Reviews

Selected Topics from Forty Years of Natural Products Research: Betalains to Flavonoids, Antiviral Proteins, and Neurotoxic Nonprotein Amino Acids†

Tom J. Mabry*

Phytochemical Laboratories, Molecular Cell and Developmental Biology, The University of Texas at Austin, Austin, Texas 78712

Received October 19, 2001

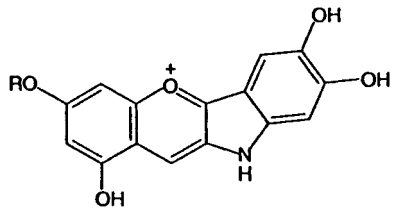
The elucidation by NMR and chemical methods of the unique structure of betanidin, the aglycon of the red-violet beet pigment betanin, forty years ago at the University of Zürich, Switzerland, was the beginning of my plant chemistry research program. Many of the same chemical and spectral techniques developed in Zürich have been used at The University of Texas at Austin for the structure analysis of members of many other classes of natural products including especially flavonoids, terpenoids, and alkaloids. Investigations at UT-Austin have concerned many topics such as biochemical and molecular systematics, biosynthetic pathways, structure−activity relationships, and the medicinal importance of natural products and included studies of antiviral proteins in the genus *Phytolacca* and neurotoxic nonprotein amino acids from cycads and other sources. Following the betalain story and an account of the early development of my UT-Austin biochemical systematic program, the *Phytolacca* and neurotoxin investigations are discussed herein.

Introduction

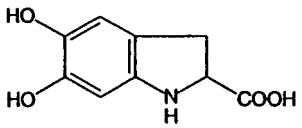
My forty years of natural products research began with my postdoctorate at the University of Zürich and has continued for four decades at The University of Texas at Austin. Here I discuss only four topics, namely, betalains, flavonoids, antiviral proteins, and neurotoxic nonprotein amino acids, which together reflect the origin in Zürich of our natural products chemistry program, followed by the beginning of our biochemical systematic research at UT-Austin, and finally the last two topics, antiviral proteins and neurotoxins, which illustrate the diversity of our more recent investigations. Some of our other research projects are noted in the last section of this paper.

Betalain Research

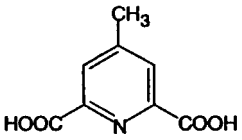
No other activity influenced my career as much as my involvement in work on the unique structures and intriguing distribution of the red-violet pigments now known as betalains. I joined Professor Andre Dreiding's group in 1960 in The Organic Chemistry Institute, The University of Zürich, with my Ph.D. in organic chemistry freshly in hand from Rice University, Houston. Dreiding suggested I work with Dr. Hugo Wyler, an outstanding postdoctorate and later Professor of Chemistry, University of Lausanne, on the only plant chemistry project in his lab, namely, the puzzling problem of the structures of the red-violet beet pigments, sometimes referred to as "nitrogenous anthocyanins" (**1**) to account for their anthocyanin-like color and the fact that they were known to contain nitrogen. Wyler's detailed work in the 1950s on betanidin (**5b**), the aglycon of the main beet pigment betanin (**5a**), had afforded two key degradation products, **2** and **3**, which suggested that betanidin contained three carboxyl and two aromatic hydroxyl groups.



1 A "nitrogenous anthocyanin", R=glycosyl



2 Degradation product from betanidin



3 Degradation product from betanidin

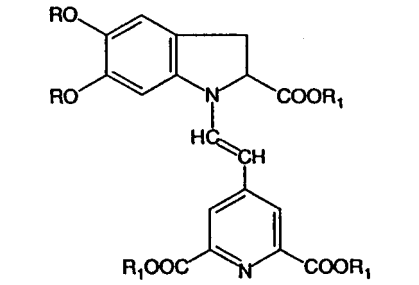
Therefore, my first proposal was for a very mild methylation of betanidin using diazomethane in ether. Dreiding "confessed" to me in June 2001 that he had been "appalled" by the very concept of my diazomethane experiment because it involved adding a few drops of an aqueous methanol solution/slurry of the salt-like betanidin, which is insoluble in organic solvents as well as most other

† Based on the Research Achievement Award lecture given at the 42nd Annual Meeting of the American Society of Pharmacognosy, Oaxaca, Mexico, July 18, 2001.

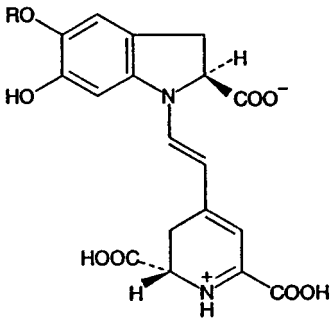
* To whom correspondence should be addressed. Tel: (512) 471-1900. Fax: (512) 232-3402. E-mail: mabry@mail.utexas.edu.

10.1021/np010524s CCC: $20.00
Published on Web 12/04/2001

solvents, to several liters of ether containing a large amount of freshly prepared diazomethane. To the surprise of everyone in the lab including Dreiding, the procedure worked and without a fire or explosion (most of my co-workers left the lab during the experiment!), affording overnight a few chloroform-soluble golden-yellow crystals of a compound we named pentamethylneobetanidin[1] (**4b**). The neobetanidins (see **4**), all of which were readily characterized by NMR, were the first products from betanidin to contain all its carbon atoms; thus, when Wyler's NMR data for **2** and **3** were compared with the NMR spectra of the neobetanidins, as for example, diacetylneobetanidin trimethyl ester (**4c**; Figure 1), it was evident that the neobetanidins contained the ring systems of **2** and **3** connected by a *trans* double bond.



4a Neobetanidin, R=R_1=H
b Pentamethylneobetanidin, R=R_1=CH_3
c Diacetylneobetanidin trimethyl ester, R=Ac, R_1=CH_3 (see Figure 1)



5a Betanin, R=glucosyl
b Betanidin, R=H

The best (but nevertheless very poor) NMR spectrum of the highly insoluble betanidin was obtained by dissolving a little betanidin in trifluoroacetic acid and recording the spectrum in a sealed tube. Comparison of the "poor" betanidin spectrum with the spectra of the neobetanidins led in a few days to the conclusion that betanidin was a dihydroneobetanidin (**5b**), a compound in which the nitrogen system is sufficiently basic to form a stable but "difficult to chemically manipulate" salt-like zwitterion. Thus, to the astonishment of the "nitrogenous anthocyanin" proponents, the neobetanidin studies had quickly resolved the long-standing problem of the structures of the beet pigments,[1] which are all members of a new class of pigments we named betalains.[2] In the next few years, our groups in Zürich and Austin established the unique biosynthetic pathway to betanidin from two molecules of DOPA: one molecule giving cyclodopa with the second undergoing a most unusual cleavage and recyclization to form betalamic acid (**6**).[3] In 1972 we reported betalamic acid to be a naturally occurring yellow pigment in the flowers of such plants as *Beta valgaris*, *Celosia cristata*,

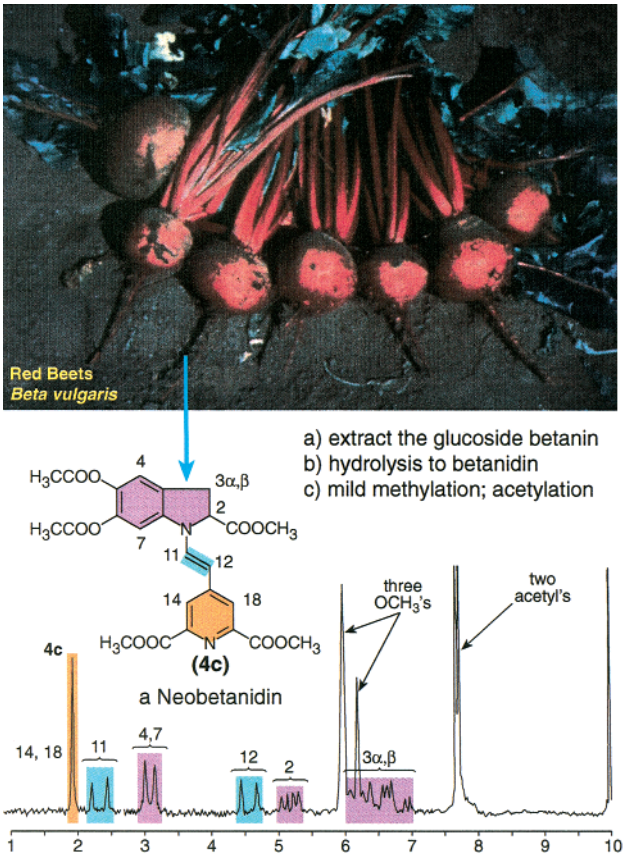
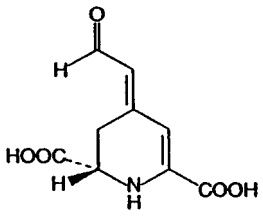


