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The Chemistry of Biotic Interactions in Perspective: Small Molecules Take Center Stage

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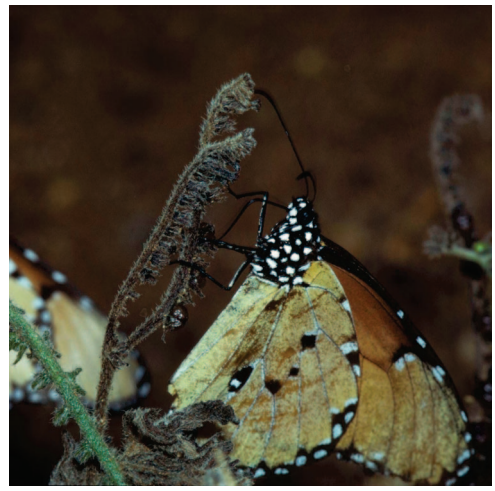

The important discoveries made during the last two centuries which are largely responsible for our current understanding of organic chemistry in general, and of natural products chemistry and chemical ecology in particular, are reviewed. A brief personal history follows, including an account of a few examples from our own work which illustrate the importance of interdisciplinary, collaborative research in gaining insights that are not likely to have been achieved by either a chemist or a biologist working alone. Some possible future developments in natural products chemistry and chemical ecology, assuming that we can mobilize appropriate support and enthusiasm for these disciplines, are imagined. Finally, friends, teachers, colleagues, and students who have contributed most importantly to the author's scientific development or who have served as sources of inspiration are gratefully acknowledged.

How thinking about chemistry changes over the years! Yesterday's most complex "natural products" have become today's "small molecules," without any modification of their structures or stereochemistry. How did this remarkable transformation come about? To what do we owe this dramatic, descriptive downsizing? The answer is at the least three-fold. Revolutionary progress, particularly during the last half-century, in the arts of separation, structure determination, and stereocontrolled synthesis has allowed us to characterize completely and quickly a very large number of the compounds that occur in nature, including many that are responsible for a wide range of intraspecific and interspecific biotic interactions.

High-performance liquid chromatography and capillary column gas−liquid chromatography have enabled chemists to separate even the most complex mixtures of both nonvolatile and volatile components into their individual components. Not

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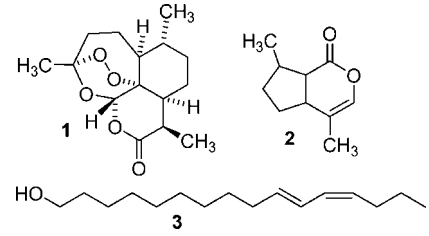
only are these techniques spectacular (especially from the viewpoint of any observer who grew up before they came into existence) with respect to their ability to separate the most similar compounds from one another, but their applicability to samples in the microgram or even nanogram range has allowed chemists access to problems that would have been completely unapproachable throughout the first half of the 20th century, when crystallization, distillation, and sublimation were still the only physical methods available for the separation and purification of organic compounds. The direct coupling of mass spectrometers (or other detection devices) with either high-performance liquid chromatographs or gas−liquid chromatographs now makes the identification and quantification of individual components (particularly if they are known compounds) in mixtures both quick and straightforward. For crystallizable compounds, structure determination via single-crystal X-ray diffraction has matured from an esoteric art, often requiring years of effort for the determination of a single, three-dimensional structure, to a nearly routine procedure that can often be completed in a day or so. In addition, the discovery and ever increasing power of nuclear magnetic resonance spectroscopy, about which more will be said later in this essay, has made complete structure determination (although not necessarily including complete stereochemical assignments) possible on a microgram scale.

The consequence of these advances is that separations and structural characterizations that six decades ago, using "classical means," would have been impossible, or would have required many years of effort at best, can often be carried out by a talented graduate student in a matter of hours or days. Finally, the art of organic synthesis has continued to advance rapidly ever since the early stereorational Stork synthesis of cantharidin and the brilliant, collaborative Eschenmoser/Woodward synthesis of vitamin B-12.[1,2] Consequently, the synthetic confirmation of natural product structures determined by physical means, as well as the provision of synthetic (and, if desired, isotopically labeled) samples of natural products in quantities appropriate for biological testing, is becoming ever more rapid. Under these circumstances, the modest generic term "small molecule" for the vast array of biologically active natural and non-natural compounds of molecular weight below about 2000 does not seem entirely inappropriate.

This Perspective, written on the occasion of the Hundredth Anniversary of the founding of the American Chemical Society's Division of Organic Chemistry, presents a brief and highly personal account of how our knowledge of the chemistry of natural products, as well as our appreciation of the of role of these compounds in biotic communication and defense, has evolved. A few of our own contributions to this field are discussed, and those individuals who have most influenced our work are gratefully and explicitly acknowledged. We include an attempt to foresee some of the advances in organic chemistry, and particularly in natural products chemistry and the closely related field of chemical ecology, that may be expected over the next hundred years, provided that we can establish and sustain an appropriate level of support for this exciting area of science, and that the curiosity of bright young students will draw sufficient numbers of them into the almost overwhelmingly complex endeavor of elucidating the varied roles played by "small molecules" in nature.

