New Heteroaromatic Boron Compounds. XIX.[1,2] Water-Soluble Derivatives of 10,9-Borazarophenanthrene and 2,1-Borazaronaphthalene as Potential Agents for Neutron Capture Therapy

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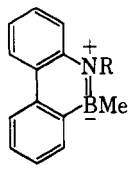
A number of aminoalkyl derivatives of 10-methyl-10,9-borazarophenanthrene and of 2-methyl-2,1-borazaronaphthalene have been prepared by N-alkylation of the parent compounds *via* the N-lithio derivatives for test as possible agents for the neutron capture therapy of cancer. Several other derivatives of these rings systems also are described.

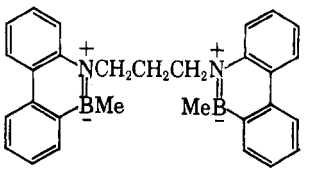
The use of boron compounds for the neutron irradiation therapy of cancer has been hampered by the lack of stable, nontoxic compounds of boron.

Earlier papers[4] of this series have described the preparation of a new class of organoboron compounds containing boron atoms in six-membered heteroaromatic rings; compounds of this type show remarkable resistance to hydrolysis or oxidation. Here we describe the preparation of water-soluble derivatives of two of these ring systems, 10,9-borazarophenanthrene and 2,1-borazaronaphthalene, for test as potential agents for neutron capture therapy.

Dewar and Maitlis[5] found that 10-methyl-10,9-borazarophenanthrene (Ia) could be N-methylated to Ib by treating the N-lithio derivative (Ic) with dimethyl sulfate. We decided to use this reaction to introduce alkyl groups containing a solubilizing substituent.



Ia, R = H
b, R = Me
c, R = Li
d, R = $-CH_2CH_2CH_2Cl$
e, R = $-CH_2CH{=}CH_2$
f, R = —COOEt

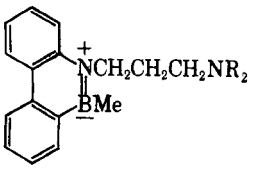


II

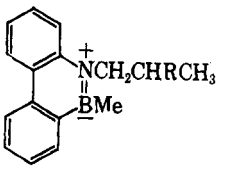
Preliminary experiments in this direction encountered difficulties since the N-alkylation of borazarophenanthrene *via* the N-lithio derivative proved not to be a general reaction. Only unchanged Ia was isolated from the reaction of Ic with ethyl chloroacetate, ethyl β-chloro- or β-bromopropionate, β-chloroethyl- or γ-chloropropyldimethylamine, or acrylonitrile, while 1,3-dibromopropane gave products containing appreciable quantities of the bisborazarophenanthrylpropane (II), even when an excess of dibromide was used.

We finally obtained compounds of the desired type by two different routes. The first of these involved the condensation of Ic with 1-bromo-3-chloropropane to give the 9-(3-chloro-1-propyl) derivatives (Id), followed by reaction with secondary amines to form a series of 9-(3-dialkylamino-1-propyl)-10-methyl-10,9-borazarophenanthrenes.

The intermediate chloropropyl derivative (Id) proved very difficult to purify and the reactions had to be carried out with crude material. However the amines were well characterized.



IIIa, R = Me
b, R = Et
c, R = *n*-Bu
d, NR_2 = piperidino
e, NR_2 = morpholino



IVa, R = Br
b, R = NMe_2
c, R = NEt_2
d, R = NPr_2
e, R = NBu_2
f, R = N-piperidino
g, R = N-morpholino
h, R = CN

The second route involved addition of hydrogen bromide to the double bond of 9-allyl-10-methyl-10,9-borazarophenanthrene (Ie), followed again by reaction with secondary amines. The allyl derivative (Ie) was obtained in good yield from Ic and allyl bromide, but it showed unexpected reluctance to react with hydrogen bromide. We finally brought about addition by passing dry hydrogen bromide through fused Ie at 150°. Since the same product was obtained with or without the addition of benzoyl peroxide as catalyst, and since the amines derived from the bromide were different from the 3-dialkylamino-1-propyl isomers (III), the bromide was formulated as 9-(2-bromo-1-propyl)-10-methyl-10,9-borazarophenanthrene (IVa).

