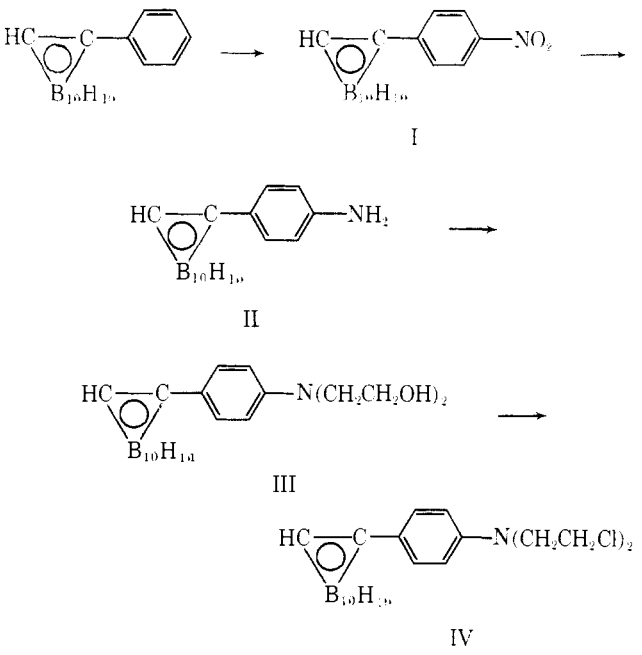
SCHEME I



diffusable substances, *p*-carboxybenzeneboronic acid and $Na_2B_{10}H_{10}$, which are rapidly excreted. However, there was no appreciably elevated levels in tumor compared with blood and consequently such compounds would not appear to offer much promise in the treatment of tumors by neutron-capture irradiation.[10a]

Experimental Section[11]

Nitration of Phenylcarborane.—To 50 ml of fuming HNO_3, containing a crystal of urea and cooled to −15°, was added with stirring 5.0 g of powdered phenylcarborane.[4a] The time of addition was 30 min, and during this period the temperature was maintained between −10 and −15°. The solution was stirred an additional 30 min during which time the temperature was allowed to rise to 10°. The mixture was poured into ice–water, filtered, washed, and dried, yielding 5.6 g of crude nitro compound, mp 115–126°. Recrystallization from methanol gave two products. The less soluble one amounted to 2.7 g, mp 155–160°, and was purified by successive recrystallizations from methanol, mp 164–165°.

Anal. Calcd for $C_8H_{15}B_{10}NO_2$: C, 36.20; H, 5.69; B, 40.78; N, 5.28. Found: C, 36.34; H, 5.87; B, 40.83; N, 5.25.

The second fraction, isolated from the mother liquors, was 2.2 g and began to melt at 115°. Even after repetitive recrystallizations from methanol or hexane, the melting point range was still broad, from 118 to 123°. Only this lower melting isomeric mixture was appreciably soluble in hexane. Based on the failure to separate the *meta* and *para* isomers, it would appear that this product exists as mixed crystals.

Anal. Calcd for $C_8H_{15}B_{10}NO_2$: C, 36.20; H, 5.69; B, 40.78; N, 5.28. Found: C, 36.18; H, 5.64; B, 40.58; N, 5.41.

***p*-Aminophenylcarborane (II).**—To a solution of 2.0 g of I in 40 ml of methanol was added 100 mg of PtO_2. The mixture was catalytically reduced until the uptake of hydrogen was completed. The brown solution was filtered to remove the catalyst and then poured into an ice–water mixture. An oily brown solid separated (1.6 g) and this, upon dissolution in ethyl ether, left a black residue which was removed by filtration from the yellow solution. Concentration of this supernatant left 1.35 g of a light yellow crystalline solid, mp 97–100°. Recrystallization from a small volume of hexane gave white crystals, mp 105–106°.

Anal. Calcd for $C_8H_{17}B_{10}N$: C, 40.81; H, 7.28; B, 45.96; N, 5.95. Found: C, 40.98; H, 7.11; B, 45.75; N, 5.93.

A solution of 800 mg of I in 10 ml of methanol together with 42 mg of PtO_2 was maintained at room temperature. No reaction occurred for approximately 1 hr but then the evolution of hydrogen began with the formation of platinum black. After standing for 2 hr, the solution was refluxed for 30 min, filtered and poured into ice–water. The product was filtered and recrystallized from hexane, yielding 300 mg of II as determined by melting point and infrared spectrum.