While the Division of Organic Chemistry of the American Chemical Society has now celebrated its hundredth year, the discipline of organic chemistry itself is at least twice that age. The brilliant Swedish chemist Jöns Jacob Berzelius published his pioneering monograph on "Animal Chemistry" in 1806.[3] In the forward-looking preface of this volume, addressed to King Gustav IV Adolf, Berzelius wrote, "Of all the sciences contributing to medicine, chemistry is the primary one, and apart from the general light it throws on the entire art of healing, it will soon bestow on some of its branches a perfection such as one never could have anticipated." Only fourteen years later, Caventou and Pelletier characterized quinine as the antimalarial constituent of the bark of the Peruvian "fever tree", *Cinchona* spp., making good on Berzelius' promise that the study of chemistry would contribute to the advance of medicine in important ways.[4] While malaria remains a very serious problem, current research on the synthesis and possible large-scale microbiological production of the antimalarial drug artemisinin (**1**) demonstrates that chemists have not abandoned this mission.[5]



Thus, starting seriously in the early 19th century, the race to elucidate the chemistry of naturally occurring compounds isolated from biological sources was on, with the ultimate, although hardly entirely realistic hope of understanding life itself in chemical terms. Early biologically oriented chemical research focused not only on plant constituents of interest, for example, as drugs and dyes, such as morphine, cocaine, quinine, strychnine, nicotine, indigo, and alizarin, but also on animal metabolites of special interest, including cholesterol, cochineal, Tyrian purple, cantharidin, and muskone. Our own early research on structural, mechanistic, and stereochemical aspects of morphine[6] and tropane alkaloid[7] chemistry, as well as our elucidation of the mechanism of the cinenic acid rearrangement,[8] belongs to this tradition. However, this work was pursued entirely without regard to any biological consideration and represented our personal fascination with molecular rather than biological behavior.

A well-known English nursery rhyme reveals that quite early on, society expressed curiosity about the constituents of living organisms.[9] This curiosity naturally extended to the composition of *Homo sapiens*, and remarkably enough, it was sufficiently sophisticated to incorporate the concept of chemical sexual dimorphism.

"What are little boys made of, made of?
What are little boys made of?
Snips and snails and puppy dogs' tails,
That is what little boys are made of."
"What are little girls made of, made of?
What are little girls made of?
Sugar and spice, and everything nice,
That is what little girls are made of."

In the early nineteenth century, it was only in the realms of *isolation* and *purification* that efforts to advance our chemical knowledge of the constituents of living organisms had any possibility of being rewarded. Given the severely limited experimental techniques available up to the midnineteenth

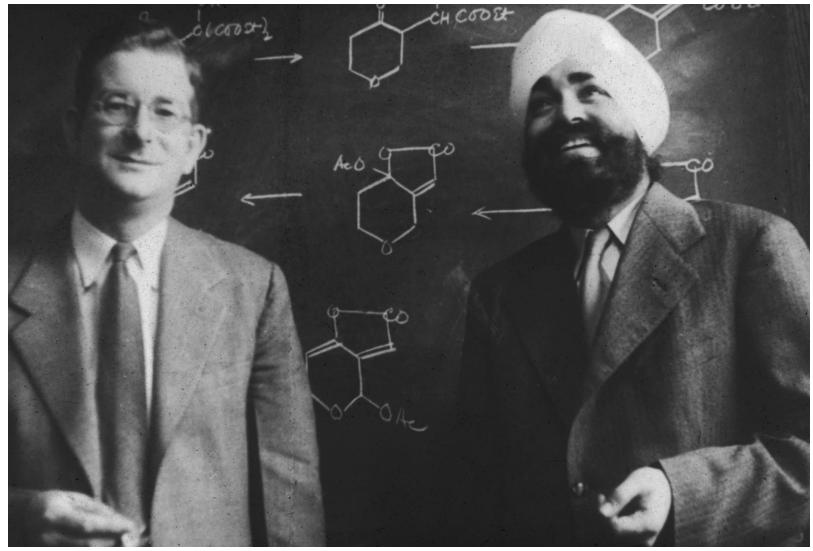


FIGURE 1. Professor R. B. Woodward with Dr. Gurbaksh Singh celebrating their total synthesis of the antibiotic *patulin* (1950).

century, as well as the lack of any understanding of the principles of molecular structure, it was obviously impossible to completely characterize organic compounds or to devise their rational synthesis. Nevertheless, the realization that the element carbon lay at the heart of compounds isolated from organisms led to the independent study of what is now called organic chemistry. Subsequent to the development of structural theory, the most imaginative and painstaking combination of meticulous experimental work and rigorous logic made it possible to deduce the structures of many thousands of compounds from plant, animal, and microbial sources. By the midtwentieth century, nature's chemical vocabulary of amino acids, nucleosides, carbohydrates, lipids, terpenes, steroids, alkaloids, flavonoids, and porphyrins was largely defined. The nursery rhyme questions could be answered properly, not only with respect to girls and boys, but also for the biotic world quite generally, and with a remarkably detailed degree of chemical sophistication.