Figure 1. Methylation and acetylation of betanidin (**5b**), the aglycon of the glucoside betanin (**5a**) from the red beet, gave diacetyl neobetanidin trimethyl ester (**4c**), whose NMR spectrum quickly led to the structures of all the beet pigments since **4c** clearly contained the rings of degradation products **2** and **3** connected by a *trans* double bond.

and *Portulaca grandiflora* and showed that it could be readily converted in vitro to betanidin and other betalains by simply shaking for a few minutes an acidic solution containing betalamic acid and the appropriate amino acid.[4]



6 Betalamic acid

While the first years of my natural products-based biochemical systematic program at The University of Texas are discussed in the next section, I mention here that our interest at UT-Austin in the unusual and very limited distribution of the structurally unique betalains led to thirty years of collaborative research with Professor Dietmar Behnke, University of Heidelberg, Germany. Electrophoretic examination of red pigments from throughout the plant kingdom established that the betalains only occurred in about 10 plant families and were mutually exclusive with anthocyanins. When these chemical data were combined with Behnke's outstanding results on the distribution and unique ultrastructural features of several forms of sieve element plastids, much of today's understanding of relationships among both betalain and anthocyanin caryophyllaceous groups was established.[5] These combined chemical and ultrastructural data indicate that the beta-

Table 1. Order Cayophyllales[5]

Suborder Chenopodiineae (betalain families)	
Aizoaceae	Didiereaceae
Amaranthaceae	Nyctaginaceae
Basellaceae	Phytolaccaceae
Cactaceae	Portulacaceae
Chenopodiaceae	
Suborder Caryophyllineae (anthocyanin families)	
Caryophyllaceae	
Molluginaceae	

lain families, including such difficult to align groups as the Cactaceae, are all closely related and belong in the order Caryophyllales together with the anthocyanin-containing Caryophyllaceae and Molluginaceae (Table 1).[5,6] It is, however, noteworthy that new parsimony analyses of extensive molecular data (chloroplast *rbc*L, ndhF, and ORF2280 sequences) obtained by one of my recent Ph.D. students (John Clement)[6] indicate that the anthocyanin-containing Caryophyllaceae is most closely related to two of the betalain families, namely, the Chenopodiaceae and Amaranthaceae, rather than the anthocyanin-containing Molluginaceae.[6] Clement's findings add another puzzle in our attempts to understand the relationships among the families universally recognized as members of the Caryophyllales and also suggest that the origin of the betalains within this order was more complex than a single caryophyllaceous ancestor undergoing a one-time loss of anthocyanins with a subsequent gain of betalains.

UT-Austin's Biochemical Systematics Program

While in Zürich I reluctantly[7] accepted an offer to organize a Phytochemistry Laboratory in the Department of Botany, The University of Texas at Austin, as part of a newly formed Biochemical Systematics Program. The UT-Austin research initially dealt with the 15 or so species in the southeastern United States legume genus *Baptisia* as well as many members of the sunflower family, the Asteraceae. Two botany professors, Ralph Alston and Billie Turner, and their many Ph.D. students were preparing hundreds of two-dimensional paper chromatograms of methanolic extracts of leaf material from throughout plant populations for species and genera comparisons (Figure 2). When the large (46 × 57 cm) chromatograms were viewed under UV light, many fluorescence "spots" were observed and the patterns of these "spots" were generally species specific. Significantly, hybrids tended to exhibit the combined patterns of the parent species. However, it quickly became evident that the structural nature of the compounds represented by the "spots" (Figure 2) would be necessary if one were to draw meaningful systematic conclusions.

After arriving January 1, 1962, to an empty lab with one small chemical bench, I immediately began to secure funds to purchase UV, NMR, and MS instruments as well as glassware, chemicals, and general lab equipment. A training program was organized for the botany students in chemical techniques for the structural characterization of flavonoids and other natural products including isolation procedures (utilizing column chromatography with such materials as cellulose, Polyclar, Sephadex, and silica gel). Because the Ph.D. students were not chemists, it was necessary to adopt safe, simple procedures for the structure analysis of the different classes of natural products, primarily by spectroscopy (UV, NMR, and EIMS). Thus, to obtain suitable chloroform-soluble derivatives for NMR of the flavonoids, most of which occur as glycosides, *all*

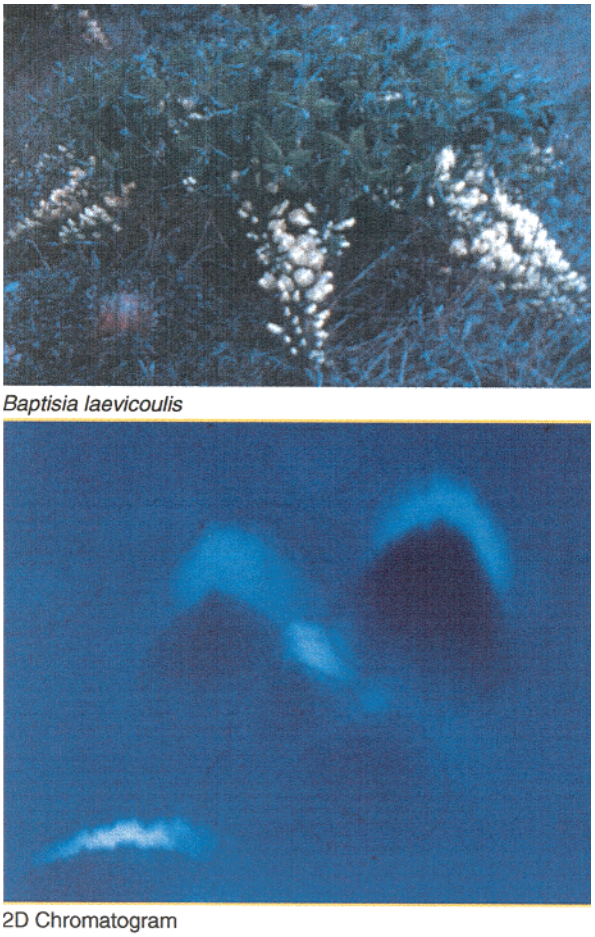


Figure 2. The biochemical systematic investigations underway at UT-Austin in 1962 utilized 2D paper chromatography to distinguish species and recognize hybrids in the legume genus *Baptista* as well as other taxa. My phytochemistry laboratory was charged with providing structures for the fluorescent "spots" detected when the chromatograms were viewed under UV light.

hydroxyl groups in both the aglycon and glycosyl moieties were derivatized in an easy one-step trimethylsilylation reaction: hexamethyldisilazane and trimethylchlorosilane were added to a pryidine solution of each flavonoid, and the solutions were allowed to stand for a few minutes at room temperature. Procedures were also carefully standardized for the UV analysis of all available flavonoids in MeOH using several reagents (NaOMe, $AlCl_3$, $AlCl_3$−HCl_3, HOAc, H_3BO_3) (Figure 3). Our book[8a] with all the *interpreted* NMR and UV data as well as all the detailed isolation and derivatization procedures became the working "flavonoid lab manual" of my co-workers for over thirty years and is still utilized by many others worldwide. Similar data for other classes of natural products were also assembled,[8b,c] including, in particular, sesquiterpene lactones.[8b]

Soon, field botanists were deriving flavonoid, terpenoid, and alkaloid structures, and the biochemical systematics party at UT-Austin was on. Over the years, the research program expanded to include a wide range of projects, most of which were related to systematic and evolutionary questions as well as the biosynthesis and role of natural products in plants, and the potential value of these compounds for man. Although only two other projects, antiviral proteins and neurotoxic nonprotein amino acids, are discussed here, the subjects of some of our other interesting investigations are tabulated in the final section.

