of a *m*-hydroxy group, compound **2**, resulted in a 2–3-fold lower affinity for A_1 receptors, but a more than 10-fold lower affinity for A_2 receptors. The A_2/A_1 selectivity ratio (IC_{50} A_2/IC_{50} A_1) of 690 obtained with compound **2** makes it nearly as selective for A_1 receptors as CPA.[13] The *m*-iodo analogue, compound **3**, showed similar A_1 selectivity. Since the affinities of compounds **2** and **3** at A_1 receptors were much less affected than those at A_2 receptors, it appeared that the affinity of phenyladenosines for A_2 receptors was selectively decreased by meta substitution. Results with three other meta-substituted analogues, compounds **4–6**, tend to support this conclusion as these compounds had much lower affinity for A_2 than for A_1 receptors. Although the meta substitution of the phenyladenosines resulted in dramatic decreases in affinity for A_2 receptors, para substitution caused much less attenuation in A_2 affinity (compounds **9–12**). Except for the *p*-methoxy analogue, compound **12**, the A_2 selectivity ratios for these compounds were not much different than for the parent compound **1**. The decrease in A_2 affinity caused by meta substitution appears to be due to steric factors as the introduction of a small substituent like fluoro, compound **7**, did not cause a substantial decrease in A_2 affinity compared to either its *para*-isomer, compound **8**, or the unsubstituted analogue, compound **1** (Table II). The present results show that the introduction of a bulky group at the meta position of N^6-phenyladenosine causes a selective decrease in A_2 affinity. A simple explanation for this observation could be that the rat brain A_2 receptor, like that in the dog coronary artery,[5-7] has a specialized region to interact with the N^6 domain of the adenosine molecule and the bulky meta substituents on compound **1** do not fit into this region.

Recently,[7,15] a number of phenyl-substituted N^6-phenyladenosines were evaluated for their abilities to increase coronary blood flow via a putative A_2 receptor. The meta-substituted analogues were found to have a lower potency than their para-substituted counterparts in increasing blood flow; furthermore, a compound with a relatively bulky meta substituent, the *m*-methyl analogue, was less potent than a compound with a smaller meta substituent, the *m*-fluoro compound. These results suggest that the deleterious effect of a bulky meta substituent on A_2 affinity observed in our in vitro assay with rat brain adenosine receptors is also seen in vivo with dog coronary artery adenosine receptors.

In conclusion, we have shown that substituents on the phenyl ring of N^6-phenyladenosine have marked effects on the selectivity of these compounds for A_1 and A_2 receptors. Substitutions with *m*-hydroxyl and *m*-iodo groups cause minimal change in affinities at A_1 receptors but lead to drastic reductions in the affinities for A_2 receptors. Thus, these meta-substituted phenyladenosines are highly selective for A_1 receptors. These compounds may be useful in future studies concerned with characterization of the properties of adenosine receptors.

(15) Daly, J. W.; Padgett, W.; Thompson, R. D.; Kusachi, S.; Bugni, W. J.; Olsson, R. A. *Biochem. Pharmacol.* **1986**, *35*, 2467–2481.
(16) Bruns, R. F. *Can. J. Physiol.* **1980**, *58*, 673–691.

Book Reviews

Neuromethods: Series 1: Neurochemistry. Edited by Alan A. Boulton and Glen B. Baker. Humana Press, Clifton, New Jersey.

The objective of Neuromethods, a new handbook series, is to provide a comprehensive guide for establishing laboratory methods of interest to the neuroscientist. The neurochemistry series is edited by Alan A. Boulton of the University of Saskatchewan and Glen B. Baker of the University of Alberta with additional editors for most volumes. Series 1, entitled Neurochemistry, will be issued in at least 11 volumes. Vol. 1, General Techniques, Vol. 2, Amines and their Metabolites, and Volume 3, Amino Acids, have already been published. Vol. 4 (Receptor Binding Methods) and Vol. 5 (Enzymes) are scheduled for publication in 1986. Future volumes, covering a range of topics (peptides, lipids, physicochemical techniques, carbohydrates, nucleosides, and nucleotides, brain electrolytes, water spaces, and proteins) are planned. Hopefully the editors are considering the preparation of volumes on immunology and molecular biology techniques. Each chapter is formatted to cover an introduction to techniques, application of the techniques, detailed experimental procedures, trouble shooting and pitfalls, technique variations, and appropriate literature citations. Many chapters contain a wealth of detail: information rarely mentioned in manuscripts that can be critical for establishing a novel technique successfully. The most efficient way of acquiring a new laboratory procedure is to watch somebody else do it and then repeat the technique in their presence. This is often impractical. A handbook that describes procedures in detail and provides extensive background material can substitute for, and occasionally be an improvement on, hands-on technique acquisition. If the first three volumes of the series are indicators of overall quality, the series will be an important source for neuroscientists.

