of 400, 200, and 100 mg/kg given to groups of six mice. These doses, as well as those of V and VI given daily, were administered in CMC + Tween 80. A value of T/C of 125% is considered to represent a significant increase in survival time of treated mice; a value of T/C below 85% is considered to be caused by a toxic dose.

The dioxaborolane (IIa) and the dioxaborinane (IIb) administered on day 2 in either CMC or SO were toxic at 400 mg/kg, produced values of T/C in the range of 140–147% at 200 mg/kg, and showed no significant activity or only borderline activity (for IIb in CMC, T/C = 125%) at 100 mg/kg. Unfortunately, the average weight-change differences between the treated and control animals at 200 mg/kg were excessive (−5.8 to −6.0 g). Daily treatment (intraperitoneal) of L1210 with IIb in CMC significantly increased survival time, and the weight-change difference was somewhat more favorable. Results were as follows (schedule, dose in mg/kg/day, average weight difference in grams, T/C): qd 1–15, 100, −4.6, 80% (toxic); qd 1–9, 75, −3.6, 144%; qd 1–15, 50, −4.0, 152%; qd 1–9, 50, −2.8, 160%; qd 1–9, 33, −1.9, 129%; qd 1–9, 22, −0.9, 120%; mortality on day 5, 0/6 for all tests. Administered in SO, IIb was rated nontoxic (mortality, 0/6) and inactive (T/C = 104%) at 100 mg/kg/day (qd 1–15), although the host weight difference (−4.2 g) suggested that T/C was depressed by toxicity to the host. IIa initially

(15) Mice were implanted intraperitoneally with 10^5 L1210 cells on day 0. Day 2 means that a single dose was injected on the second day (ca. 48 hr) after implantation; qd 1–15 and qd 1–9 mean that daily injections were initiated on the first day (ca. 24 hr) after implantation and were continued until death or the day specified by the second number. Mortality and average weight changes of host animals were determined 4 days after the first (for daily treatment) or only (for day 2) injection. T/C = ratio in % of survival time of treated to control mice.

displayed slight activity at 100 mg/kg/day when it was administered (qd 1–15) in CMC (T/C = 131%) or in SO (sc, T/C = 126%), but in subsequent trials the values of T/C (112%, CMC; 121%, SO) were below the criterion of 125%.

The dithia derivatives (IIc and IId) were toxic at 400 mg/kg/day when given in either CMC or SO on day 2, and IIc was also toxic at 200 mg/kg in SO. Lower doses on day 2 or daily treatment (qd 1–15) did not reveal significant activity except for the fact that IIc displayed borderline activity when given in SO on day 2 at 100 mg/kg (T/C = 125%). An initial observation of borderline activity (T/C = 129%) for IIc given subcutaneously in SO at 75 mg/kg/day, qd 1–15, was not confirmed on retesting (T/C = 116%). The latter dose of IIc was rated toxic when given intraperitoneally in CMC, qd 1–15, because of a low value of T/C (80%).

V was not active at nontoxic doses (100 mg/kg for day 2, 50 mg/kg/day for qd 1–15), and VI was not active and not toxic in the day 2 or qd 1–15 (400 mg/kg/day) tests.

Sarcoma 180.—Four organoboron derivatives were tested against S180 in mice as follows: IIa at 100 and 50 mg/kg/day in SO; IIIa, IIIb, and IIIf at 500, 500, and 250 mg/kg/day, respectively, in saline. All were injected within 5 min. IIa produced a value of T/C (tumor wt) of 42% at 100 mg/kg/day, but the difference between the average weight change of the treated and control animals was high ($\Delta W = -4.7$ g). The remaining tests showed no evidence of activity or toxicity.

Cell Culture.—The cytotoxicities of the bis(2-chloroethyl)amino derivatives were similar in magnitude except for the fact that VI was considerably more cytotoxic than IIa–d and V (Table II).

TABLE II

CYTOTOXICITY[a]

Compd	ED_{50},[b] μg/ml
IIa	7.9
IIb	7.8
IIc	3.3
IId	6.0
V	4.3
VI	0.80

[a] HEp 2 cells except that IIa was tested *vs.* Eagle's KB cells. [b] ED_{50} is the concentration of a compound that inhibits cell growth to 50% of the growth of untreated control cells as determined by protein determinations.