As a graduate student in R. B. Woodward's research group at Harvard (1948−1952), I experienced the study of organic chemistry with both joy and wonder. The application of infrared and ultraviolet spectroscopy to structure determination, the elucidation of reaction mechanisms, the definition of relative and absolute stereochemistry, and the creation of new synthetic strategies along with their application to the total synthesis of challenging target molecules fostered a unique spirit of intellectual excitement among my fellow graduate students and postdoctorals (Figure 1). At Louis Fieser's invitation, the young D. H. R. Barton presented an inspiring series of lectures on the then new subject of conformational analysis. Gilbert Stork, then a young Assistant Professor, contributed greatly to this stimulating atmosphere.

On joining the Department of Chemistry at Cornell University in 1952 as an independent DuPont Postdoctoral Fellow "with the rank of Instructor", I had the opportunity to study whatever chemical problem(s) interested me. It was my boyhood friend, Michael P. Cava, at the time a postdoctoral fellow with R. B. Woodward, who had mentioned to me that the structure of the active component of "catnip" had not yet been determined and that this might prove to be an interesting research project (Figure 2). Conveniently, the firm of Fritsche Brothers in New Jersey listed "oil of catnip" (from the mint, *Nepeta cataria*) in their

FIGURE 2. The catnip plant, *Nepeta cataria*, mysteriously intriguing to felines.

catalog of essential oils. Earlier work by Professor Samuel McElvain and E. J Eisenbraun at the University of Wisconsin had established that the component of this oil that excited felines (boldly they carried out bioassays on both male and female lions) was a C_{10} lactone, which they named nepetalactone.[10] We took up this problem at Cornell and soon showed that nepetalactone was an isoprenoid enol lactone with the structure shown (**2**).[11]

Although very many terpenoid structures had already been determined when we did this work, none of them had nepetalactone's methylcyclopentanoid carbon skeleton. As it has turned out, nepetalactone provided the first example of a large family

of terpenes, now designated as "iridoids," of particular importance as plant defensive compounds, insect pheromones, and alkaloid biosynthetic precursors.[12] The case for nepetalactone's role as a plant defensive agent has been made, although curiously the question of why catnip should interest cats (of both sexes) remains a mystery.[13] I was pleased to learn recently that a team of chemists and biologists working at the DuPont company have discovered that the closely related dihydronepetalactone, an insect defensive compound which we had found in a rove beetle, as well as some of its derivatives, are particularly effective as insect repellants.[14,15] (Even the most off-beat lines of research may not be entirely without practical value and may ultimately contribute to "useful knowledge.")

While we studied catnip oil out of pure curiosity (in fact, always one of my strongest motivations), most natural products have been sought and studied by chemists because of their clear potential for human use (as dyes, analgesics, antibiotics, fragrances, flavors, etc.). Up until the midtwentieth century, however, chemists were rarely inclined to ask or try to answer an intriguing question that looks beyond chemistry itself: *how can we understand the occurrence in so many plants, animals, and microbes of a variety of idiosyncratic "secondary metabolites" which do not appear to be essential to their primary metabolism?* Were compounds such as plant alkaloids simply waste products, or did they play significant, but as yet undetected biological roles, hence providing an unrecognized adaptive advantage for the plants that produced them? The chemical community was much too busy with the more immediately exciting and productive challenges of discovering, isolating, characterizing, and synthesizing compounds of value in medicine, agriculture, and other essential areas of human endeavor to address this basic question.

Nevertheless, although chemists by and large were otherwise engaged, a number of forward-looking nineteenth century biologists searched for and succeeded in elucidating some of the biological role(s) of natural products.[16] For example, Eric Stahl established quite clearly that several essential oils and bitter-tasting compounds can serve to *protect* plants from herbivores (such as slugs and snails).[17] He also discovered that there is real complexity to this type of interaction. For example, it is possible to distinguish between *generalist* herbivores and *specialist* herbivores; a given plant metabolite might serve as a feeding deterrent for the generalist but as a feeding stimulant for the specialist. Overall, specific plant metabolites were shown to play a beneficial role in the lives of their producers, not by influencing their internal chemistry, but rather by their effects on external organisms!

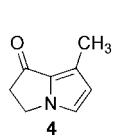
The nineteenth century also saw the discovery of bacterial chemotaxis, which provided a striking example of the adaptive behavior of the simplest, unicellular organisms in response to external attractive and repulsive chemical cues.[18] Remarkably, both of these seminal lines of research fell into oblivion. In part, this may have been the result of describing these early discoveries in teleological terms. Perhaps equally importantly, it may also be true that most chemists (then as now) had neither the time nor the inclination to place their work in a larger context by keeping up with research in fields other than their own. Finally, the experimental techniques needed to characterize biologically active compounds often available only in submilligram quantities simply did not exist. As a result, it was only much later that Julius Adler began to apply modern chemical, biochemical, and genetic tools to the study of bacterial chemotaxis and that Gottfried Fraenkel interpreted plant−insect chemical interactions in modern evolutionary terms.[19,20] Soon thereafter, as a result of a relentlessly pursued campaign of about two decades, Adolf Butenandt was able to fully characterize bombykol (**3**), the sex attractant of the female silkworm moth, *Bombyx mori*.[21] It was largely as a consequence of this seminal research that it gradually became apparent to the organic chemical community that naturally occurring small molecules constitute the vocabulary for an extensive family of languages. The realization that communication via the transmission of signal molecules does not always depend on a single compound, but often requires mixtures whose components need to occur in specific ratios, has taught us that chemical communication is a much more complex phenomenon than was originally imagined. On the biological side, our understanding of receptor mechanisms and of behavioral and/or developmental responses is still in its infancy. That we might be able to understand, and perhaps even to control in a species-specific manner, some aspects of biological behavior as well as development via relatively simple chemical signaling agents was a revelation! Moreover, it had become clear that most, if not all, organisms from bacteria to slime molds, from marine algae to the tallest trees, from worms to mammals, are capable of producing, emitting, receiving, and responding either behaviorably or developmentally to chemical signals. These signals function both within a species, in which case the molecular messengers are termed *pheromones*, and between members of different species. Key terms, such as *allomone,* and *kairomone* (interspecies signals of adaptive value to the producing organism or receiving organism, respectively), were coined, providing a fresh vocabulary with which to describe a vast array of biotic interactions.[22,23] We now recognize that *molecular signaling*, via "natural products" or "secondary metabolites" (now "small molecules"), joins with *light* and *sound* signaling as a primary means of communication in the biotic world.