4-[Bis(2-hydroxyethyl)amino]phenylcarborane (III).—To a solution of 9.0 g of II in 80 ml of glacial acetic acid was added 12 ml of ethylene oxide. The solution was swirled to effect complete mixing and an additional 6 ml was added. The solution remained overnight at room temperature prior to being poured into a large excess of ice–water. A viscous gum formed which slowly solidified, yielding 10.8 g. The product (10.6 g) was recrystallized from a small volume of benzene, mp 117–120°. The analytical sample had mp 120–121°.

Anal. Calcd for $C_{12}H_{25}B_{10}NO_2$: C, 44.54; H, 7.78; B, 33.44; N, 4.33. Found: C, 44.50; H, 7.39; B, 33.44; N, 4.49.

4-[Bis(2-chloroethyl)amino]phenylcarborane (IV).—To a solution of 1.3 g of III in 20 ml of $CHCl_3$ was added 1.2 ml of $SOCl_2$ in 5 ml of $CHCl_3$. The mixture was refluxed for 3 hr. An additional amount of $SOCl_2$ was added equal to the first quantity and heating was continued for 30 min. The solution was concentrated to dryness at room temperature, more chloroform was added, and the concentration procedure was repeated. A yellow oil remained which was applied to a column of Florisil, 15 cm long and 1.25 cm in diameter, in a minimum volume of $CHCl_3$. The major portion of the compound was eluted with 100% hexane and a hexane solution containing 3% CH_2Cl_2. Removal of the solvent left an oil which gradually solidified (545 mg). Successive recrystallizations from petroleum ether gave a white crystalline product, mp 77–78°.

Anal. Calcd for $C_{12}H_{23}B_{10}Cl_2N$: C, 39.99; H, 6.43; B, 30.02; Cl, 19.67; N, 3.89. Found: C, 40.20; H, 6.78; B, 29.63; Cl, 19.53; N, 4.12.

Acknowledgments.—The authors wish to thank Professor William H. Sweet, Chief of Neurosurgery at the Massachusetts General Hospital, for his interest and encouragement. The technical assistance of Misses Mary Hagney and Beverly Whitman, Mrs. Janette Messer, and Mr. John Lyons is gratefully acknowledged.

(10a) NOTE ADDED IN PROOF.—Following the acceptance of this paper the work of M. F. Hawthorne, *et al.*, *J. Am. Chem. Soc.*, **87**, 4746 (1965), has appeared.

(11) All analyses were performed by Schwarzkopf Microanalytical Laboratories, New York, N. Y. All melting points were taken on a Fisher-Johns melting point apparatus and are corrected.

L-(+)-2β-Tropanyl Diphenylborinate

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As part of a study[3] of the central nervous system (CNS) effects of esters of the isomeric 2-tropanols,[4] we have prepared the title compound and have made a brief study of its pharmacological behavior. 2-Aminoethyl diphenylborinate[5] (often referred to as β,β-diphenylboroxazolidine[6]) has been used conveniently as a standard for comparison.

Our ability to prepare a stable diphenylborinate from the 2β (axial) isomer but not from the 2α (equa-

(1) To whom correspondence should be directed.

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(3) Contract DA18-108-AMC-103(A) with the U. S. Army Chemical Research and Development Laboratories, Edgewood Arsenal, Md.

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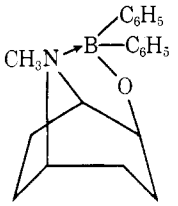
torial) isomer of 2-tropanol is additional evidence in favor of the configurational assignments made for these isomers.[4] Boroxazolidine ring structure is possible only in the axial isomer (I).



I

Although the pharmacological activity of organic boron compounds has been of interest for some time, we were particularly interested in the discovery[7] that certain aromatic boronic acids readily enter the CNS, which in turn led to the development of cyclic boronates of diols as analgesics and tranquilizers.[8-10] Esters of boronic acids are notoriously unstable to hydrolysis, however. Some increase in resistance to hydrolysis has been achieved in the cyclic boronates by extensive replacement of hydrogen by alkyl or aryl groups.[11]

A notable increase in hydrolytic stability is observed in the β-aminoalkyl diarylborinates, which have been investigated extensively by Zimmerman,[12] and whose stability is ascribed to the boroxazolidine ring structure. An attempt has been made to prepare amino acid derivatives of triptych boroxazolidines for use in brain tumor therapy by neutron capture.[13] The diphenylborinates of a variety of amino alcohols have been described as thymoleptic agents and antidepressants,[14] and these esters have also been studied as analogs of antihistaminic benzhydryl ethers.[15] The significance of properly constituted nitrogen-containing boronic and borinic acid derivatives as enzyme analogs has been discussed.[16]