It is true that analogous 2-haloalkyl amines commonly undergo interchange of the halogen and amine functions *via* intermediate ethyleneimine derivatives; however, such a rearrangement is most unlikely to have taken place here since the nitrogen atom in 10,9-borazarophenanthrene shows almost no basic or nucleophilic properties and since formation of a spiroethyleneimine intermediate would involve destruction of the aromaticity of the central ring.

The bromide (IVa) reacted with a series of secondary amines to give the aminopropylborazarophenanthrenes (IVb–g). These were different from the corresponding 3-dialkylamino-1-propyl derivatives (III), as was shown by a comparison of their infrared spectra and by mixture melting point depression. We also prepared the nitrile (IVh) from IVa and potassium

(1) Part XVIII: M. J. S. Dewar and W. M. Poesche, *J. Am. Chem. Soc.*, **85**, 2253 (1963).

(2) This work was supported by the Atomic Energy Commission under Contract No. AEC 889.

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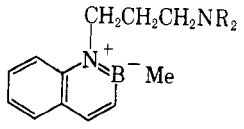
(4) For recent paper and references, see M. J. S. Dewar and R. Dietz, *J. Org. Chem.*, **26**, 3253 (1961).

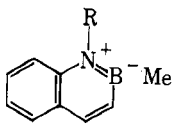
(5) M. J. S. Dewar and P. M. Maitlis, *J. Am. Chem. Soc.*, **83**, 187 (1961).

cyanide in aqueous ethanol in the hope of obtaining the corresponding acid; however, the nitrile proved very resistant to hydrolysis. This resistance to hydrolysis incidentally supports the proposed structure of the bromide (IVa); if this had been the isomeric 1-bromo-2-propylborazarophenanthrene, the derived cyanide would have been a primary nitrile and should have hydrolyzed easily under the conditions we used.

We also prepared a series of 1-(3-dialkylamino-1-propyl)-2-methyl-2,1-borazaronaphthalene derivatives (V) in a similar manner from 2-methyl-2,1-borazaronaphthalene (VIa). Methyllithium with VIa gave the N-lithio derivative (VIb), which reacted smoothly with dimethyl sulfate, allyl bromide, or 1-bromo-3-chloropropane to give the N-methyl, N-allyl, and N-(3-chloro-1-propyl) derivatives (VIc, VId, and VIe), respectively. The chloropropyl derivative (VIe) in turn reacted normally with secondary amines to give the 9-(3-dialkylamino-1-propyl) derivatives (V). In this case, attempts to prepare the isomeric N-(2-dialkylamino-1-propyl) derivatives failed since we were unable to add hydrogen bromide to the double bond of VId, even under drastic conditions.



Va, R = Me
b, R = Et
c, NR_2 = piperidino
d, NR_2 = morpholino
e, R = CN



VIa, R = H
b, R = Li
c, R = Me
d, R = $-CH_2CH{=}CH_2$
e, R = $-CH_2CH_2CH_2Cl$
f, R = $-COOEt$

In the course of this work we also prepared the cyanopropyl derivative (Ve) from VIe and potassium cyanide, and the urethane (VIf) from VIb and ethyl chloroformate. The urethane seemed quite stable to aerial oxidation, unlike the corresponding derivative (If) of 10,9-borazarophenanthrene which undergoes rapid oxidative demethylation in air.[6] The stability of VIf to oxidation indicates that 2,1-borazaronaphthalene is a more aromatic system than 10,9-borazarophenanthrene, as would be expected from analogy with naphthalene and phenanthrene.

Samples of IIIb, IIId, and IIIe, and of Vc and Vd, were tested for antibacterial activity.[7] They showed little or no growth inhibitory effect against *Escherichia coli*, *Lactobacillus arabinosus* 17-5, or *Leuconostoc dextranieum*, even in saturated solution.