My own first serious involvement with research on chemical communication grew from my extended scientific collaboration with Thomas Eisner, who joined the faculty of Cornell University's Department of Entomology immediately after completing his doctoral studies at Harvard in 1957, five years after I had come to Cornell (vide infra). I was, at the time, looking for an area of research that was not already well-populated, that nevertheless had the potential for significant discovery, and that would be fun to pursue. Tom was anxious to find a collaborator who could characterize the compounds responsible for the insect and plant interactions he was discovering. Our initial joint explorations were concerned with the chemical defense mechanisms of various insects and other terrestrial arthropods (Figure 3).[24] This was an area of biology that Tom knew intimately. While arthropod chemical warfare is a fascinating phenomenon, it had been almost completely ignored by chemists up to this point. This meant that we could do research in this field without being subjected to the intense competitive pressure characteristic at the time of the area of natural product synthesis, in which dozens of brilliant colleagues often pursued the same objective. We subsequently extended our investigations to include the study of the chemistry underlying insect communication, in particular lepidopteran courtship. At the time, nothing was known about male-produced pheromones, so this was a wide open area. These studies led us to decades of collaborative chemical and biological research which yielded a number of entirely unanticipated results of

FIGURE 3. The author's first chemical study of arthropod defenses with Thomas Eisner was carried out on the whip scorpion, *Mastigoproctus giganteus*, whose defensive spray consists of a mixture of acetic and caprylic acids.

interest far beyond our initial objectives.[25] In the five decades I have spent pursuing ecologically interesting chemistry, no other set of problems has been as enjoyable or as rewarding.

Our entry into pheromone chemistry was made possible because we happened to have convenient access to a particularly interesting Trinidad danaid butterfly, *Lycorea ceres*. Tom pointed out to me that it had long been known that in many species of danaids, males possess a unique pair of organs called "hairpencils," that can be everted from the tip of their abdomen. While the hairpencils' exact function was unknown, they were assumed to play a role in courtship. We undertook to examine the chemistry associated with these organs in *L. ceres*, and we were able to characterize the three major, volatile components in the dichloromethane extract prepared from a quantity of dissected hairpencils.[26] Of these three compounds, we found a pyrrolizidine derivative (**4**) (subsequently named danaidone) to be especially intriguing. No structure of this sort had ever been isolated from any animal source. However, pyrrolizidine alkaloids were well-known from a variety of plants. We wondered whether there might be a connection between these alkaloid-containing plants and *L. ceres* males, and we also wondered whether danaidone might serve as a signaling molecule.



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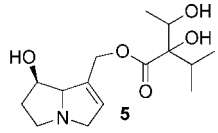

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To attack these two questions directly would have been extremely difficult, since Trinidad is far from Ithaca, and the courtship behavior of *L. ceres*, which takes place high above the canopy of trees, would be hard to observe. Fortunately, there is another danaid species, *Danaus gilippus berenice* (the Florida Queen butterfly) which is much more readily accessible. Furthermore, courtship behavior in this species had been carefully documented, and there was excellent evidence that the male Florida Queen everts his hairpencils and brushes them across the female's antennae during courtship. (Were it not for this earlier entirely independent study of insect reproductive biology, our own chemical elucidation of plant alkaloid sequestration and subsequent exploitation by insects might not have occurred.) We turned to the chemistry of these butterfly hairpencils and once more found danaidone, accompanied by an isoprenoid alcohol.[27]

To examine the relationship between hairpencil chemistry and courtship behavior, Tom Eisner and his graduate student, Tom Pliske, built a large flying cage in central Florida and raised a large number of Florida Queen butterflies in captivity on their normal milkweed diet. We were disappointed at first to learn that the raised-in-captivity males were much less successful than wild males in inducing females to mate, although they appeared to use their hairpencils in the normal way during courtship. However, chemical analysis of their hairpencils revealed that they lacked danaidone. In fact, the application of synthetic danaidone to these hairpencils restored the ability of these chemically deficient males to court successfully. The pheromonal role of danaidone was thereby established.[28] However, the reason for the absence of danaidone from our raised-in-captivity males was then unclear, and the question of how wild males obtained their heterocyclic pheromone became central to our understanding of danaid courtship. A definitive, but not entirely unexpected, answer to this question came from some research we were able to pursue in Africa.