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Neuromethods. Volume 1. General Neurochemical Techniques. Edited by Alan A. Boulton and Glen B. Baker. Humana Press, Clifton, New Jersey. 1986. xix + 555 pp. 16 × 24 cm. ISBN 0-89603-075-X. $64.50.

The inaugural volume of this new methodological series consists of 14 chapters. The overall theme of the volume is to introduce a variety of approaches to central nervous system (CNS) research including techniques for brain dissection, electrophysiological recording, lesioning, histochemical mapping, and so on. Chapter 1, written by M. Palkovits, outlines techniques for microdissection of individual brain nuclei and areas. It includes justification for the technique, potential applications, detailed descriptions of the methods, and a valuable list of references for stereotaxic maps of avian and mammalian brains. The next chapter (A. Pellegrino de Iraldi and G. Rodriguez de Lores) contains procedures for preparing subcellular fractions, synaptosomes, subsynaptic fractions, etc. It is clearly written and provides an extensive bibliography. Past successes and potential uses of tissue slice preparations are described by P. Lipton (Chapter 3). CNS cell and tissue culture techniques, a rapidly expanding but technically difficult field, are outlined in Chapter 4 (L. Hertz, B. H. J. Ju-

urlink, S. Szuchet, and W. Walz). The isolation and culturing of cerebral cortical cells, granule cells, astroglial cells, oligodendrocytes, references for cell lines, uses of tissue culture, and a vast bibliography are clearly documented. The next chapter (R. Mishra, D. Mulliken-Kilpatrick, K. H. Sonnenfeld, C. P. Mishra, and A. J. Bloom) is essentially a comprehensive course on the preparation of monoclonal antibodies. Diagrams and flow charts supplement detailed descriptions of the multistep procedures. The chapter's lucid style is marred by the compactness of the introduction. Both the theoretical underpinnings and methods of microiontophoresis and micropressure techniques used to identify central neurotransmitters are thoroughly treated by J. A. MacDonald (Chapter 6). Methods for electrical and chemical stimulation of brain tissue in vivo are described in Chapter 7 (A. J. Greenshaw), followed by perfusion techniques in Chapter 8 by Pittman, Disturnal, Riphagen, Veale, and Bauce. The rationale and techniques for correlating behavior with spontaneously occurring patterns of brain electrical activity are reviewed in the following chapter (C. H. Vanderwolf and L.-W. S. Leung). The section begins with an introduction to behavior and behavioral monitoring and evolves into a description of electrophysiological recordings in freely moving animals. Schallert and Wilcox document methods and consequences of neurotransmitter-selective brain lesions, but limit the their account to neurotoxins for catecholamines (6-hydroxydopamine), serotonin (5,7-dihydroxytryptamine), and acetylcholine (aziridinium ion of ethylcholine). Blood–brain barrier permeability and transport are approached strictly methodologically in Chapter 11 (Q. R. Smith). The following chapter outlines the principles, techniques, and applications of axonal transport (S. T. Brady). The use of human postmortem brain tissue for neurological and psychiatric disease research is the subject of Chapter 13 by G. P. Reynolds. The author provides useful guidelines and stresses potential variables in handling of postmortem tissue. The chapter is somewhat outdated. Inclusion of a segment on the very promising technique of positron emission tomography (PET) scanning would have enhanced the section. In the final chapter (14) H. B. Sarnat outlines histochemical mapping techniques.

Volume 1 of Neuromethods is an excellent introductory text of the series. Although there are variations in emphasis in each chapter, the majority fulfill the goal of the series. It also reflects the current eclectic nature of neuroscience research.