Preliminary tests of the same compounds as possible agents for neutron capture therapy[8] also proved disappointing. The compounds were very toxic; mice receiving intravenous injections of 9 μg. B/g., or intraperitoneal injections of 17.5 μg. B/g., died immediately. The compounds were selectively concentrated in the brains of cancerous mice rather than in brain tumors. However the toxic symptoms indicated that the compounds were stable *in vivo*, suggesting that similar compounds of a more "biological" type may prove effective.

(6) M. J. S. Dewar and P. M. Maitlis, *Tetrahedron*, **15**, 3545 (1961).
(7) By Professor William Shive, University of Texas.
(8) By Dr. Albert M. Saloway at the Massachusetts General Hospital.

Experimental

9-(3-Chloro-1-propyl)-10-methyl-10,9-borazarophenanthrene (Id).—A solution of 10-methyl-10,9-borazarophenanthrene (7 g.) in benzene (40 ml.) was titrated under nitrogen with ethereal methyllithium, the end point being marked by a persistent yellow color.[4] The resulting solution of Ic was added dropwise over 40 min. to a solution of 1-bromo-3-chloropropane (22.8 g.) in boiling benzene (75 ml.) under nitrogen and the solution boiled under reflux overnight. Hydrolysis and evaporation of the solvent in a vacuum gave a brown semisolid mass (7.6 g.) of crude Id which could not be distilled or purified by chromatography. It seemed likely that Id is itself a liquid at ordinary temperatures and that the product was contaminated with the bisborazarophenanthrylpropane (II).

9-(3-Dimethylamino-1-propyl)-10-methyl-10,9-borazaro-9-phenanthrene.—A solution of dimethylamine (12.5 g. of 40% aqueous solution) and crude Id (3 g.) in ethanol (100 ml.) was boiled under reflux for 6 hr. and the solvent was distilled. The residue was treated with dilute hydrochloric acid and neutral material was removed with ether. Basification of the aqueous layer and ether extraction gave the **amine IIIa** which crystallized from petroleum ether (b.p. 30–35°) in pale needles (1.8 g., 58%), m.p. 69–71°.

Anal. Calcd. for $C_{18}H_{23}BN_2$: C, 77.7; H, 8.3; N, 10.1; B, 4.0. Found: C, 78.0; H, 8.1; N, 10.0; B, 3.9.

9-(3-Diethylamino-1-propyl)-10-methyl-10,9-borazaro-9-phenanthrene.—Prepared similarly from crude Id (4 g.), the **amine IIIb** was isolated as an oil (2.47 g., 55%), b.p. 140–142° (0.04 mm.), $n^{28}D$ 1.6013.

Anal. Calcd. for $C_{20}H_{27}BN_2$: C, 78.4; H, 8.8; N, 9.1; B, 3.6. Found: C, 78.2; H, 8.7; N, 8.9; B, 3.6.

9-(3-Dibutylamino-1-propyl)-10-methyl-10,9-borazaro-9-phenanthrene.—Prepared similarly from crude Id (3 g.), the **amine IIIc** was isolated as an oil (2.64 g., 66%), b.p. 154–156° (0.04 mm.), $n^{26}D$ 1.5610.

Anal. Calcd. for $C_{24}H_{35}BN_2$: C, 79.6; H, 9.7; N, 7.7; B, 3.0. Found: C, 79.8; H, 9.7; N, 7.6; B, 2.8.

9-(3-N-Piperidino-1-propyl)-10-methyl-10,9-borazaro-9-phenanthrene.—Prepared similarly from crude Id (3 g.), the **amine IIId** crystallized from ethanol in white needles (2.4 g., 68%), m.p. 99–100°.

Anal. Calcd. for $C_{21}H_{27}BN_2$: C, 79.2; H, 8.5; N, 8.8; B, 3.4. Found: C, 79.4; H, 8.8; N, 8.5; B, 3.4.