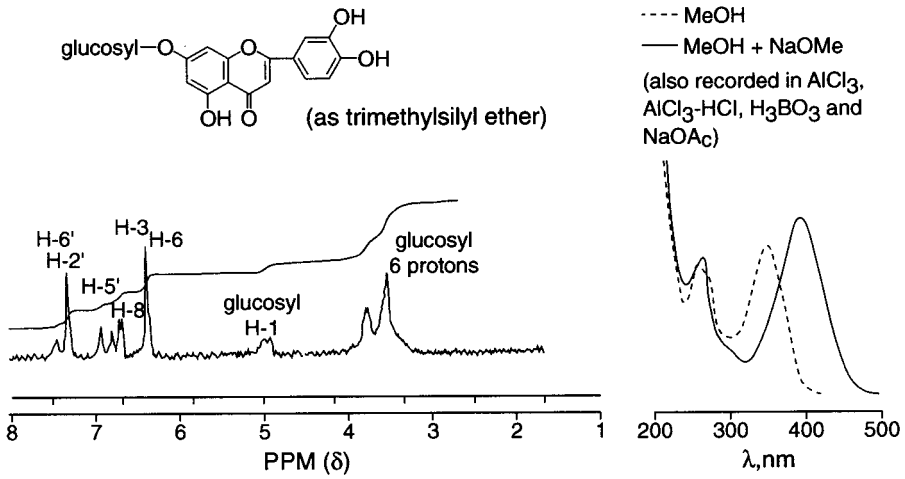


Figure 3. In the mid-1960s NMR data for flavonoid trimethylsilyl ethers as well as UV spectra for all available flavonoids were standardized with complete interpretations.[8a]

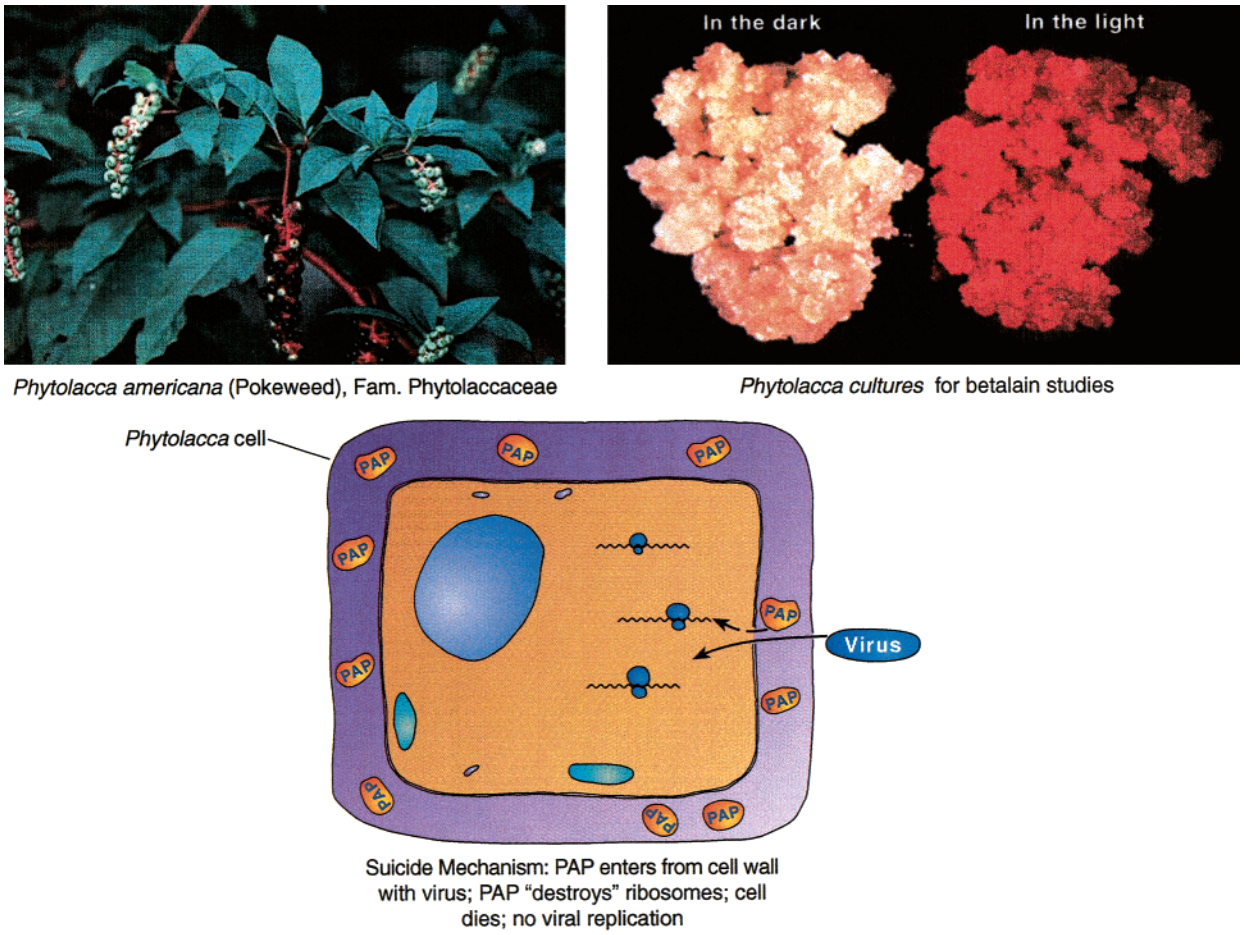


Figure 4. Ph.D. student Maureen Bonness worked on betalains in cell cultures of *Phytolacca americana* before initiating studies of the mechanism of action of *Phytolacca* antiviral proteins. She found that these proteins are fully active and in high concentration in the cell walls, and when the cells are breached by viruses, the antiviral proteins also enter, inactivating the ribosomes, causing cell death, and thereby preventing viral replication.

Antiviral Proteins from *Phytolacca*: Research Led by Maureen Bonness[9]

In the course of investigating the red beet pigments in cultures of *Phytolacca americana*, pokeweed (family Phytolaccaceae), Ph.D. student Maureen Bonness learned that the mechanism of action of another group of compounds in this species, the antiviral proteins, had not yet been clarified (Figure 4). She decided to investigate these remarkable proteins known as "PAP" for "pokeweed antiviral proteins", thus developing an entirely new field of study in my laboratory. The general name for this class of proteins is "RIPs" for "ribosome inactivating proteins" because they inactivate ribosomes inside cells by removing a specific adenine from the small ribosomal subunit. Maureen, now an ecological biologist in south Florida, wanted to understand more about the interaction between the antiviral proteins and ribosomes within *Phytolacca americana* and bring new data to bear on the hypothesized mechanism of action for the RIPs. She meticulously isolated ribosomes from suspension cultures of two *Phytolacca*

species and obtained for the first time highly active ribosomes. Other workers had always extracted inactive ribosomes from *Phytolacca* leaves, presumably because the ribosomes had come in contact with the antiviral proteins during the isolation process. Maureen was able to demonstrate that *Phytolacca* ribosomes are quite sensitive to attack by *Phytolacca* antiviral proteins and that the *Phytolacca* suspension cells do not contain a soluble factor that protects *Phytolacca* ribosomes from endogenous antiviral proteins.[9,10a] Bonness and co-workers established that *Phytolacca* antiviral proteins are sequestered in leaf cell walls in fully active form and in very high concentration;[10b] also, antibody testing of seven additional species of *Phytolacca* (mostly from Mexico) indicated that all these species produced similar antiviral proteins. Maureen's doctoral studies[9,10] helped clarify the local suicide model for PAP's in vivo antiviral mechanism, that is, that these antiviral proteins, being in high concentration in active form in plant cell walls, may serve as readily available ribosome-inactivating (and thus cell-killing) agents when cells are breached by viruses, thereby preventing viral replication (Figure 4).

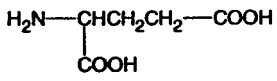
There remains considerable interest in RIPs because of their potent antiviral activity. Monsanto scientists as well as other groups have been able to genetically engineer crop plants with virus protection by incorporation of an RIP gene.[11] More recently, recombinant DNA containing genes for *Phytolacca* PAP and for a peptide specific for a receptor on a tumor cell has yielded a recombinant factor that can bind and inhibit the growth of these tumor cells,[12] dramatically increasing interest in the application of these powerful antiviral proteins as agents against many other viruses including HIV, the AIDS virus.[13]

Neurotoxic Nonprotein Amino Acids: Research Led by Delia Brownson[14,15]

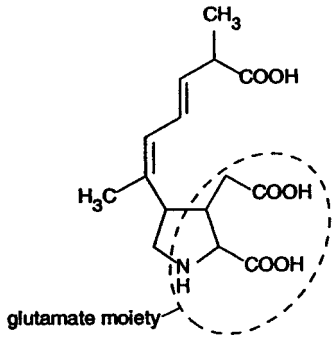
The final topic selected for the Oaxaca presentation describes our effort to bring new evidence to bear on the question of whether a nonprotein amino acid from the Guam cycad *Cycas micronesica* is a factor in the neurodisease that occurs among the native population on the island of Guam in the western Pacific. The disease,[16] which is referred to in this paper as the "Guam disease", has been extensively studied among the Chamorro population on Guam, where it is known as "lytico-bodig". The discussions here cover (1) the excitatory mechanism of nonprotein amino acids;[17] (2) the neurotoxicity of two well-known excitatory nonprotein amino acids, domoic acid[18] (**8**) and β-oxalylaminoalanine (BOAA)[19] (**9**); and (3) Delia Brownson's data on the Guam cycad toxin, β-methylaminoalanine (BMAA) (**10**), which suggest how BMAA might be involved in the Guam neurodisease.

