Notes

Carboranes. I. Nitrogen Mustards[1]

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Failures in the use of *p*-carboxybenzeneboronic acid and sodium decahydrodecaborate ($Na_2B_{10}H_{10}$) for the treatment of brain tumor patients by neutron-capture therapy[2] prompted the synthesis of boron-containing alkylating agents. The rationale for such synthetic efforts is that these compounds would have a twofold purpose: (1) direct inhibition of tumor growth, and (2) alkylation of neoplastic nucleic acids[3] placing a neutron absorber in tumor chromosomes, whereby tumor cell replication would be disrupted upon thermal neutron bombardment.

The high chemical stability of the carborane moiety[4a-d,5a-d,6a-c] with its large percentage of boron encouraged our preparation of an alkylating agent containing this structure. For this purpose, 4-[bis-(2-chloroethyl)amino]phenylcarborane has been synthesized and evaluated biologically.

Discussion and Results

Nitration of phenylcarborane[6a] afforded in nearly equal amounts two mononitrophenylcarborane fractions. The higher melting product, mp 164–165° (I), was first reported by Zakharkin, *et al.*,[7,8] and characterized by them[7] by a very elegant oxidation procedure to *p*-nitrobenzoic acid. In addition to being degraded to *p*-nitrobenzoic, the structure of this nitrophenylcarborane was demonstrated by its pmr spectrum obtained in deuteriochloroform: two doublets ($J \approx 9$ cps) for each of two protons on the aromatic nucleus, one at τ 1.76 for the protons α to the nitro function and the other at τ 2.30 for those adjacent to the carborane nucleus. This spectrum constitutes a typical A_2X_2 pattern, indicative of a *para*-disubstituted aromatic system.[9] The hydrogen on the carbon atom of the carborane nucleus occurred as a broad one-proton absorption at τ 5.87, compared with τ 6.03 for the comparable proton on phenylcarborane itself. The lower melting product, which occurred to a somewhat small extent, had a broader melting point range, 115–121°, and even successive recrystallizations failed to alter this appreciably. The pmr spectrum indicated that this product was a mixture composed of approximately 50% of the *p*-nitro isomer and a compound with a doublet ($J \approx 2$ cps) at τ 1.61 and a series of multiplets ranging from τ 2.40 to 2.15. These were too ill-defined to allow any accurate assignments but would seem to be best explained by a *meta*-substituted nitrocarborane. This postulation was shown to be correct by oxidizing[7] the lower melting nitrocarborane to a mixture of *m*- and *p*-nitrobenzoic acids which were separated by fractional crystallization. The structure of these acids was elucidated by melting point, mixture melting point, and infrared spectra.

Catalytic reduction of I by PtO_2 and hydrogen yielded *p*-aminophenylcarborane (II). This same compound was obtained by refluxing a methanolic solution of I in the presence of PtO_2. In this case, the catalyst and compound were reduced by the evolved hydrogen furnished in part by the carborane moiety. Reduction of the catalyst occurred as well with 1-bromomethylcarborane, phenylcarborane, $Na_2B_{10}H_{10}$, and $Na_2B_{12}H_{12}$. The amine II was treated with ethylene oxide in acetic acid to furnish 4-[bis(2-hydroxyethyl)-amino]phenylcarborane (III). Reaction of III with thionyl chloride in chloroform resulted in the formation of the nitrogen mustard, 4-[bis(2-chloroethyl)-amine]phenylcarborane (IV) (see Scheme I).

This mustard was evaluated by four daily injections of 70 μg of boron/g into C3H mice bearing subcutaneously transplanted ependymomas.[10] The animals were sacrificed 2 days following the last injection and tissues were analyzed for boron content. The results are summarized in Table I. The compound was bound to some extent in all tissues in contrast with the freely

Table I

Tissue Distribution Ratio[a]

Tumor:brain	1.9 (1.6–2.2)
Tumor:muscle	1.8 (1.6–1.9)
Tumor:blood	0.6 (0.5–0.7)

[a] Total dose 280 μg of boron. Values are average of four or five mice with the range of the values shown in parentheses.

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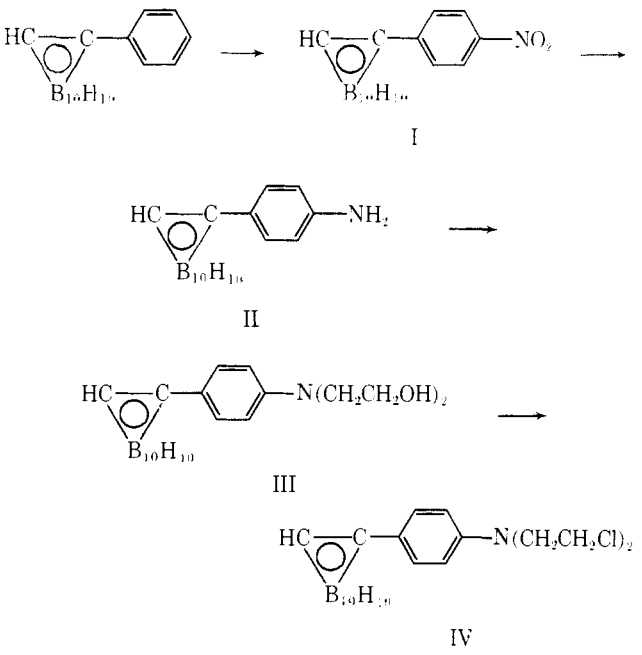
SCHEME I



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, 39.09; H, 6.43; B, 30.02; Cl, 19.67; N, 3.89. Found: C, 40.20; H, 6.78; B, 29.63; Cl, 19.33; N, 4.12.

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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-

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(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.

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