9-(3-N-Morpholino-1-propyl)-10-methyl-10,9-borazaro-9-phenanthrene.—Prepared similarly from crude Id (4 g.), the **amine IIIe** crystallized from ethanol in small needles (3.0 g., 64%), m.p. 129–130°.

Anal. Calcd. for $C_{20}H_{25}BN_2O$: C, 75.0; H, 7.8; N, 8.7; B, 3.4. Found: C, 75.4; H, 7.9; N, 8.5; B, 3.5.

9-Allyl-10-methyl-10,9-borazarophenanthrene.—Allyl bromide (12.5 g.) in dry benzene (40 ml.) was added to a solution of Ic prepared as above from Ib (8 g.) and the mixture was boiled under reflux. The next day the solution was cooled and hydrolyzed, and the benzene layer was evaporated giving the **allyl derivative (Ie)** which crystallized from methanol in white needles (7.2 g., 75%), m.p. 73–74°.

Anal. Calcd. for $C_{16}H_{16}BN$: C, 82.4; H, 6.9; N, 6.0. Found: C, 82.3; H, 7.2; N, 6.2.

9-(2-Bromo-1-propyl)-10-methyl-10,9-borazarophenanthrene.—A mixture of Ie (3.7 g.) and benzoyl peroxide (0.2 g.) was heated to 90° in a small flask and a current of dry hydrogen bromide passed through the melt. The temperature was raised gradually to 150° and held there for 3 hr. The resulting **bromopropyl derivative (IVa)** crystallized from ethanol in white needles (2.8 g., 56%), m.p. 124–125°.

Anal. Calcd. for $C_{16}H_{17}BBrN$: C, 61.1; H, 5.4; N, 4.5; Br, 25.5. Found: C, 61.6; H, 5.6; N, 4.5; Br, 25.8.

9-(2-Dimethylamino-1-propyl)-10,9-borazarophenanthrene.—Prepared from IVa (2.5 g.) in the same way as the isomer IIIa, the **amine IVb** was isolated as an oil (1.28 g., 58%), b.p. 160–162° (0.4 mm.).

Anal. Calcd. for $C_{18}H_{23}BN_2$: C, 77.7; H, 8.3; N, 10.1. Found: C, 77.3; H, 8.1; N, 8.8.

9-(2-Diethylamino-1-propyl)-10-methyl-10,9-borazarophenanthrene.—Prepared similarly from IVa (1.5 g.), the **amine IVc** crystallized from ethanol in white needles (1.19 g., 82%), m.p. 104–105°.

Anal. Calcd. for $C_{20}H_{27}BN$: C, 78.4; H, 8.8; N, 9.1. Found: C, 78.7; H, 9.1; N, 9.1.

9-(2-Dipropylamino-1-propyl)-10-methyl-10,9-borazarophenanthrene.—Prepared similarly from IVa (3.1 g.), the **amine IVd** was isolated as an oil (2.14 g., 65%), b.p. 156–158° (0.03 mm.).

Anal. Calcd. for $C_{24}H_{25}BN_2$: N, 7.7; B, 3.0. Found: N, 7.3; B, 3.0.

9-(2-Dibutylamino-1-propyl)-10-methyl-10,9-borazarophenanthrene.—Prepared similarly from IVa (4.0 g.), the **amine IVe** was isolated as an oil (2.86 g., 62%), b.p. 168–170° (0.04 mm.).

Anal. Calcd. for $C_{24}H_{25}BN_2$: N, 7.7; B, 3.0. Found: N, 7.3; B, 3.0.

9-(2-N-Piperidino-1-propyl)-10-methyl-10,9-borazarophenanthrene.—Prepared similarly from IVa (1.5 g.), the **amine IVf** crystallized from ethanol in small plates (1.1 g., 72%), m.p. 116–117°, depressed on admixture with IIId.

Anal. Calcd. for $C_{21}H_{27}BN$: C, 79.2; H, 8.5; N, 8.8. Found: C, 79.0; H, 8.4; N, 8.6.