The Excitatory Mechanism of Nonprotein Amino Acids.[14,15,17] It has long been known that compounds structurally similar to the neurotransmitter glutamic acid (**7**) are often "excitatory" because they can open glutamate ion channels in the brain, which can lead to an imbalance of neuronal cytosolic Ca^{2+}, resulting in abnormal "excited" behavior. Thus, excitotoxic nonprotein amino acids usually contain a glutamate-like moiety, that is, one basic amine and two carboxyl groups connected by a short carbon chain. Because the opening of ion channels can lead to excess Ca^{2+} in brain cells, which is a major cause of neurodiseases, some of these excitatory nonprotein amino acids are also neurotoxic.[17] Here we consider three excitatory nonprotein amino acids, two of which are well known to cause neurodiseases, while the third, which we investigated, has been implicated in the Guam disease, the devastating neurodisease that occurs among the native population on Guam.

Domoate Exposure.[14,15,18] Domoic acid is an example of a well-established excitatory nonprotein amino acid that is also neurotoxic. In 1987, human consumption of blue mussels that had fed on domoic acid-producing diatoms led to an outbreak of "amnesic shellfish poisoning" on Prince Edward Island, Canada.[14,15,18] The mussels had concentrated the domoic acid, and it was quickly established that the single compound domoic acid had caused the neurodisease. In this incident over 100 people sustained permanent brain damage, memory impairment, and seizure activity. Several people died, and autopsies revealed lesions in certain regions of the brain including the hypothalamus.[18] Therefore, in recent years U.S. and Canadian laws require that shellfish that have fed on blooms of domoic acid-producing diatoms and are destined for the marketplace must be tested for the presence of domoic acid. While domoic acid (**8**) is structurally more complex than glutamic acid (**7**), it nevertheless does contain a glutamate moiety, which may account for its excitotoxic/neurotoxic activity.

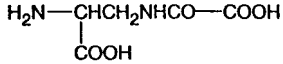


7 Glutamic acid



8 Domoic acid

Neurolathyrism.[14,15,19] Neurolathyrism is another neurological syndrome caused by an excitotoxin of dietary origin. The disease is endemic to certain parts of Africa and Asia, particularly Ethiopia, Bangladesh, and India, and the name reflects the association of the disease with ingestion of seeds of the legume *Lathyrus sativus* (the chickling pea), which often is a staple food during periods of drought.[19] This neurodegenerative disease is characterized by muscle weakness involving the legs, often culminating in irreversible paralysis of the legs. Autopsies of individuals with neurolathyrism reveal damage to cells in the motor cortex and spinal cord. The symptoms of neurolathyrism generally occur after 2−3 months of excessive consumption of the *L. sativus* seeds. The nonprotein amino acid β-oxalylaminoalanine (**9**), which is found in *L. sativus* seeds, has been established as the sole cause of neurolathyrism: injection of adult monkeys with pure BOAA caused paralysis of the lower limbs and all the other symptoms of neurolathyrism.[19] BOAA (**9**) is structurally very similar to glutamic acid (**7**) and thus is in accord with the structural requirements for the excitotoxic/neurotoxic theory for nonprotein amino acids.



9 ß-Oxalylaminoalanine (BOAA)

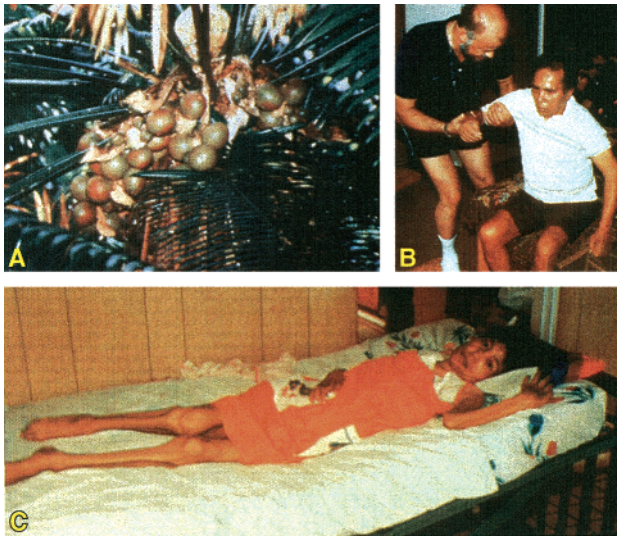
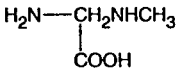


Figure 5. Seeds from the Guam cycad *Cycas micronesica* (A) contain *β*-methylaminoalanine (BMAA), a nonprotein amino acid which has been implicated in the Guam neurodisease, a disease that has behavioral symptoms and pathological features of Parkinson's (B), ALS (C), and Alzheimer's.

The Guam Disease, a Neurodegenerative Disorder in the Western Pacific.[14−16,20] Delia Brownson's 1996 results provide yet another clue as to how the nonprotein amino acid *β*-methylaminoalanine (BMAA) (**10**) from seeds of the Guam cycad *Cycas micronesica* might be involved in the neurodisease that is referred to here as the Guam disease.[14−16,20]



10 ß-Methylaminoalanine (BMAA)

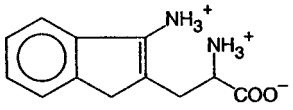
The disorder is of high incidence in several genetically and geographically distinct ethnic groups in the western Pacific, occurring in the indigenous populations of the Mariana Islands (Guam, Rota), Irian Jaya, and the Kii Peninsula of Japan.[14−16] The disease has been studied most extensively among the Chamorro population of Guam, where some patients manifest signs of parkinsonism characterized by slowed movements, tremor, and rigidity, while others exhibit the progressive limb weakness common with amyotrophic lateral sclerosis (ALS) (Figure 5). Still other patients develop cognitive dysfunction typical of dementia found in patients with Alzheimer's.

Epidemiological studies strongly suggest that the Guam disease represents neurological damage caused by some environmental factor. While the incidence of the Guam disease tends to cluster among families, it lacks a demonstrable genetic or infectious origin. Family members such as spouses who are not genetically related may each develop the disorder, whereas offspring who no longer live on Guam or no longer practice the traditional Chamorro lifestyle are less likely to develop the disease. Among the ethnic groups in the western Pacific with a high incidence of the Guam disease, traditional medical and dietary use of cycads has been documented and this use has changed in a manner correlated with the prevalence of the Guam disease.[16] The high incidence of the disease on Guam was detected in the years following World War II, and it is well known that the Chamorros relied heavily on the seeds of cycads as a source of dietary starch during the Japanese occupation of Guam from 1941 to 1944.[16] Traditional use of cycads by the Chamorros has decreased with westernization of their lifestyle, in accord with the lower incidence of the disease today.[20]

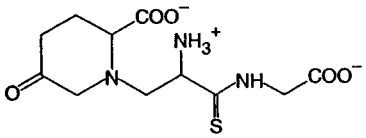
Although six decades have passed since the suggestion was made that among the native populations in the western Pacific the Guam disease might be correlated to the consumption of cycad seeds, this hypothesis has been difficult to substantiate or discount.[21] First, it should be noted that the nonprotein amino acid *β*-*N*-methylaminoalanine (BMAA) (**10**) from the seeds of the Guam cycad does not contain the suggested structural requirements for excitotoxic/neurotoxic activity; that is, it has two basic amine groups instead of one and one carboxyl group instead of two. Nevertheless, BMAA was found to be convulsant when administered to chicks, mice, rats, and rabbits. In mice, BMAA induced abnormal behavioral activity including muscle spasms and seizures and in young rats produced neurological dysfunctions related to acute neuron degeneration. In 1987 Spencer and co-workers[16c] reported that after being fed BMAA daily for 12 weeks macaques exhibited tremors, weakness of forelimbs, immobility, and disinterest in their surroundings, symptoms that progressed over several months to include irritability, blank staring, and a slowed, shuffling gait. Upon autopsy, neuronal damage was evident in the motor cortex, spinal cord, and the substantia nigra. Thus, the behavioral symptoms and pathological features in the macaques were similar to those observed in the Chamorro patients with the Guam disease.