Experimental Section

Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values. Melting points were determined with a Kofler Heizbank (gradiently heated bar) apparatus or with a Mettler FP-1 automatic apparatus. Nmr data were determined with a Varian A-60A spectrometer and are given in parts per million downfield from Me_4Si.

2-[Bis(2-chloroethyl)amino]-1,3,2-diheteroboracycloalkanes (IIa–d).—The calculated amount of concentrated aqueous KOH was added with vigorous stirring to a mixture, cooled in an ice bath, of 100 ml of $CHCl_3$ and 50 g of bis(2-chloroethyl)amine hydrochloride dissolved in 50 ml of H_2O. The mixture was stirred at 0–5° for 5 min, and the organic layer was dried (Na_2SO_4), filtered, and freed of volatile material *in vacuo*. This procedure usually gave *ca.* 35 g of bis(2-chloroethyl)amine free base, which was used immediately. A solution of the free base in 125 ml of $CHCl_3$ was cooled in an ice bath and was treated, dropwise and with stirring, during 1 hr with a 25-ml $CHCl_3$ solution of 0.125 mole of the appropriate 2-chloro derivative (Ia–d).[16] The mixture was stirred at 0–5° for 3 hr, allowed to stand overnight at −15 to −20°, and filtered to remove a precipitate. The residue obtained by evaporating the solvent *in vacuo* from the filtrate was purified as follows: by short-path distillation (IIa, IIb); by vaporization onto a cold-finger condenser placed a short distance above the level of the liquid in a distillation flask or vacuum sublimator (IId); or by dissolution in petroleum ether (bp 30–60°) (C_6H_6), filtration, and evaporation of the solvents (IIc); nmr of IIa ($CDCl_3$): A_2B_2 system centered at *ca.* δ 3.4 ($N(CH_2CH_2Cl)_2$), 4.13 (s, OCH_2CH_2O). Other data for IIa–d are given in Table III.

TABLE III

1,3,2-DIHETEROBOROLANES AND 1,3,2-DIHETEROBORINANES

Compd	Bp, °C[a] or mp, °C	% yield	Formula	Analyses
IIa	68–78 (1)[b,c]	44	$C_6H_{12}BCl_2NO_2$	C, H, B, Cl, N
IIb	88 (1)[b]	21	$C_7H_{14}BCl_2NO_2$	C, H, B, Cl, N
IIc	45–46[c]	87	$C_6H_{12}BCl_2NS_2$	C, H, B, Cl, N, S
IId	56–57[c]	91	$C_7H_{14}BCl_2NS_2$	C, H, B, Cl, N, S
IIIa	28 (1.2)[b]	30	$C_6H_{14}BNO_2$	C, H, B, N
IIIb	45 (1.0)[b]	35	$C_7H_{16}BNO_2$	C, H, B, N
IIIc	75–77 (0.2)[b]	26	$C_6H_{14}BNS_2$	C, H, B, N, S
IIId	60–62 (50)[b]	51	$C_7H_{16}BNS_2$	C, H, B, N, S
IIIe	34–40 (5)[b]	32	$C_{15}H_{26}BN_3$	C, H, B, N
IIIf	78 (4)[b]	28	$C_{21}H_{22}BN_3$	C, H, B, N

[a] Temperature range for collection of product; not intended to represent boiling point. [b] Microns instead of mm. [c] Determined with a Mettler FP-1 automatic melting point apparatus. [d] J. A. Blau, W. Gerrard, and M. F. Lappert [*J. Chem. Soc.*, 667 (1960)] reported bp 36° (0.4 mm). [e] A. Finch, P. J. Gardner, J. C. Lockhart, and E. J. Pearo [*ibid.*, 1428 (1962)] reported bp 33–34° (0.01 mm).