9-(2-N-Morpholino-1-propyl)-10-methyl-10,9-borazarophenanthrene.—Prepared similarly from IVa (2.0 g.), the **amine IVg** crystallized from ethanol in small plates (1.55 g. 76%), m.p. 129–130°, depressed on admixture with IIIe.

Anal. Calcd. for $C_{20}H_{25}BN_2O$: C, 75.0; H, 7.8; N, 8.7. Found: C, 75.2; H, 7.7; N, 8.8.

9-(2-Cyano-1-propyl)-10-methyl-10,9-borazarophenanthrene.—A solution of potassium cyanide (0.93 g.) in water (20 ml.) was added to one of IVa (1.5 g.) in ethanol (80 ml.) and the mixture was boiled overnight and then evaporated under vacuum. Ether extraction of the residue gave the **nitrile IVh** which crystallized from ethanol in small prisms (1.00 g., 80%), m.p. 177–178°.

Anal. Calcd. for $C_{17}H_{17}BN_2$: C, 78.5; H, 6.5; N, 10.8. Found: C, 78.7; H, 6.2; N, 10.9.

1,2-Dimethyl-2,1-borazaronaphthalene.—An ethereal solution of methyllithium, prepared from lithium (1.0 g.) and methyl iodide (6.5 g.), was added dropwise to a vigorously stirred benzene solution of VIa (5.0 g.) under nitrogen at room temperature. A benzene solution of dimethyl sulfate (11 g.) was then added and the mixture was boiled 3 hr. under reflux. Hydrolysis and ether extraction gave **1,2-dimethyl-2,1-borazaronaphthalene (VIc)** as an oil (4.4 g., 80%), b.p. 76–78° (0.5 mm.).

Anal. Calcd. for $C_{10}H_{12}BN$: C, 76.4; H, 7.6; N, 8.9; B, 7.0. Found: C, 76.2; H, 7.8; N, 8.9; B, 6.7.

1-Allyl-2-methyl-2,1-borazaronaphthalene.—Prepared similarly from allyl bromide (10.8 g.), the **allylmethylborazaronaphthalene (VId)** was isolated as an oil (4.99 g., 78%), b.p. 74° (0.04 mm.).

Anal. Calcd. for $C_{12}H_{14}BN$: C, 78.7; H, 7.6; N, 7.6. Found: C, 78.3; H, 7.2; N, 7.8.

Ethyl 2-Methyl-2,1-borazaronaphthalene-1-carboxylate.—Prepared similarly from ethyl chloroformate (9.5 g.), the **urethane (VIf)** was isolated as an oil (5.7 g., 76%), b.p. 96–98° (0.4 mm.).

Anal. Calcd. for $C_{12}H_{14}BNO_2$: C, 67.0; H, 6.5; N, 6.5. Found: C, 66.7; H, 6.8; N, 6.5.

1-(3-Chloro-1-propyl)-2-methyl-2,1-borazaronaphthalene.—Prepared similarly from 1-bromo-3-chloropropane (22.0 g.), the **chloropropyl derivative (VIe)** distilled at 100–102° (2 mm.) as an oil which crystallized, m.p. 70.0°.

Anal. Calcd. for $C_{12}H_{15}BClN$: C, 65.6; H, 6.8; N, 6.4; Cl, 16.2; B, 5.0. Found: C, 66.1; H, 7.3; N, 6.4; Cl, 16.0; B, 5.2.

1-(3-Dimethylamino-1-propyl)-2-methyl-2,1-borazaronaphthalene.—Prepared in the same way as III from VIe (3.0 g.) and dimethylamine (15.5 g. of 40% aqueous solution), the **amine Va** was isolated as an oil (2.23 g., 72%), b.p. 110° (1.0 mm.), $n^{28}D$ 1.5608.

Anal. Calcd. for $C_{14}H_{21}BN_2$: C, 73.7; H, 9.2; B, 4.8. Found: C, 73.5; H, 9.3; B, 4.8.

1-(3-Dimethylamino-1-propyl)-2-methyl-2,1-borazaronaphthalene.—Prepared similarly from VIe (3.0 g.), the **amine Vb** formed an oil (2.27 g., 65%), b.p. 119–121° (1.0 mm.), $n^{29}D$ 1.5970.