We received NIH funding in 1992 to further investigate how BMAA might cause the Guam disease and to conduct analytical work on many other species of cycads for their nonprotein amino acids. For the latter studies we collaborated (under the auspices of an NSF COBASE grant for interactions with Eastern European scientists) with Dr. Petr Husek, Prague, Czech Republic. Husek had developed a derivatization procedure for amino acids allowing rapid GC (and GC−MS) profiling of the amino acids in aqueous samples from hospital patients.[22] In our lab, amino acid mixtures were extracted from cycad plant material with aqueous ethanol, and the extracts were passed over columns of cation-exchange resins prior to the Husek derivatization procedure in pyridine/water with ethyl chloroformate followed by ethanol treatment, all at room temperature. Mixtures of *N*-ethoxycarbonyl ethyl esters were obtained (Figure 6), which were subjected to GC and GC−MS analysis; this method was used for the detection and identification of the amino acids in many cycad species.[14,23]

When new nonprotein amino acids such as **11** and **12** (from seeds of *Cycas revoluta*) were encountered, they were structurally characterized.[23]



11 Cycasindene



12 Cycasthioamide

The second aspect of our NIH-funded studies to determine if BMAA is a factor in the Guam neurodisease proved

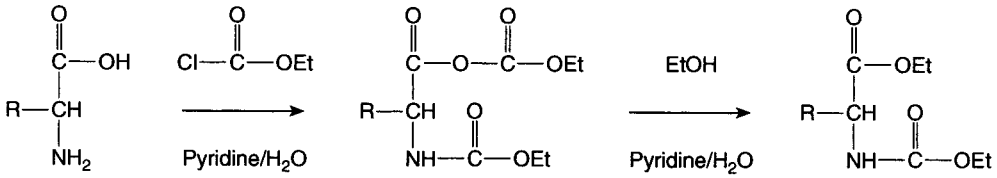


Figure 6. To profile by GC the amino acids in leaf and seed material of many cycad species, the amino acids in the extracts were derivatized using ethyl chloroformate followed by ethanol in a procedure developed by Petr Husek, Prague.

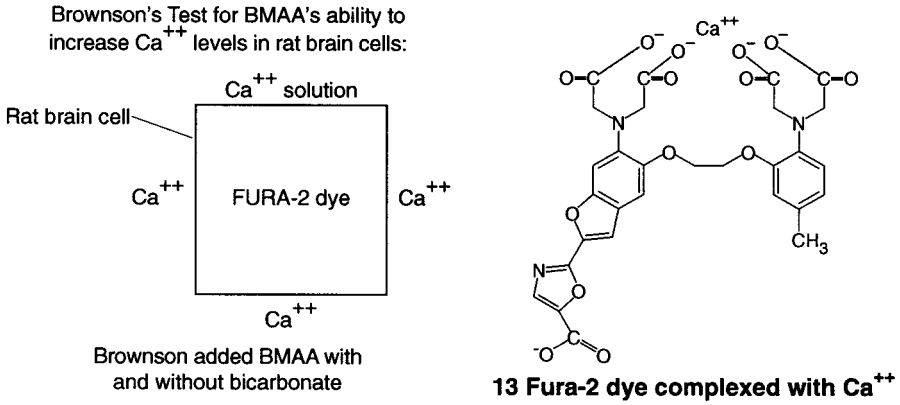


Figure 7. Ph.D. student Delia Brownson developed a procedure using fresh brain cells from newborn rats and the dye fura-2 to test whether BMAA (**10**) could increase Ca^{2+} levels in the rat brain cells; for results see Figure 8.

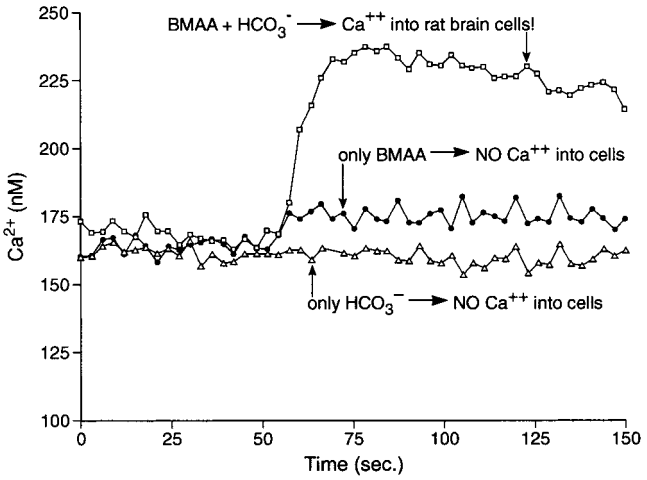
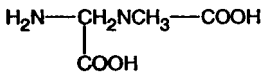


Figure 8. Brownson showed that BMAA (**10**) could indeed increase Ca^{2+} levels in the rat brain cells, but only in the presence of bicarbonate, implicating the carbamate of BMAA (**14**), a derivative that is structurally similar to glutamic acid (**7**).

to be a more difficult matter. Since it is well known that excess Ca^{2+} in brain cells can produce the damage associated with various neurodiseases, Ph.D. student Delia Brownson spent several semesters developing procedures for evaluating the ability of BMAA to elevate the intracellular calcium levels in dissociated newborn rat brain cells. Brownson employed freshly isolated rat brain cells which she loaded with the fura-2 dye, a dye that changes its fluorescent spectrum when complexed with Ca^{2+} (see **13**, Figure 7). She then determined under what conditions, if any, BMAA could cause Ca^{2+} to enter the fura-2-loaded brain cells and produce the easily measured spectral changes. Intracellular calcium levels did, in fact, increase in a concentration-dependent manner in the rat brain cells when they were treated with BMAA, but the BMAA-mediated Ca^{2+} increases were clearly dependent not only on extracellular calcium concentrations but also on the presence of bicarbonate ions (Figure 8). Moreover, the bicarbonate dependence was shown not to result from the increased sodium concentration or pH changes of the solution.

Brownson's findings support the hypothesis that a product of BMAA combined with CO_2 might be the culprit involved in opening ion channels allowing calcium ion levels to elevate in the brain cells. A BMAA-carbamate (**14**)



has previously been shown to be formed at about 9% concentration in an equilibrium reaction at physiological pH's in the presence of bicarbonate or CO_2; the carbamate, unlike BMAA **(10)**, has a structure similar to glutamic acid (compare **7**, **10**, and **14**).[17a] Therefore, Brownson's findings suggest that the carbamate of BMAA (**14**) may be a factor in the Guam disease. Before closing this section, one other intriguing finding for BMAA is worth mentioning. As noted above, the Guam disease occurs in two other areas in the western Pacific, one being Irian Jaya, where the neurodisease is prevalent among members of the Asmat tribe, and the other is the Kii peninsula, Japan; in both these regions *Cycas revoluta* produces abundant seeds that are medicinally used by both indigenous populations. We found that, in addition to **11** and **12**, the seeds of *Cycas revoluta* also contain BMAA!

Other Research Activities

In addition to John Clement, Maureen Bonness, and Delia Brownson, who are mentioned above, other outstanding students include Morris Cranmer, Gene Miller, Al Wohlpart, Bud Kroschewsky, Jim Wallace, Tom Swift, Genie Brackenridge, Janis Potter, Walter Renold, James Mears, Geraldine Howard, Bill Dement, Christina Chang, Linda Kimler, Bill Padolina (his son Gani will finish in 2002 with me), Mann-chin Shen, Zeinab Baset, Saifu Dossaji, Neil Carman, Dan Hosage, Anne Joughin, Eloy Rodriguez, Fred Seaman, Dennis Clark, Gary Brammer, Jim Gill, Dan DiFeo, Charles Bohnstedt, Anne Joughin,

Hugh Waldrum, Munira Al-Khubaizi, Barbara Timmermann, Paula Neuman, Laura Serven, Kathleen Kerr, Scott Lewis, Susan McCormick, Mark Leidig, Bob Kerr, Johnathan Gershenzon, Ed Stewart, Doris de Luengo, John Norris, Douglas Gage, Nianbai Fang, Ki-Joong Kim, Feng Gao, Esther Lee, Nick Mirante, Paul Pare, George Mitchell-Tapping, Patricia Koch, Bomao Miao, Hani Moubasher, Jackqueline Froemming, Fayez Kandil, Ming Liu, David Qin Liu, Val Bishop, Espanta Seradge, Hong Lu, Meide Pan, Carol Mandelbaum, Schalk Van Rooyen, Eman Haggag, and finally a very fine student who worked closely with my group and finished in 2001 in Poland, Malgorzata Wojcinska. Some of the diverse research areas of these students as well as those of a number of unlisted excellent postdoctorates are noted below.