We have examined the potential use of L-(+)-2β-tropanyl diphenylborinate and 2-aminoethyl diphenylborinate in neutron-capture brain tumor therapy by the technique described previously.[17] The results described in Table I show that neither compound is useful because of toxicity and failure to be absorbed preferentially in tumor. In a preliminary pharmacological study in mice, 2-aminoethyl diphenylborinate (in polyethylene glycol 200, iv) caused decreased activity, tremors, and lachrymation with a MED_{50} of 18 mg/kg. In an earlier study of this compound,[18] ataxia, tremor, and convulsion was reported at 140 mg/kg and the LD_{50} was 182 ± 13 mg/kg. The substance is a powerful antiseptic.[19] L-(+)-2β-Tropanyl diphenylborinate (10% by vol in glycerol formal, iv) showed very weak mydriasis at 20 mg/kg, the highest dose studied.

TABLE I

TISSUE DISTRIBUTION STUDIES[a]

Time, min	Tissue distribution ratio: Tumor:brain	Tumor:muscle	Tumor:blood
2-Aminoethyl Diphenylborinate[b]			
30	1.2	1.2	0.5
120	0.4	0.8	0.3
300	0.9	1.2	0.8
L-(+)-2β-Tropanyl Diphenylborinate[c]			
30	0.8	0.6	0.4
120	0.6	1.0	0.4
300	0.7	0.7	0.8

[a] For procedure see ref 17b; in the present work 2.3 μg of boron/g was administered intraperitoneally to C3H mice. In conducting the research reported herein, the investigators adhered to the "Principles of Laboratory Animal Care" as established by the National Society for Medical Research. [b] Dose in excess of 3.0 μg of boron/g caused severe convulsions and death. [c] Dose in excess of 4.5 μg of boron/g caused severe convulsions and death.

Experimental Section

2-Aminoethyl Diphenylborinate (β,β-Diphenylboroxazolidine).—Crude diphenylborinic acid[20] (44 g, 0.24 mole) was dissolved in 50 ml of ether and the solution was stirred vigorously at 0° while there was added a mixture of 44 g (0.74 mole) of 2-aminoethanol and 44 ml of water. The crude ester (20 g, 90%) separated at the interface. After two recrystallizations from ethyl alcohol, it had mp 192–194°, lit.[21] mp 192°. This compound is known to be very stable.[22]

L-(+)-2β-Tropanyl Diphenylborinate.—A solution of 22 g (0.12 mole) of crude diphenylborinic acid[20] in 22 ml of ether was stirred vigorously at 0° while a solution of 2.8 g (0.02 mole) of L-(−)-2β-tropanol[4] in 25 ml of water was added. Separation of a solid at the interface began after 3 hr and stirring was continued overnight. The 5.8 g (95%) of crude product was recrystallized three times from ethyl alcohol to give 1.7 g of stout colorless rods, mp 197–199°, $[\alpha]^{26}D$ +100° (*c* 2.5, acetone).

Anal. Calcd for $C_{20}H_{24}BNO$: C, 78.70; H, 7.93; B, 3.54; N, 4.59. Found: C, 78.78; H, 7.99; B, 3.60; N, 4.52.

L-(+)-2β-Tropanyl diphenylborinate is stable at room temperature. It is soluble in hot alcohols and is insoluble in cold ether, water, $CHCl_3$, and CS_2.

The above procedure was carried out using the isomeric L-(+)-2α-tropanol.[4] No significant separation of solid was observed even after 10 days of stirring at room temperature.

Infrared Spectra.—Spectra of the above diphenylborinates in hydrocarbon and fluorocarbon mulls were compared with those recorded[21,23,24] for a variety of β-aminoalkyl diphenylborinates. Absorptions characteristic of boron–nitrogen and boron–aryl bonds were observed. The boron–oxygen stretching frequency at 1340 cm^{-1} was absent. Splitting of the out-of-plane C–H aromatic deformation frequencies, which occurs when more than one phenyl group is linked to a boron atom,[23] was found near 750 cm^{-1} in our sample of 2-aminoethyl diphenylborinate but was not observed clearly at this frequency in the case of the

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tropanyl ester. This phenomenon may be associated with some geometrical interaction of the two phenyl groups with the large tropanol ring.

Acknowledgment.—We wish to thank Dr. Monis Manning for the analysis of infrared spectra, and Dr. Franklin J. Rosenberg, Sterling–Winthrop Research Institute, for preliminary pharmacological data. The study of absorption of drugs in tumors was supported at the Massachusetts General Hospital by grants from the U. S. Atomic Energy Commission, U. S. Public Health Service, and the John A. Hartford Foundation, Inc.