In the early 1970s, I served along with my good friend Koji Nakanishi from Columbia University as one of the founding research directors of the International Centre for Insect Physiology and Ecology (ICIPE) in Nairobi, Kenya. The idea of establishing this basic, interdisciplinary research laboratory in East Africa was due to Carl Djerassi (Stanford University) and Thomas Odhiambo, a Reader in Zoology at the University of Nairobi. It was a great privilege to participate in this undertaking, and it provided the opportunity to collaborate with the late Dietrich Schneider, a fellow ICIPE research director, Director of the Max Planck Institute for Behavioral Physiology in Seewiesen, Germany, and inventor of the "electroantennogram" (EAG) technique for recording electrical signals from insect antennae. It was Schneider's wife, Heidi, who noticed during a field trip in East Africa that adult African Monarch (*Danaus chrysippus*) butterflies were strongly attracted to a local plant, *Heliotropium steudneri*. Interestingly, it was only males who were thus attracted. They seemed to prefer senescent plants and could be observed to suck in droplets of plant juices. We were eager to see what it might be in *H. steudneri* that seemed to be so important to the male African monarchs, and we were delighted to discover that the plants were laden with lycopsamine (**5**), a previously characterized pyrrolizidine alkaloid. As might be anticipated, we were able to show that danaidone was present on the hairpencils of those males with access to *H. steudneri* (or to the pure alkaloid), but that it was missing from hairpencils of males without access to this alkaloid.[29] Our early conjecture, based on structural similarity, that the male pheromone was derived from a plant alkaloid was thus confirmed (Figure 4).

Assuming that the Florida Queen male depends similarly on a plant alkaloid as a biosynthetic danaidone precursor, we have a remarkably bizarre story: to court successfully, these male butterflies need (1) to locate a pyrrolizidine-alkaloid-containing plant, (2) to ingest the juice of this plant and sequester the alkaloid, (3) to convert the plant alkaloid into danaidone, and finally, (4) to signal a female by applying their pheromonal secretion to her antennae during the courtship ritual. What could possibly be the adaptive advantage to these insects of making successful courtship dependent on a chemical signal whose

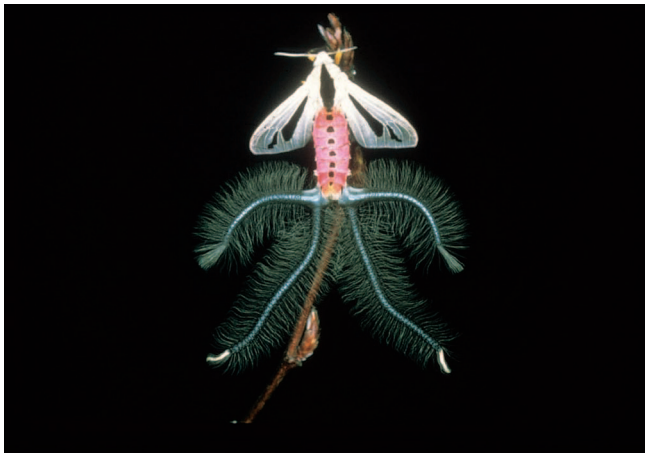
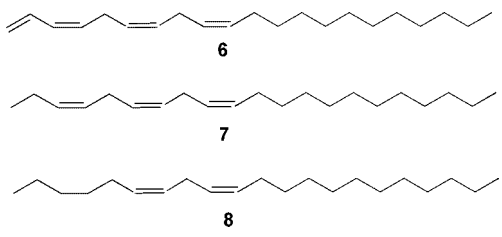


FIGURE 4. The hydroxydanaidal disseminating scent organs of a male arctiid moth (*Creatonotus transiens*) require dietary pyrrolizidine alkaloid for their development as well as for pheromone biosynthesis.

biosynthesis requires a toxic plant secondary metabolite as its biosynthetic source?

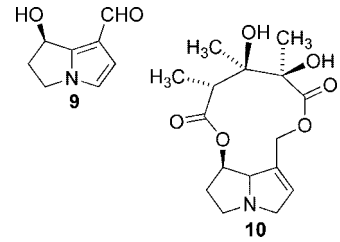
It was Tom Eisner's thought that to understand in more detail what was going on, we should work with a lepidopteran species whose *food plant* contains a pyrrolizidine alkaloid. The handsome arctiid moth *Utetheisa ornatrix*, which feeds on *Crotalaria* spp., fulfilled this requirement beautifully. The Archbold Biological Station in Lake Placid, FL, provided a convenient base at which to study these moths.

We found that courtship in *Utetheisa* involves two discreet stages. In the first stage, the sexes are brought together by a sex attractant pheromone released by the female after sunset. (This behavior contrasts with that of danaid butterflies, whose courtship is initiated by daytime visual pursuit of females by males.) The female pheromone proved to be a mixture of three C_{21}-unsaturated hydrocarbons, a tetraene (**6**), a triene (**7**), and a diene (**8**). Interestingly, we found that the hydrocarbons were released in short pulses rather than continuously, providing the first demonstration of temporal patterning in an aerial pheromonal signal.[30] (This pulsing appears to extend the range of the attractive signal.) Not surprisingly, production of this hydrocarbon mixture persisted in females raised on an alkaloid-free diet of pinto beans.