- Systematic and evolutionary investigations involving chemical studies[24] of geographical races, disjunct taxa, ploidy levels as well as DNA−RNA hybridization and chloroplast DNA sequence analyses;[25]
- Development of new UV, NMR, HPLC, and GC techniques;[26]
- Chemistry of biosynthetic pathways and cell development;[27]
- Complex structural investigations;[28]
- Unusual taxonomic distribution patterns;[29]
- Bioactivities including antitumor, antifungal, anticataract, antibacterial, antioxidant, and dermatological activities;[30]
- Chemistry of plant−insect interactions including inhibition and deterrence, growth inhibition, and resistant plants;[31]
- Phytoestrogens, phytoalexins, and metabolic channeling in the phenylpropanoid pathway.[32]

Acknowledgment. The research discussed in detail here represents the work of only a few co-workers out of more than sixty gifted graduate students and hundreds of dedicated postdoctorates, technicians, and undergraduate researchers, all of whom contributed to the productivity of my program; I salute all of them with warm wishes and heartfelt gratitude. In addition, support from many sources is gratefully acknowledged, including the National Science Foundation, the National Institutes of Health, and especially the Robert A. Welch Foundation (Grant F-130). Finally, I want to express my deepest appreciation to my loving, understanding wife, Helga, who continues to provide not only excitement and surprises but also stability and purpose to all my academic pursuits as well as my life in general.

References and Notes

(1) (a) Mabry, T. J.; Wyler, W.; Sassu, G.; Mercier, M.; Parikh, I.; Dreiding, A. S. *Helv. Chim. Acta* **1962**, *45*, 640−647. (b) Wyler, H.; Mabry, T. J.; Dreiding, A. S. *Helv. Chim. Acta* **1963**, *46*, 1745−1748. (c) Wilcox, M. E.; Wyler, H.; Mabry, T. J.; Dreiding, A. S. *Helv. Chim. Acta* **1965**, *48*, 252−258.

(2) (a) Mabry, T. J.; Dreiding, A. S. In *Recent Advances in Phytochemistry*; Mabry, T. J., Alston, R. R., Runeckles, V. C., Eds.; Appleton-Century-Crofts: New York, 1968; Vol. 1, Chapter 4, pp 145−160. (b) Mabry, T. J. In *The Chemistry of Alkaloids*; Pelletier, S. W., Ed.; Reinhold: New York, 1969; Chapter 13, pp 367−384. (c) Mabry, T. J.; Chang C.; Kimler, L. In *Recent Advances in Phytochemistry*; Runeckles, V. C., Tso, T. C., Eds.; Academic Press: New York, 1973; Vol. 5, pp 105−134.

(3) Miller, H. E.; Rösler, H.; Wohlpart, A.; Wyler, H.; Wilcox, M. E.; Frohofer, H.; Mabry, T. J.; Dreiding, A. S. *Helv. Chim. Acta* **1968**, *51*, 1470−1474.

(4) (a) Kimler, L.; Larson, R. A.; Messenger, L.; Moore, J. B.; Mabry, T. J. *Chem. Commun.* **1971**, 1329−1330. (b) Mabry, T. J.; Kimler, L.; Larson, R. A. *Z. Physiol. Chem.* **1971**, *352*, 127.

(5) (a) Behnke, H.-D.; Mabry, T. J. In *Plant Systematics and Evolution: Evolution of Centrospermous Families*; Mabry, T. J., Behnke, H.-D., Eds.; Springer-Verlag: Vienna, 1976; Vol. 126, pp 31−54 and 79−94. (b) Behnke, H.-D.; Mabry, T. J. In *Caryophyllales: Evolution and Systematics*; Behnke, H.-D., Mabry, T. J., Eds.; Springer-Verlag: Heidelberg, 1994; Chapters 5 and 10, pp 87−121 and 247−261.

(6) Clement, J. S. Pigment Dichotomy and Molecular Evolution in the Caryophyllales. Ph.D. Thesis, The University of Texas at Austin, TX, 1997; pp 1−97.

(7) My reluctance to accept the position in the UT-Austin Department of Botany stemmed from my desire to remain in the domain of classical organic chemistry. In his 1960 offer to me to develop a phytochemisty program in botany, Professor Ralph Alston wrote, "we need someone immediately." My post-doctorate in Zürich had just been extended for all of 1961 by NIH; therefore I answered that "they were to be congratulated for their exciting plans to develop a chemically-based systematic program but since I was continuing my work in Zürich for another 15 months, I was not available." The response from Alston was, "we will hold the position open for you." I agonized for a month before replying, "I will come to Texas to organize a phytochemistry program but with the understanding that after two years I will move on for my planned career in chemistry." Well, once at UT-Austin, I soon recognized that I was indeed fortunate to be one of the first chemists in a group of biologists who were excited to study, understand, and enjoy the world of plants around us and at the same time were deeply concerned with preserving and protecting this green earth for future generations. Within six years I was a full Professor envying no one as I cherished my continually challenging extraordinary position, which was supported by several large fully equipped phytochemistry laboratories (GC, UV, NMR, MS, and GC−MS instruments), all staffed with excellent botany Ph.D. students and remarkable international postdoctorates who were organic chemists and biochemists. I proudly report that my role in complex biological chemistry investigations and my stimulating interactions with a large number of fascinating colleagues and special friends continue still today to be a "great, exhilarating forty-year ride"! It is written that "a man is not old until regrets take the place of dreams". Well, I'm pleased to start each sunrise with dreams filled with love and hope; happily, a few of the dreams are even realistic. Just as in my weekly card game with seven good friends, I urge each new day to "cut the cards, deal me a hand, and let us play"!

(8) (a) Mabry, T. J.; Markham, K. R.; Thomas, M. B. *The Systematic Identification of Flavonoids*; Springer-Verlag: Heidelberg, New York, 1970; pp 1−354. (b) Yoshioka, H. T.; Mabry, T. J.; Timmermann, B. *Sesquiterpene Lactones*; The University of Tokyo Press: Tokyo, 1973; pp 1−544. (c) Brackenridge, G. The Ultraviolet Spectral Analysis of Coumarins. MS Thesis, The University of Texas at Austin, TX, 1968; pp 1−45.

(9) Bonness, M. S. Pokeweed Antiviral Protein Inactivates Pokeweed Ribosomes; Implications for the Antiviral Mechanism. Ph.D. Thesis, The University of Texas at Austin, TX, 1992; pp 1−146.

(10) (a) Bonness, M. S.; Ready, M. P.; Irvin, J. D.; Mabry, T. J. *Plant J.* **1994**, *5*, 173−183. (b) Lu, H. Ribosome-Inactivating Proteins from *Phytolacca* Leaves are Sequestered in the Cell Wall in an Active Form. MS Thesis, The University of Texas at Austin, TX, 1996; pp 1−69.

(11) Lodge, J. K.; Kaniewski, W. K.; Turner, N. E. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 7089−7093.

(12) Schlick, J. L.; Dulieu, P.; Desvoyes, B.; Adami, P.; Radom, J.; Jouvenot, M. *FEBS Lett.* **2000**, *472*, 241−246.

(13) McKim, F. M.; Bellomy, K.; O'Neill, K.; Messinger, Y.; Johnson, T.; Chen, C.-L. *J. Pharm. Exp. Ther.* **1999**, *291*, 1301−1307.

(14) Brownson, D. M. A Study of Known Excitotoxic Compounds and Isolated Non-Protein Amino Acids from Cycads. Ph.D. Thesis, The University of Texas at Austin, TX, 1996; pp 1−155.

(15) Brownson, D. M.; Mabry, T. J.; Leslie, S. Manuscript in preparation.

(16) (a) Whiting, M. G. *Econ. Bot.* **1963**, *17*, 270−302. (b) Vega, A.; Bell, E. A.; Nunn, P. B. *Phytochemistry* **1967**, *6*, 759−761. (c) Kurland, L. T. *Fed. Proc.* **1972**, *31*, 1540−1543. (d) Spencer, P. S.; Nunn, P. B.; Hugon, J.; Ludolph, A. C.; Ross, S. M.; Roy, D. N.; Robertson, R. C. *Science* **1987**, *237*, 517−522. (e) Spencer, P. S.; Ohta, M.; Palmer, V. S. *Lancet* **1987**, *ii*, 1462−1463. (f) Spencer, P. S.; Palmer, V. S.; Herman, A.; Asmedi, A. *Lancet* **1987**, *ii* 1273−1274.

(17) (a) Nunn, P. B.; Seelig, M.; Zagoren, J. C.; Spencer, P. S. *Brain Res.* **1987**, *410*, 375−379. (b) Ross, S. M.; Seelig, M.; Spencer, P. S. *Brain Res.* **1987**, *425*, 120−127. (c) Ross, S. M.; Spencer, P. S. *Synapse* **1987**, *1*, 248−253. (d) Rothman, S. M.; Olney, J. W. *Trends Neurosci. 10*, 299−302. (e) Nunn, P. B.; O'Brien, P. *FEBS Lett.* **1989**, *251*, 31−35. (f) Seawright, A. A.; Brown, A. W.; Nolan, C. C.; Cavanagh, J. B. *Neuropathol. Appl. Neurobiol.* **1990**, *16*, 153−169. (g) Meldrum, B.; Garthwaite, J. *Trends Pharmacol. Sci.* **1990**, *11*, 379−387. (h) Frandsen, A.; Schousboe, A. *J. Neurochem.* **1993**, *60*, 1202−1211. (i) Meldrun, B. *Brain Res. Rev.* **1993**, *18*, 293−314.

