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Potential Anticancer Agents.[1] LXII. The Relationship of Chemical Structure to Antileukemic Activity with Analogs of 1-Methyl-3-nitro-1-nitrosoguanidine (NSC-9369). II

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In a continued investigation of the relationship of structure to antileukemic activity of 1-methyl-3-nitro-1-nitrosoguanidine (NSC-9369), an additional eight nitroso amides bearing an N-(2-substituted ethyl) group were synthesized and evaluated against Leukemia L-1210. The most effective analog was found to be 1-(2-chloroethyl)-1-nitrosourea (NSC-47547).

The first paper[2] on analogs of 1-methyl-3-nitro-1-nitrosoguanidine (I) (NSC-9369)[3] described Phases I and II of the structure-activity study. It was clear that the 2-chloroethyl analog (II) and the 2-bromoethyl analog (III) were superior to the originally discovered lead (I). In this first paper were also posed the following questions: Are other 2-substituted ethyl analogs even more effective than II

(1) This program is carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. SA-43-ph-1892. The opinions expressed in this paper are those of the authors and are not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper in this series, see E. J. Reist, J. H. Osiecki, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **83**, 2208 (1961).

(2) W. A. Skinner, H. F. Gram, M. O. Greene, J. Greenberg and B. R. Baker, *J. Med. Pharm. Chem.*, **2**, 299 (1960).

(3) The NSC accession numbers used in this paper were assigned by the Cancer Chemotherapy National Service Center.

Penetration of Brain and Brain Tumor by Aromatic Compounds as a Function of Molecular Substituents. III[1,2]

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To a great extent there is a correlation between high aqueous/lipid solvent partition coefficients of a series of substituted aromatic boronic acids and the high tumor/brain ratios of these compounds in mice with subcutaneously transplanted gliomas. There are, however, exceptions to this observation and the mechanism of transport into the central nervous system of compounds with low lipid solubility remains obscure. The position of groups on an aromatic nucleus is of importance in determining the degree of penetration of brain. An attempt is made to correlate chemical and physical properties with biologic attributes.

An understanding of the types of compounds which will penetrate brain tumors but not the brain is essential in the treatment of such neoplasms by neutron capture irradiation[3] and by chemotherapy.[4] Previous studies[5,6] have shown a definite correlation between brain tumor/brain ratio of various substituted benzeneboronic acids in C3H mice and their lipid solubility. A histologically-reproducible tumor, such as this ependymoma, was used throughout. By comparing the amount of a compound in this tissue with the amount in normal brain, the necessity of maintaining a constant blood level, in order to ascertain the permeation of the brain, becomes unnecessary. In this way both tissues are subjected to the same fluctuation in blood concentration and the ratio becomes a true measure of the

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(2) For Papers I and II: see references 5 and 6.

(3) W. H. Sweet, A. H. Soloway, and G. L. Brownell, *Acta Union Int. Contre le Cancer*, **16**, 1216 (1960).

(4) V. H. Mark, R. N. Kjellberg, R. G. Ojemann, and A. H. Soloway, *Neurol.*, **10**, 772 (1960).

(5) A. H. Soloway, *Science*, **128**, 1572 (1958).

(6) A. H. Soloway, B. Whitman, and J. R. Messer, *J. Pharmacol. Exptl. Therap.*, **129**, 310 (1960).

permeability of brain relative to this tissue by the compound under such conditions.

Substances with a high lipid solubility invariably penetrated the brain readily, were toxic, and gave poor tumor/brain ratios as measured by their boron content. Only among those substances with low lipid solubility were compounds obtained whose ability to penetrate the central nervous system was restricted. Many of these hydrophilic ones were relatively non-toxic and some did give high tumor/brain boron ratios.[7] However, two groups of compounds with low lipid solubility gave poor ratios. These were the amines, with the exception of those containing a carboxylic acid function, and the phenols. Such substances penetrated the brain nearly as well as the tumor and were quite toxic.