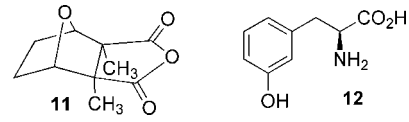
In the second, sexually selective phase of *Utetheisa* courtship, a courting male flutters around the female, everts his courtship organs ("coremata"), and thrusts them against the female. Males raised on a *Crotalaria* diet were generally successful in courtship, and we found their coremata to contain a pyrrolizidine aldehyde, hydroxydanaidal (**9**). In contrast, males raised on a pinto bean (alkaloid-free) diet lacked hydroxydanaidal, and were unsuccessful in courtship. From these observations, it became clear that hydroxydanaidal served a pheromonal role, and that its production required a dietary pyrrolizidine alkaloid.[31]

The significance of these observations became apparent when we found that males actually *transfer* monocrotaline (**10**, the chief alkaloid in *Crotalaria spectabilis*) via their spermatophore to females during mating. The females are able to incorporate this male-donated alkaloid into their eggs, thereby rendering the eggs unpalatable to egg-predators, such as lady bugs. In addition, the females themselves gain protection from enemies such as spiders by virtue of the alkaloidal "nuptial gift" that a chemically protected male provides.[32] Since our analyses of field-collected females showed that some females had not sequestered monocrotaline successfully, the ability of a male to provide a supply of plant toxin takes on particular significance.



In the biologist's vocabulary, what we are seeing is a female exercising *sexual selection* on the basis of a chemical cue. There is a very simple rationale for this behavior. The courtship pheromone, hydroxydanaidal, provides definitive evidence that the male displaying it has been successful in sequestering the plant toxin which is its essential precursor. Such a male can therefore be expected to provide this toxin as a nuptial gift. The selectively receptive female then has an enhanced ability to protect herself and her offspring (via "parental endowment") from predation.

We have found a chemically entirely different, but strategically similar, example of the exploitation of a toxin acquired from a dietary source being used for both signaling and parental endowment in the case of the beetle *Neopyrochroa flabellata*. In this instance, the toxin is the notorious, vesicant isoprenoid, cantharidin (**11**), produced by meloid beetles ("Spanish fly") and exploited by *N. flabellata* both as a male courtship pheromone and as an egg-protecting nuptial gift.[33]



Most recently, in collaboration with Alan Savitzky, Deborah Hutchinson, and Akira Mori at Old Dominion University and the University of Kyoto, we have uncovered a noninsectan case of a group of dietarily acquired defensive agents being used in parental endowment.[34] The Asian snake, *Rhabdophis tigrinis*, feeds preferentially on toads whose skin glands are laden with cardiotonic bufadienolides (Figure 5). Female snakes store these (chemically modified) steroids in their nuchal glands (just behind their heads), use them defensively, and also incorporate them into their eggs. Consequently, hatchlings from chemically protected dams (female parents) are endowed with defensive chemicals until they are large enough to consume toads themselves (Figure 6). Interestingly, cardiotonic steroids play an important role in firefly defense as well (Figure 7).[35]

It is clear from these examples that the ability of humans to seek out and exploit specific, naturally occurring compounds

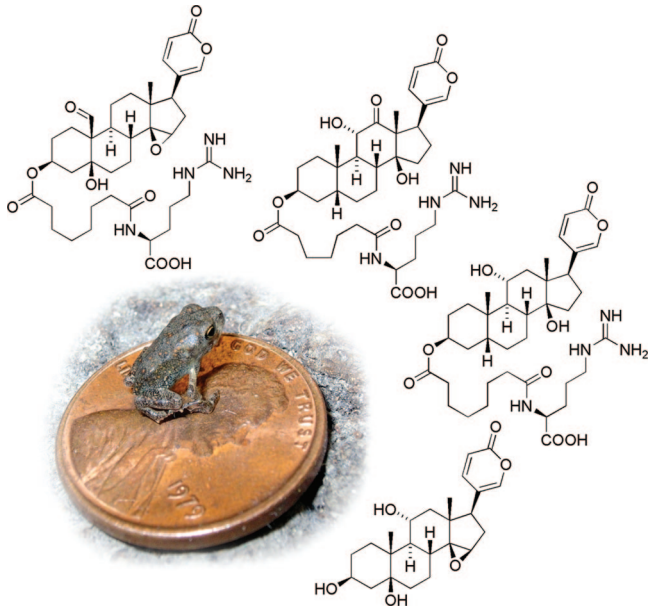


FIGURE 5. Metamorph toad *(Bufo terrestris)*. Adults of this species store highly toxic bufadienolides in their skin glands.

for our own benefit is not, in fact, unique. Nevertheless, our ability to take advantage of what we can learn, as well as use directly, from nature's chemical storehouse certainly represents an opportunity that no other species on earth enjoys. *The urgent need to take full advantage of what nature can teach us, in the face of the rapid loss of species diversity on earth, is now abundantly apparent*.[36,37]