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Neuromethods. Volume 2. Amines and Their Metabolites. Edited by Alan A. Boulton, Glen B. Baker, and Judith M. Baker. Humana Press, Clifton, New Jersey. 1985. xxi + 543 pp. 16 × 24 cm. ISBN 0-89603-076-8. $64.50.

The second volume in this series focuses primarily on the detection and measurement of biogenic amines and their metabolites in brain tissue. Assay methods for catecholamines and indolamines predominate in most chapters, but methods for trace amines are also included. The first chapter, by J. M. Baker, R. F. Butterworth, and W. G. Dewhurst provides a clear summary of both advantages and disadvantages of fluorescence analysis of amines and their metabolites. Costlier, but more sensitive methods, are detailed in subsequent chapters. R. T. Coutts, G. B. Baker, and A. J. Nazarali outline procedures for gas chromatographic separation of biogenic amines. Their approach is that of a literature review, supplemented with experimental procedures. The following chapters include amine assays by radioenzymatic micromethods (Chapter 3, J. M. Saavedra), by amperometric or fluorometric methods following separation by high-performance liquid chromatography (Chapter 4, G. M. Anderson), by immunological methods (Chapter 6, G. M. Brown and L. J. Grota), and by mass spectrometry following gas chromatographic separation (Chapter 7, F. Karoum, Chapter 8, D. A. Durden). The measurement of biogenic amine levels in freely moving animals, by voltammetry, is covered in Chapter 5 (J. B. Justice, A. C. Michael, D. B. Neill). Two shortcomings of the technique, artifacts and imprecision, are clearly stated. The chapters are written in distinctive styles; some are literature surveys, others are descriptions of procedures. The methods offer a range of sensitivities and selectivities, and are applicable to various tissue preparations. In the final three chapters the topics diverge. Autoradiographic localization of amine receptors (R. A. Leslie, C. Shaw, H. A. Robertson, K. M. Murphy), turnover rates of amines (J. Korf), and a comprehensive description of neuronal amine transport by G. Baker and L. Dyck are featured. In general, most chapters fulfill the objectives of the series, to provide the reader with a handbook that can be used to survey and assess currently used methods. In many sections the references are current. In some chapters they are largely pre-1980 but they reflect the rapid conversion of laboratories to newer techniques as soon as they evolve. Some sections contain enough information to attempt a method without scurrying to the library to look up primary sources. Other chapters, however, require further effort. The volume is well worth the cost.

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Neuromethods. Volume 3. Amino Acids. Edited by Alan A. Boulton, Glen B. Baker, and James D. Wood. Humana Press, Clifton, New Jersey. 1985. xx + 281 pp. 16 × 24 cm. ISBN 0-89603-077-6. $45.00.

Volume 3 in this series is a collection of currently used procedures for the analysis of amino acids. The first three chapters document the well-established techniques of automated amino acid analysis and gas chromatography. Chapter 1 (J. A. Sturman, D. A. Applegarth) contains a detailed account of the methods, limitations, and interpretations of automated amino acid analysis. Useful tables of normal concentration ranges of amino acids in body fluids and a list of the clinical implications of levels outside the normal range are included. Many of the references are pre-1980. Derivatization of amino acids in preparation for gas chromatography is the focus of Chapter 2 (R. T. Coutts, J. M. Yeung). The section is written as a survey of the literature, but the gaps are amply filled by the following chapter on gas chromatography–mass fragmentography of amino acids (Chapter 3, P. L. Wood, D. L. Cheney). Detailed descriptions of tissue preparation, column selection, derivative formation, and applications to brain GABA and glutamate dynamics are documented. High-performance liquid chromatography (HPLC) is currently the method of choice for separating amino acids in the central nervous system because it is both ultrasensitive and reproducible. The description of this technology by P. Lindroth, A. Hamberger, and M. Sandberg is outstanding. Progress invariably leads to mounting equipment costs and complexity, and the response is to attempt development of simpler, less expensive methods. One alternative—the double isotope dansyl microassay—method appears in Chapter 4 (R. F. Butterworth). Another option, radioreceptor assays for amino acids, a sensitive but not very selective method, is described in Chapter 6. J. W. Ferkany features a lengthy introduction to radioreceptor assay theory, a detailed protocol for assay of [^{3}H]GABA binding sites, and references for other binding assay systems. Subsequent chapters deal with more subtle aspects of amino acid detection. Cellular and subcellular localization of amino acids by immunocytochemistry is the subject of Chapter 7 (J.-Y. Wu, C.-T. Lin). The focus once more is on GABA with references provided to other amino acids. A concise and excellent chapter on in vitro autoradiographic localization of amino acid receptors and uptake sites is presented by S. Young III in Chapter 8. Brief descriptions of the technical aspects of localization of glycine and glutamic acid receptors are given. This methodology is increasingly popular because it is now possible to quantify binding sites in discrete brain regions without destroying tissue topography. Amino acid turnover is dealt with in Chapter 9 (F. Fonnum) and uptake and release in the following and final chapter (W. Walz).