Tertiary Phosphines and Phosphine Oxides Containing a 2-Haloethyl Group[1]

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2-Haloethylphosphines and -phosphine oxides may be considered as phosphorus analogs of nitrogen mustards. Heretofore, tertiary phosphine oxides containing a 2-haloethyl group have attracted interest as intermediates for the synthesis of the corresponding vinyl derivatives, which can function as monomers in the synthesis of organophosphorus polymers or copolymers. The existing methods for synthesis of the phosphine oxides, as well as the phosphines, are few in number. The preparation of only one monofunctional 2-haloethyl tertiary phosphine has been described,[2,3] and in that instance the compound was not obtained in pure form. Abbiss, *et al.*,[4] have described the synthesis of a bifunctional phosphorus mustard, bis(2-chloroethyl)-phenylphosphine oxide, which was obtained in analytical purity, and a related phosphine, bis(2-chloroethyl)-phenylphosphine, which was not isolated in pure form. Earlier, Hitchcock and Mann[2] obtained bis(2-bromoethyl)phenylphosphine hydrobromide as an impure gum. Three synthetic pathways have been reported[5-9] for the monofunctional 2-haloethylphosphine oxides, but only two of these have been used to obtain pure specimens. Because of our interest in obtaining the phosphines and phosphine oxides as characterizable products that could be evaluated biologically, we have investigated several routes for their preparation.

As mentioned, Hitchcock and Mann[2] reported the only 2-haloethyl tertiary phosphine heretofore appearing in the literature, 2-bromoethylethylphenylphosphine, as an uncharacterized liquid that was quaternized to a diphosphonium dibromide. We have synthesized 2-chloroethyldiphenylphosphine (I) by addition of lithium diphenylphosphide to excess 1,2-dichloroethane in tetrahydrofuran solution (eq 1). The compound was obtained as a low-melting solid of analytical purity after vacuum distillation and crystallization from petroleum ether. Addition of 1,2-dichloroethane to the phosphide gave only ethylenebis(diphenylphosphine). Earlier, we had synthesized 2-ethoxyethyldiphenylphosphine (II) by treatment of lithium diphenylphosphide with 2-chloroethyl ethyl ether and expected to prepare the 2-haloethylphosphine (I) by cleavage of the ether linkage followed by halogenation. However, we abandoned further investigation of the latter route since I was obtained by the direct method.

$$(C_6H_5)_3P \xrightarrow[THF]{Li} [(C_6H_5)_2PLi] \xrightarrow[THF]{ClCH_2CH_2X} (C_6H_5)_2PCH_2CH_2X + LiCl \quad (1)$$

I, X = Cl
II, X = OC_2H_5

We have used two synthetic pathways to obtain 2-haloethyl tertiary phosphine oxides in analytical purity. 2-Bromoethyldi-*sec*-butyl- and -diphenylphosphine oxides (III and IV, respectively) were conveniently prepared by means of the Michaelis–Arbuzov reaction between excess 1,2-dibromoethane and the appropriate ethyl disubstituted phosphinite (eq 2).

$$R_2PCl + EtOH \xrightarrow{Et_3N} R_2POEt \xrightarrow[\Delta]{BrCH_2CH_2Br} BrCH_2CH_2\overset{O}{\overset{\uparrow}{P}}R_2 \quad (2)$$

III, R = *sec*-C_4H_9
IV, R = C_6H_5

Ethylenebis(disubstituted phosphine oxides) were obtained in low yield as by-products. This method was reported by Rabinowitz and Pellon[5] who did not attempt purification of the 2-bromoethyl derivatives but dehydrohalogenated them in order to obtain the corresponding vinyl compounds for polymerization studies. Hellmann and Bader[6] prepared 2-chloroethyldiphenylphosphine oxide as a crystalline solid by the rearrangement of bis(chloromethyl)diphenylphosphonium chloride in aqueous solution, and Kabachnik and co-workers[7] and Cooper[8] prepared the same compound in the pure state by the Michaelis–Arbuzov rearrangement of 2-chloroethyl diphenylphosphinite. Miller[9] reported the preparation of $R_2P(O)CH_2CH_2X$ (R = C_2H_5, C_6H_5, and *n*-C_8H_{17}; X = halogen) by the latter method and their conversion to the corresponding vinyl derivatives but gave no indication as to whether the 2-haloethyl compounds were obtained in pure form.

Our second method, which was used to synthesize 2-bromoethyldimethylphosphine oxide (V) in low yield, is represented by eq 3. Decomposition of the phosphine oxide–magnesium salt complex under mild conditions gave difficultly purifiable mixtures, whereas isolation of 2-ethoxyethyldimethylphosphine oxide (VI) was readily accomplished when the Grignard mixture

(1) This investigation was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. PH-43-64-51, and by the C. F. Kettering Foundation.

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