(18) (a) Teitelbaum, J. S.; ZaTorre, R. J.; Carpenter, S.; Gendron, D.; Evans, A. C.; Gjedde, A. *N. Engl. J. Med.* **1990**, *322*, 1781−1787. (b) Perl, T. M.; Bedard, L.; Kosatsky, T.; Hockin, J. C.; Todd, E. C. D.; Remis, R. S. *N. Engl. J. Med.* **1990**, *322*, 1775−1780.

(19) (a) Spencer, P. S.; Ludolph, A. C.; Dwivedi, M. P.; Roy, D. N.; Hugon, J.; Schaumburg, H. H. *Lancet* **1986**, *ii*, 1066−1067. (b) La Bella, V.; Alexianu, M. E.; Colom, L. V.; Ionescu, A.; Mohamed, A. H.; Appel, S. H. *Neuroscience* **1996**, *70*, 1039−1052. (c) Staton, P. C.; Bristow, D. R. *J. Neurochem.* **1997**, *69*, 1508−1518.

(20) Stone, R. *Science* **1993**, *261*, 424−426.

(21) Duncan, M. W.; Steele, J. C.; Koplan, I. J.; Markey, S. P. *Neurology* **1990**, *40*, 767−772.

(22) (a) Husek, P.; Sweeley, C. C. *J High Resolut. Chromatogr.* **1991**, *14*, 251−753. (b) Husek, P. *J. Chromatogr.* **1991**, *552*, 139−230. (c) Husek, P. *J. Chromatogr.* **1991**, *552*, 289−299.

(23) (a) Pan, M. Non-Protein Amino Acids and Azoxyglycosides from Cycad Seeds. Ph.D. Thesis, The University of Texas at Austin, TX, 1997; pp 1−144. (b) Pan, M.; Bonness, M. S.; Mabry, T. J. *Biochem. Syst. Ecol.* **1995**, *23*, 575−576. (c) Pan, M.; Mabry, T. J.; Cao, P.; Moini, M. J. *Chromatogr. (A)* **1997**, *787*, 288−294. (d) Pan, M.; Mabry, T. J.; Beale, J. M.; Mamiya, B. M. *Phytochemistry* **1997**, *45*, 517−519.

(24) (a) Carmen, N. J.; Mabry, T. J. *Biochem. Syst. Ecol.* **1975**, *3*, 19−23. (b) McMillan, C.; Chavez, P. I.; Plettman, S. G.; Mabry, T. J. *Biochem Syst. Ecol.* **1975**, *2*, 181−184. (c) Seigler, D. S.; Smith, D. M.; Mabry, T. J. *Biochem. Syst. Ecol.* **1975**, *3*, 5−6. (d) Star, A. E.; Seigler, D. S.; Mabry, T. J.; Smith, D. M. *Biochem. Syst. Ecol.* **1975**, *2*, 109−112. (e) Hartman, R. L.; Bacon, J. D.; Bohnstedt, C. *Brittonia* **1975**, *27*, 317−327. (f) McMillan, C.; Mabry, T. J.; Chavez, P. I. *Am. J. Bot.* **1976**, *63*, 317−323. (g) Crawford, D. J.; Mabry, T. J. *Biochem. Syst. Ecol.* **1978**, *6*, 189−192. (h) Seaman, F. C.; Mabry, T. J. *Biochem. Syst. Ecol.* **1979**, *7*, 3−6. (i) Seaman, F. C.; Mabry, T. J. *Biochem. Syst. Ecol.* **1979**, *7*, 7−12. (j) Mabry, T. J.; Timmermann, B. N.; Heil, N.; Powell, A. M. *Plant Syst. Ecol.* **1981**, *137*, 275−280. (k) Gershenzon, J.; Mabry, T. J. *Nordic J. Botany* **1982**, *3*, 5−34. (l) Gershenzon, J.; Mabry, T. J. *Phytochemistry* **1984**, *23*, 1959−1966. (m) Gershenzon, J.; Stewart, E.; Mabry, T. J. *J. Nat. Prod.* **1984**, *47*, 748−749. (n) Bacon, J. D.; Fang, N.; Mabry, T. J. *Plant Syst. Evol.* **1986**, *151*, 223−228. (o) Miller, H. E.; Mabry, T. J.; Turner, B. L.; Payne, W. W. *Am. J. Bot.* **1968**, *55*, 316−324. (p) Wohlpart, A.; Mabry, T. J. *Plant Physiol.* **1968**, *43*, 457−459.

(25) (a) Mabry, T. J. *Plant Syst. Evol.* **1976**, *126*, 79−94. (b) Kim, K.-J.; Mabry, T. J. *Plant Syst. Evol.* **1991**, *177*, 53−69. (c) McDonald, J. A.; Mabry, T. J. *Plant Syst. Evol.* **1992**, *180*, 243−259. (d) Maio, B.; Turner, B. L.; Mabry, T. J. *Plant Syst. Evol.* **1995**, *194*, 241−255. (e) Maio, B.; Turner, B. L.; Simpson, B.; Mabry, T. J. *Plant Syst. Evol.* **1995**, *195*, 1−12. (f) Miao, B.; Turner, B. L.; Mabry, T. J. *Am. J. Bot.* **1995**, *82*, 919−923. (g) Miao, B.; Turner, B.; Mabry, T. J. *Am. J. Bot.* **1995**, *82*, 924−932.

(26) (a) Sakakibara, M.; Mabry, T. J. *Rev. Latinoam. Quim.* **1977**, *8*, 99−100. (b) Sakakibara, M.; Mabry, T. J. *Rev. Latinoam. Quim.* **1978**, *9*, 92−94. (c) Markham, K. R.; Ternai, B.; Stanley, R.; Geiger, H.; Mabry, T. J. *Tetrahedron* **1978**, *34*, 1389−1397. (d) Rösler, K. H.; Wong, D. P. C.; Mabry, T. J. *J. Nat. Prod.* **1985**, *48*, 837−840. (e) Gao, F.; Shoulders, B. A.; Hirose, Y.; Mabry, T. J. *Rev. Latinoam. Quim.* **1987**, *18*, 77−79. (f) Oh, C.-H.; Kim, K.-R.; Brownson, D.; Mabry, T. J. *J. Chromatogr.* **1994**, *669*, 125−137. (g) Oh, C.-H.; Brownson, D.; Mabry, T. J. *Plant. Med.* **1995**, *61*, 66−70. (h) Oh, C.-H.; Kim, J.-H.; Kim, K.-R.; Mabry, T. J. *J. Chromatogr.* **1995**, *708*, 131−141. (i) Oh, C.-H.; Mabry, T. J.; Kim, K.-R.; Kim, J.-H. *J. Chromatogr. Sci.* **1995**, *33*, 399−404. (j) Markham, K. R.; Mabry, T. J. *Phytochemistry* **1968**, *7*, 1197−1200. (k) Yoshioka, H.; Mabry, T. J.; Irwin, M. A.; Geissman, T. A.; Samek, Z. *Tetrahedron* **1971**, *27*, 3317−3322. (l) Tori, K.; Horibe, I.; Yoshioka, H.; Mabry, T. J. *J. Chem. Soc. B* **1971**, 1084−1088. (m) Rodriquez, E.; Carmen, N.; Mabry, T. J. *Phytochemistry* **1972**, *11*, 409−410. (n) Mears, J.; Mabry, T. J. *Phytochemistry* **1972**, *11*, 411−412. (o) Schmid, R. D.; Mues, R.; McRenolds, J. H.; Vander Velde, G.; Nakatani, N.; Rodriquez, E.; Mabry, T. J. *Phytochemistry* **1973**, *12*, 2765−2772. (p) Dossaji, S. F.; Mabry, T. J.; Wallace, J. W. *Rev. Latinoam. Quim.* **1975**, *6*, 37−45. (q) Bacon, J. D.; Mabry, T. J.; Mears, J. A. *Rev. Latinoam. Quim.* **1976**, *7*, 83−86.