The third volume in the series maintains the standards es-

tablished by Volumes 1 and 2. Some chapters provide all the background and details necessary to start up a method in a laboratory. Others are written as literature reviews and therefore require the reader to trace original sources for experimental detail. Nevertheless the volume provides an excellent overview of currently used methods for analysis of amino acids in static and dynamic states.

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Neuromethods. Volume 5. Neurotransmitter Enzymes. Edited by Alan A. Boulton, Glen B. Baker, and Peter H. Yu. Humana Press, Clifton, NJ. 1986. xxv + 619 pp. 16 × 23 cm. ISBN 0-89603-079-2. $69.50.

The neurotransmitter enzymes have been and continue to be the subject of intense research. Such studies should promote a better understanding of the nature of neurotransmission. This, in turn, should enable a better understanding of the significance of these brain enzymes in neurological and psychiatric illnesses with the concomitant development of new therapeutic strategies. Indeed, modulation of some of these brain enzymes, namely GABA-transaminase and monoamine oxidase, has already led to therapeutic agents for the treatment of epilepsy and depression, respectively.

The book consists of 17 chapters and a comprehensive index. Each chapter presents a brief, clearly written introduction, followed by a description of the mechanism of the enzyme reaction, its substrates, function, occurrence, and distribution, in addition to its relationship to neurological and/or mental disorders. Further, reviews of each of the enzyme's properties, inhibitors, purification, and determination of activity are presented. Commonly used assay methods are described in detail. Overall, this volume offers critical information and practical assays for important brain enzymes that play pivotal roles in neurotransmitter metabolism and neuronal function.

The first seven chapters describe enzymes involved in the metabolism of biogenic amines. Specifically discussed are phenylalanine, tyrosine, and tryptophan hydroxylase, aromatic L-amino acid decarboxylase, dopamine β-hydroxylase, monoamine methyl transferases, i.e., phenylethanolamine *N*-methyltransferase, catechol *O*-methyltransferase as well as histidine decarboxylase and monoamine oxidase. The next two chapters focus on the principal enzymes of the cholinergic system, namely choline acetyltransferase and acetylcholine esterase. The key enzymes of the GABA system, i.e., glutamate decarboxylase and GABA transaminase, are discussed in Chapters 10 and 11. The following chapter deals with proteinases and peptidases. Enzymes, i.e., Na^+/K^+-ATPase, adenylate cyclase, and calmodulin-dependent protein kinase, that are important in ion transport, receptor binding, and subsequent protein phosphorylation, respectively, are the subjects of the next three chapters. The final two chapters describe two metabolic enzymes, *S*-adenosyl-L-homocysteine hydrolase and phenol sulfotransferase, that have been the subjects of a considerable amount of recent research.

Each of the chapters is written in a clear and carefully referenced manner by an active expert researcher in the field. The introduction to each chapter assumes no previous expertise in the area. Consequently, the subject matter serves as an excellent introduction that enables an up-to-date understanding of the important brain enzymes. The only weakness that was noted by this reviewer is that the modulators (inhibitors, substrates) for these important enzymes and structure–activity relationships among these classes are not generally treated in detail. This minor deficiency is understandable if the book is to be kept at a reasonable size.

I believe this volume will be of interest not only to neuroscientists working with brain neurotransmitters but also to most medicinal chemists interested in initiating research directed toward drugs affecting the central nervous system. A veritable wealth of information, in some instances for the first time in a collective fashion, is summarized for the brain enzymes. For this reason, I welcome the addition of this book to my library and recommend it to medicinal chemists having an interest in the development of new therapeutic modalities acting via a central mechanism.

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