[Bis(2-chloroethyl)amino]bis(o-hydroxyphenoxy)borane (V) was obtained after similar treatment of a solution of 27.4 g of bis(2-chloroethyl)amine in 100 ml of $CHCl_3$ with a solution of 13.9 g of IV[16] in 20 ml of $CHCl_3$ except that the mixture was stirred at 0° for 0.5 hr, stored in a freezer for 16 hr, and then stirred at room temperature for 2 hr. Filtration of the mixture, evaporation of the filtrate to a solid residue, and trituration of the residue with a small volume of $CHCl_3$ yielded 7 g (42%) of solid, mp 193°. Recrystallization ($CHCl_3$) gave white needles: mp 193°; nmr (DMSO-d_6) shows A_2B_2 system approaching an A_2X_2 system with multiplets centered at *ca.* δ 3.35 and 3.85 ($N(CH_2CH_2Cl)_2$), 6.5 (s, aromatic CH), 8–9 (phenolic OH). *Anal.* ($C_{16}H_{18}BCl_2NO_4$) C, H, B, Cl, N.

Tris[bis(2-chloroethyl)amino]borane (VI) was prepared by adding, dropwise during 30 min, a solution of bis(2-chloroethyl)amine free base (31.5 g, 0.22 mole) in 100 ml of $CHCl_3$ to a stirred solution of BCl_3 (4.2 g, 0.036 mole) in 100 ml of $CHCl_3$ cooled in an ice bath. The mixture was stirred for 2 hr at 0° and allowed to stand at 5° overnight. Precipitated amine hydrochloride was removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. The residue was triturated with 50 ml of dry benzene and filtered to remove more amine hydrochloride. Concentration of the filtrate *in vacuo* to 5 ml and refrigeration at 5° gave the crystalline product VI, mp 133°. *Anal.* ($C_{12}H_{24}BCl_6N_3$) C, H, B, Cl, N.

2-Chloro-1,3-dimethyl-1,3,2-diazaboracycloalkanes.—*sym*-Dimethylethylenediamine (15.8 g, 0.18 mole) was added with stirring during 0.5 hr to a solution of 21 g (0.18 mole) of BCl_3 and 150 ml of $CHCl_3$ at −70°. The mixture was allowed to warm to room temperature, and 56 ml (0.4 mole) of Et_3N was added dropwise during 0.5 hr with stirring and occasional cooling. The resulting mixture was stirred at room temperature for 1 hr, heated under reflux for 16 hr, cooled to room temperature, and filtered. Concentration of the filtrate at atmospheric pressure gave additional solid that was removed by filtration. Distillation of the filtrate yielded 7 g (30%) of 2-chloro-1,3-dimethyl-1,3,2-diazaborolane[16] (Ie), bp 47° (20 mm).

2-Chloro-1,3-dimethyl-1,3,2-diazaborinane (If) was prepared as described by Benko *et al.*[12] Upon standing several days at

(16) The preparation of Ie was subsequently reported: A. Meller and H. Marecek, *Monatsh. Chem.*, **98**, 2336 (1967).

room temperature, the liquid monomer deposited a solid, which was collected by filtration and dried (P_2O_5) *in vacuo*. Since the Cl content of the solid (found, 24.1) was the same as that of the liquid (found, 24.0; theory, 24.2), the solid is presumably a *dimer* or higher intermolecular coordination polymer of If.

2-Diethylamino-1,3,2-diheteroboracycloalkanes (IIIa–f).—The appropriate 2-chloro derivative (Ia–f) was cooled to −70° and treated dropwise with excess Et_2NH. The mixture was allowed to warm to room temperature, stirred cautiously until the exothermic reaction subsided and, then, vigorously for 1 hr, and filtered to remove a precipitate. Distillation of the appropriate filtrate gave the products IIIa–f (Table III).

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Compounds Related to Insect Juvenile Hormone. IV

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The juvenile hormone[1,2] and most compounds that have JH activity by the bioassay with *Tenebrio molitor* L.[3] are acyclic sesquiterpenes or modified sesquiterpenes[3-7] with an array of trisubstituted double bonds every fourth carbon. The purpose of the present work was to assess the JH activity of compounds in which some or all of the double bonds and/or alkyl side chains were eliminated to discover easily preparable JH mimics.