Rather than assuming that idiosyncratic secondary metabolites have no function, we see that it is much more productive to suppose that small molecules found in nature are very likely to serve an adaptive role on behalf of the organisms that produce and/or acquire them. They might be defensive agents, or they might perform a great variety of signaling roles such as mate location and courtship, gamete attraction, alarm warning, recruitment to food sources, quorum sensing in bacteria, aggregation (ranging from slime molds to bark beetles), etc. The ability of plants under attack by hervivores to turn up their production of defensive compounds (such as nicotine, in the case of tobacco) is in itself remarkable. But the ability of plants to initiate "tritrophic" interactions in which they synthesize and emit compounds which serve to attract insect enemies of attacking herbivores is one of the most startling findings in chemical ecology in recent years.[38−40] The discovery of such sophisticated roles served by nature's small molecules clearly requires a deep knowledge of the relevant natural history, along with the imagination to design quantitative bioassays. Since few chemists have this kind of expertise, collaboration between chemists and appropriately trained biologists is extremely valuable in the pursuit of problems involving natural biotic interactions.

We have recently discovered that many spider venoms, including the venom of the dreaded "brown recluse," *Loxoceles reclusa*, contain sulfated nucleosides, a group of metabolites not previously detected in nature (Figure 8).[41−43] Although we do not yet know what the biological properties of these compounds are, it would be very surprising if they do not turn out to play a significant role in the functioning of the venoms that contain them. We are now eager to find out whether the biological activities of such sulfated nucleosides will prove to be something that we ourselves may be able to exploit in medicine or agriculture.

Not all of our research in chemical ecology involves animals. In a recent study of a plant/plant chemical interaction, we have found that fescue grasses are able to inhibit the growth of nearby competing plants by releasing *m*-tyrosine (**12**) from their roots.[44] The discovery that this simple, nonprotein α-amino acid can dramatically reduce plant growth provides one more example of the now completely clear fact that molecular complexity is not a necessary attribute of compounds that display important biological activity. For the chemical ecologist, it is the overall story of how nature can exploit chemistry that is fascinating, even if the molecules involved are as simple as HCN.[45]

There are many other research stories that could be added to this list, but I believe that the general flavor of our work in chemical ecology is already clear. However, particularly for young readers, I should point out that we usually talk more about our research successes than our failures (which, nevertheless, are numerous). It is one of the privileges of academic life that we are allowed to quietly forget projects that have not worked out, so long as we end up with a reasonable yield of successful outcomes. There are, of course, occasions where much can be learned from a failure or where other researchers can at the least be saved the effort of repeating an attempt that seemed attractive but turned out not to work.

It has been suggested that readers of this Perspective (and of the others based on the 2008 ACS Division of Organic Chemistry's Centennial Symposium lectures) might be interested in the author's thoughts about the future of his/her field. Where might we be going? Most large-scale human endeavors require sustained financial support in order to progress significantly. Berzelius' attempt in 1806 to interest the King of Sweden in animal chemistry, based on its potential importance to the advancement of medicine, is not greatly different from a typical argument that might be found in a contemporary research grant application addressed to the NIH. The pursuit of science costs ever larger amounts of money. Simply the equipping of a state-of-the-art laboratory with the contemporary instrumentation which would permit a researcher to take full advantage of the analytical techniques discussed early in this essay costs several million dollars. In addition, the maintenance of this equipment, the need for supplies, and the support of research personnel are all required for research in any field of chemistry to go forward. Is our nation capable of providing sustained support of expensive activities which it sees as important? The answer from many fields of endeavor is clearly "yes." The NIH annual budget in recent years has been about $30 billion. The annual cost of our submarine defense program during the "cold war" was $10 billion (individual submarines cost from $2−4 billion each). Stanford University's annual budget is about $3.5 billion. We have invested more than $2.4 billion in new sports arenas in a dozen cities throughout the USA over the past few years. To come down from billions of dollars to millions, the annual budget for the Metropolitan Opera is $200 million. A recent issue of *The New York Times* reports that a prominent radio host, Rush Limbaugh, has recently signed an 8-year contract for $50 million per year.[46] Obviously, we have been able to invest heavily in a wide range of research, defense, cultural activities, and entertainment that we consider important. Now for a modest observation. If we were able to make 200 research grants of ca. $200,000 per year each to both early career and well-established chemical ecologists, that investment of $40