(27) (a) Fang, N.; Leidig, M.; Mabry, T. J. *Phytochemistry* **1986**, *25*, 927−934. (b) Roewer, I.; Mabry, T. J. *Plant Cell Rep.* **1988**, *7*, 197−198. (c) Bourque, J. E.; Tanner, S.; Mabry, T. J. *Plant Cell Tissue Organ Cult.* **1989**, *16*, 67−72. (d) Koch, P. E., Bonness, M. S., Lu, H.; Mabry, T. J. *Plant Cell Rep.* **1996**, *15*, 824−828. (e) Wallace, J. W.; Mabry, T. J.; Alston, R. E. *Phytochemistry* **1969**, *8*, 93−98. (f) Wu, M.; Alston, R. E.; Mabry, T. J. *J. Phycol.* **1970**, *6*, 57−61. (g) Mues, R.; Ohno, N.; Zinsmeister, H. D.; Mabry, T. J. *Phytochemistry* **1979**, *18*, 1568−1569. (h) Ulubelen, A.; Mabry, T. J. *Rev. Latinoam. Quim.* **1982**, *13*, 35.

(28) (a) Seaman, F. C.; Fischer, N.; Mabry, T. J. *Phytochemistry* **1986**, *25*, 2663−2664. (b) Lee, S. J.; Wood, A. R.; Maier, C. G.-A., Dixon, R. A.; Mabry, T. J. *Phytochemistry* **1998**, *49*, 2573−2577. (c) El-Sayed, N. H.; Emara, N. M.; Yousef, A. K.; Farag, A. M.; Mabry, T. J. *Phytochemistry* **2001**, *57*, 575−578. (d) Horhammer, J.; Mabry, T. J.; Wagner, H.; Rosprim, L.; Rösler, H. *Chem. Ber.* **1965**, *98*, 2193−2203. (e) Mabry, T. J.; Miller, H. E.; Kagen, H. B.; Renold, W. *Tetrahedron* **1966**, *22*, 1139−1146. (f) Fischer, N. H.; Mabry, T. J. *Chem. Commun.* **1967**, 1235−1236. (g) Markham, K. R.; Mabry, T. J. *Tetrahedron* **1968**, *24*, 823−827. (h) Thomas, M. B.; Mabry, T. J. *Phytochemistry* **1968**, *7*, 787−790. (i) Yoshioka, H.; Mabry, T. J.; Miller, H. E. *Chem. Commun.* **1968**, 1679−1681. (j) Yoshioka, H.; Mabry, T. J.; Higo, H. *J. Am. Chem. Soc.* **1970**, *92*, 923−927. (k) Yoshioka, H.; Porter, T. H.; Higo, A.; Mabry, T. J. *J. Org. Chem.* **1971**, *36*, 229−230. (l) Seigler, D.; Seaman, F.; Mabry, T. J. *Phytochemistry* **1971**, *10*, 485−487. (m) Begley, M. J.; Pattenden, G.; Mabry, T. J.; Miyakado, M.; Yoshioka, H. *Tetrahedron Lett.* **1975**, *13*, 1105−1106. (n) Ohno, N.; Mabry, T. J.; Zabel, V.; Watson, W. H. *Phytochemistry* **1979**, *18*, 1687−1689. (o) Timmermann, B. N.; Graham, S. A.; Mabry, T. J. *Phytochemistry* **1981**, *20*, 1762. (p) Fang, N.; Leidig, M.; Mabry, T. J. *Phytochemistry* **1985**, *24*, 2693−2698.

(29) (a) Bonness, M. S.; Mabry, T. J. *Plant Cell Rep.* **1992**, *11*, 66−70. (b) Kim, K.-R.; Kim, J.-H.; Oh, C.-H.; Mabry, T. J. *J. Chromatogr.* **1992**, *605*, 241−249. (c) Bonness, M. S.; Paré, P. W.; Mabry, T. J. *Cactus Succulent J.* **1992**, *65*, 144−147. (d) Spring, O.; Zitterell-Haid, B.; Bierner, M. W.; Mabry, T. J. *Biochem. Syst. Ecol.* **1994**, *22*, 171−195.

(30) (a) Rogers, C. E.; Gershenzon, J.; Ohno, N.; Mabry, T. J.; Stipanovic, R. D.; Kreitner, G. L. *Environ. Entomol.* **1987**, *16*, 586−592. (b) Rossiter, M.-C.; Gershenzon, J.; Mabry, T. J. *J. Chem. Ecol.* **1986**, *12*, 1505−1521. (c) Gao, F.; Wang, H.; Mabry, T. J.; Kinghorn, A. D. *Phytochemistry* **1990**, *29*, 2865−2869. (d) Osborne, R.; Grove, A.; Oh, C.-H.; Mabry, T. J.; Ng, J. C.; Seawright, A. A. *J. Ethnopharmacol.* **1994**, *43*, 67−72. (e) Masuda, T.; Jitoe, A.; Mabry, T. J. *J. Am. Oil Chem. Soc.* **1995**, *72*, 1053−1057. (f) Haggag, E. G.; Abdel Wahab, S. M.; El-Zalabany, S. M.; Abou Moustafa, E. A.; El-Kherasy, E. M.; Mabry, T. J. *Asian J. Chem.* **1998**, *10*, 583−586. (g) Lee, S.-J.; Chung, H.-Y.; Maier, C. G.-A.; Wood, A. R.; Dixon, R. A.; Mabry, T. J. *J. Agric. Food Chem.* **1998**, *46*, 3325−3329. (h) Kandil, F. E.; Soliman, A. M.; Skodack, S. R.; Mabry, T. J. *Asian J. Chem.* **1999**, *11*, 1001−1004. (i) Ahmed, K. M.; Kandil, F. E.; Mabry, T. J. *Asian J. Chem.* **1999**, *11*, 261−263. (j) El-Sayed, N. H.; Mogahed, M. I.; Haron, A. A.; Mabry, T. J. *Rev. Latinoam. Quim.* **1999**, *27*, 5−8. (k) El-Sayed, N. H.; Emam, S. S.; Mogahed, M. I.; Yousef, A. K.; Mabry, T. J. *Rev. Latinoam. Quim.* **1999**, *27*, 9−12. (l) Rustaiyan, A.; Niknejad, A.; Watson, W. H.; Zabel, V.; Mabry, T. J.; Yabuta, G.; Jones, S. B., Jr. *Rev. Latinoam. Quim.* **1978**, *9*, 200−201. (m) Mabry, T. J.; Ulubelen, A. *J. Agric. Food Chem.* **1980**, *28*, 188−196. (n) Miski, M.; Ulubelen, A.; Johansson, C.; Mabry, T. J. *J. Nat. Prod.* **1983**, *46*, 874−875. (o) Rösler, K. H.; Mabry, T. J.; Varma, S. D.; Goodwin, R. S.; Norris, J. A. *J. Nat. Prod.* **1984**, *47*, 316−319.

(31) (a) Paré P. W.; Mabry, T. J. *Haseltonia* **1993**, *1*, 61−64. (b) Burnett, W. C., Jr.; Jones, S. B., Jr.; Mabry, T. J.; Padolina, W. G. *Biochem. Syst. Ecol.* **1974**, *2*, 25−29. (c) Rodriquez, E.; Dillon, M. O.; Mabry, T. J.; Mitchell, J. C.; Towers, G. H. N. *Experientia* **1976**, *32*, 236−237. (d) Burnett, W. C., Jr.; Jones, S. B., Jr.; Mabry, T. J. *Taxon* **1977**, *26*, 203−207. (e) Burnett, W. C., Jr.; Jones, S. B., Jr.; Mabry, T. J. *Pl. Syst. Evol.* **1977**, *128*, 277−286. (f) Burnett, W. C., Jr.; Jones, S. B., Jr.; Mabry, T. J. *Am. Midland Naturalist* **1978**, *100*, 242−246.

(32) (a) Paré, P. W.; Dmitrieva, N.; Mabry, T. J. *Phytochemistry* **1991**, *30*, 1133−1135. (b) Paré, P. W.; Mischke, C. F.; Edwards, R.; Dixon, R. A.; Norman, H. A.; Mabry, T. J. *Phytochemistry* **1992**, *31*, 149−153. (c) Liu, Q.; Markham, K. R.; Paré, P. W.; Dixon, R. A.; Mabry, T. J. *Phytochemistry* **1993**, *32*, 925−928. (d) Liu, Q.; Dixon, R. A.; Mabry, T. J. *Phytochemistry* **1993**, *34*, 167−170. (e) Jitoe, A.; Masuda, T.; Mabry, T. J. *Tetrahedron Lett.* **1994**, *35*, 981−984. (f) Liu, Q.; Bonness, M. S.; Liu, M.; Seradge, E.; Dixon, R. A.; Mabry, T. J. *Arch. Biochem. Biophys.* **1995**, *321*, 397−404.

NP010524S