Table I lists the compounds and the minimum weight (ng) that caused detectable retention of juvenile characteristics. The cecropia JH and methyl farnesate 10,11-epoxide are included as references. The removal of either unsaturation caused a drastic reduction of activity.[9]

The conversion of squalene *via* its epoxide to cholesterol and the facile transformations of model acyclic terpenoids to cyclic, bicyclic, and polycyclic materials have been well documented. These results prompted us to heat our mixture of the synthetic JH isomer and the closely related methyl farnesate 10,11-epoxide with acid while conditions were controlled so as to produce mixtures rich in either mono- or bicyclic compounds. These materials were quite inactive.[10] Therefore, since the results of the present test also suggest that the double bonds must be present in the acyclic materials, one is tempted to speculate that the process of cyclization may itself be a key step in the biological scheme of juvenilization involving the cecropia-type hormone. The tenfold reduction in activity from epoxide to olefin may merely reflect a somewhat lessened proclivity for cyclization due to the lower nucleophilicity of a double bond compared with an epoxide oxygen atom, or to a requirement for prior conversion to an epoxide as in the case of the squalene–cholesterol conversion.

Recently, activity was reported in compounds of the sesamex-type,[7] and this family of materials was claimed as "synergists" for insecticidal activity. However, they seemed to function as JH materials in the *T. molitor* test rather than as synergists because they produced their effects on segments of insects that would presumably not have any JH titer, *i.e.*, no *corpora allata*. If both classes of compounds produce their action by the same general biochemical mechanism, a requirement for cyclization would appear to be remote, and a new approach to mechanism is necessary.

Experimental Section

When analyses[11] are indicated in Table I only by symbols of the elements, the analytical results obtained were within ±0.2% of the theoretical values. The identity of all new compounds was confirmed by ir spectra, and samples of >99% purity were obtained by glpc collection for analyses and testing. Ir spectra were recorded with a Perkin-Elmer 137 NaCl spectrophotometer and gas chromatograms were obtained with an Aerograph Model A-700 instrument. Methyl 10-undecenoate and its epoxide were obtained from Eastman Organic Chemicals and Aldrich Chemical Co., Inc., respectively. Company and trade names are given for identification only and do not constitute endorsement by the U. S. Department of Agriculture. The bioassay was performed on *T. molitor*[3] with Mrs. R. Henegar of this Division assisting.

Methyl 10-Oxodecanoate.—Methyl undecenoate (50.0 g, 0.252 mole) was dissolved in 200 ml of 97% HCO_2H, and the solution was warmed to 35–40°. The temperature was maintained at this level while 28.0 g (0.257 mole) of 30% H_2O_2 was added dropwise. The resulting solution was allowed to remain at 40° overnight. Then the solvent was removed, the product was taken up in Et_2O and washed with aqueous Na_2CO_3, and the ethereal phase was dried ($MgSO_4$). After removal of the solvent, the crude product was dissolved in 400 ml of MeOH containing 0.07 mole of NaOMe and heated under reflux for 3 hr. The solvent was removed, and the product was taken up in Et_2O and washed with H_2O. After drying ($MgSO_4$), the solvent was removed, and the crude diol was dissolved in 550 ml of C_6H_6. To this solution was added in one portion 78.0 g (0.167 mole, 95% purity) of $Pb(OAc)_4$. After a mild exothermic reaction, the mixture was held at 35–45° for 1 hr, poured into 800 ml of 20% AcOH, and extracted with Et_2O. The combined organic phase was washed with aqueous $NaHCO_3$, dried ($MgSO_4$), concentrated, and distilled to give 25.9 g (51%) of colorless liquid, bp 93–97° (0.14–0.19 mm). The semicarbazone was then prepared, mp 100–102° (MeOH–H_2O) (lit.[12] mp 100–101°).

Methyl 11-Methyl-10-dodecenoate.—NaH (0.26 g, 0.011 mole) was added to dry DMF under N_2, and 0.38 ml of MeOH was added thereto. After 15 min, 4.94 g (0.0114 mole) of isopropyltriphenylphosphonium iodide was added. The mixture was cooled in an ice bath, and 1.50 g (0.00714 mole) of methyl 10-oxodecanoate was added. Then the mixture was stirred at ambient temperature for 18 hr, diluted with cold H_2O, and extracted with Et_2O. The organic phase was washed (H_2O), dried ($MgSO_4$), concentrated, and finally extracted with boiling petroleum ether (bp 30–60°). The extract was concentrated

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