The purpose of this investigation in part was to determine whether the amines were an exception to the assumption that lipid solubility of a compound is one of the main factors in determining its ability to penetrate the central nervous system. Additional information was also sought relating to the effect produced by groups in an aromatic compound upon its ability to penetrate the brain. In particular, are position isomers handled in the same or in a different manner by the central nervous system? Such information would permit a correlation between the physical and chemical properties of drugs with their biological qualities.

Experimental Methods

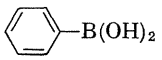
The method for determining lipid solubility is essentially the same as previously described.[6] Approximately 10 mg. of each substance was distributed between 25 ml. of a phosphate-buffered aqueous medium of pH 7.2 and 25 ml. of a lipid solvent, chloroform or benzene. The mixing was carried out in a separatory funnel and the layers were separated. Aliquots of each phase then were analyzed for boron content.[8] The values in Table I are listed in μg. of boron per ml. of each solution.

To determine tumor/brain ratios, C3H mice bearing subcutane-

(7) A. H. Soloway, R. W. Wright, and J. R. Messer, *J. Pharmacol. Exptl. Therap.*, **134**, 117 (1961).
(8) G. H. Ellis, E. G. Zook, and O. Baudisch, *Anal. Chem.*, **21**, 1345 (1949).

TABLE I

AQUEOUS/LIPID SOLVENT PARTITION COEFFICIENTS

	Aqueous[a]	Benzene[a]	Aqueous/ benzene	Aqueous[a]	Chloro- form[a]	Aqueous/ chloro- form
4-Cl[b]	6.9	5.2	1	11.8	10.8	1
4-H[b]	14.4	2.3	6	23.6	6.0	4
3-NO_2-4-NH_2[c]	20.9	0.73	29	22.0	2.2	10
3-NH_2-4-CH_3[b]	15.4	.23	67	29.2	1.9	15
4-COOH[b]	11.4	.17	67	23.3	0.32	73
3-NO_2-5-NH_2[c]	23.5	.14	170	25.4	.38	67
2-NO_2-4-NH_2[c]	22.8	.10	>200	25.2	.15	170
3-NH_2[b]	12.4	.06	>200	29.8	.44	68
3,5-$(NH_2)_2$[c]	26.0	0	>200	29.0	0	>200
2-CH_3-3,5-$(NH_2)_2$[c]	25.2	0	>200	30.0	0.04	>200

[a] Values listed are in μg. of boron/ml. [b] For aqueous/benzene values, see ref. 6. [c] The authors wish to thank Dr. Kurt Torssell of the Biokemiska Institutet in Stockholm, who very kindly supplied us with these compounds.

ously transplanted gliomas[9] were used. Fresh tumor tissue was ground in normal saline and a cellular suspension was injected in the region of the left scapula in 6-to 8-week old C3H mice. Within 7 to 10 days the tumors were large enough for use. Solutions of the compounds were prepared and injected intraperitoneally into the tumor mice. The animals were sacrificed at fixed time intervals after injection to obtain biopsy specimens for boron analysis. The boron tissue concentrations are recorded in Table II.

Results and Discussion

The aqueous/benzene and aqueous/chloroform partition coefficients of several mono- and disubstituted aromatic boronic acids are recorded in Table I. The group includes 3-amino-4-methylbenzeneboronic acid, *m*-aminobenzeneboronic acid, 3,5-diaminobenzeneboronic acid and 3,5-diamino-2-methylbenzeneboronic acid. The last three compounds have high values for their aqueous/lipid solvent coefficients in contrast with the low values for benzeneboronic acid and *p*-chlorobenzeneboronic acid. The coefficients for these amines are comparable to those observed with *p*-carboxybenzeneboronic acid. On this basis, were low lipid solubility the sole re-

(9) The authors are greatly indebted to Dr. D. M. Perese of the Department of Neurosurgery at the Roswell Park Memorial Institute in Buffalo, N. Y., for supplying us with the original subcutaneously-grown ependymoma.

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