Anal. Calcd. for $C_{16}H_{25}BN_2$: N, 10.9; B, 4.3. Found: N, 10.8; B, 4.3.

1-(3-N-Piperidino-1-propyl)-2-methyl-2,1-borazaronaphthalene.—Prepared similarly from VIe (4.0 g.), the **amine Vc** formed an oil (3.38 g., 70%), b.p. 122–124° (0.2 mm.), $n^{29}D$ 1.5670.

Anal. Calcd. for $C_{17}H_{25}BN_2$: C, 76.1; H, 9.3; N, 10.4. Found: C, 76.6; H, 9.5; N, 10.1.

1-(3-N-Morpholino-1-propyl)-2-methyl-2,1-borazaronaphthalene.—Prepared similarly from VIe (4.0 g.), the **amine Vd** (3.73 g., 76%) had b.p. 130–132° (0.2 mm.), $n^{29}D$ 1.5755.

Anal. Calcd. for $C_{16}H_{23}BN_2O$: C, 71.1; H, 8.5; N, 10.4. Found: C, 70.9; H, 8.4; N, 10.2.

1-(3-Cyano-1-propyl)-2-methyl-2,1-borazaronaphthalene.—A solution of potassium cyanide (3.6 g.) in water (20 ml.) was added to one of VIe (4.0 g.) in ethanol (125 ml.), and the mixture was boiled under reflux for 6 hr. and then evaporated. Ether extraction of the residue gave the **nitrile Ve** as an oil (2.55 g., 67%), b.p. 140–142° (0.4 mm.).

Anal. Calcd. for $C_{13}H_{15}BN_2$: C, 74.3; H, 7.1; B, 5.2. Found: C, 74.9; H, 7.6; B, 5.4.

New Heteroaromatic Compounds. XXI.[1] Some Tetracyclic Systems[2]

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Several derivatives of 5,4-borazaropyrene, of 9,10-dihydro-5,4-borazaropyrene, and of 6,5-borazarochrysene have been prepared by the general procedures previously described. In the course of this work we have developed an improved synthesis of 4-aminophenanthrene. Attempts to synthesize derivatives of 5,6- and 6,5-borazarobenz[*c*]phenanthrene failed. Limitations on the generality of a recently described[4] new cinnoline synthesis are pointed out.

Previous papers in this series have described a large number of novel heteroaromatic compounds containing boron. These compounds are remarkably stable and show a marked similarity to the related "normal" aromatics in their physical properties; it, therefore, seemed to us that corresponding analogs of carcinogenic hydrocarbons might be of biological interest. The work described here represents a step towards the synthesis of such materials, in particular, analogs of benz[*a*]pyrene.

The obvious route to 5,4-borazaropyrene (I) was by a Friedel–Crafts cyclization of the adduct from 4-aminophenanthrene (II) and boron trichloride.[5] Langenbeck and Weissenborn[6] had reported the preparation of 4-aminophenanthrene by Semmler reaction of the oxime of 4-keto-1,2,3,4-tetrahydrophenanthrene (III); however, one of us (M. J. S. D.) previously had found this reaction capricious and unsatisfactory,[7] and we can confirm that the yields are low and erratic. The

(1) Part XX: M. J. S. Dewar and R. C. Dougherty, *J. Am. Chem. Soc.*, **86**, 433 (1964).

(2) This work was supported by the National Institutes of Health through Grant No. CY-5218.

(3) Department of Chemistry, The University of Texas, Austin, Texas 78712.

(4) M. J. S. Dewar and W. H. Poesche, *J. Chem. Soc.*, 2201 (1963).

(5) *Cf.* M. J. S. Dewar, V. P. Kubba, and R. Pettit, *ibid.*, 3073 (1958).

(6) W. Langenbeck and K. Weissenborn, *Ber.*, **72**, 726 (1939).

(7) *Cf.* P. M. G. Bavin, Ph.D. thesis, London, 1954.