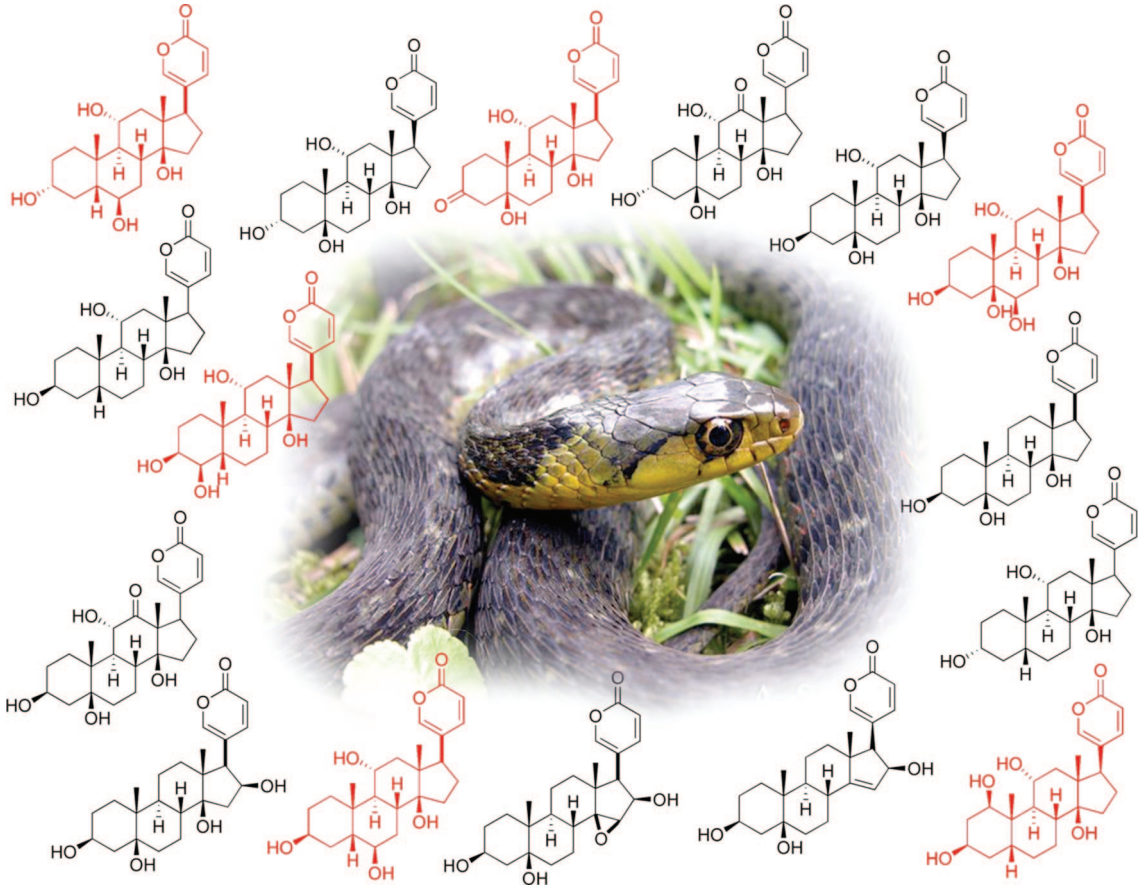


FIGURE 6. Defensive steroids isolated from the nuchal glands of the Asian snake, *Rhabdophis tigrinis*.

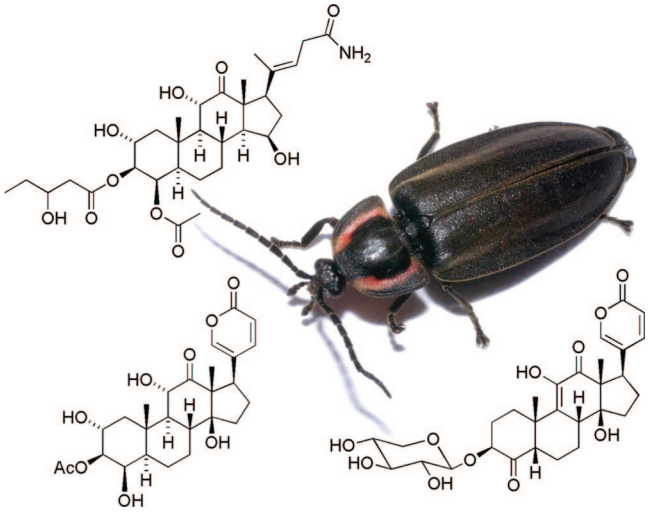


FIGURE 7. Some of the defensive steroids isolated from the diurnal firefly (*Lucidota atra*).

million/year (corresponding to less than Mr. Limbaugh's annual salary) would have an absolutely unprecedented impact. The membership of the International Society of Chemical Ecology is just below 500 (compared to ca. 160000 ACS members!). A funding surge of only $40 million annually in this area therefore would support just about the entire world's effort to understand the chemistry of biological interactions. This chemistry underlies an enormous variety of agriculture and health-related biotic interactions. It is our job as chemists to make our best effort to educate the public in general and our leaders in particular about why our area of research is both practically and theoretically important, intellectually intriguing, economically valuable, and therefore worthy of governmental and private investment on a substantial scale.

Where might a century of well-managed research support of small molecule chemistry and chemical ecology take us? Given the rapid progress in analytical techniques that we have experienced in the last few decades alone, it seems fair to anticipate that by the time of our Division's 200th Anniversary celebration, it will be routinely possible to determine the structures of compounds on the basis of experimental data obtained from only a few molecules. On the synthetic front, just as Bruce Merrifield has automated the synthesis of peptides,[47] we can expect 21st century chemists to design programmable synthesizers which will then be able to turn out synthetic samples (in useful quantities) of almost any desired "small molecule," following a computer-designed synthetic scheme. (While R. B. Woodward was fond of pointing out that nothing about previously untried organic reactions could be predicted with certainty, there is good reason to believe that by the year 2100, synthetic organic chemists, physical organic chemists, and theorists will have brought the art of organic synthesis to a level at which we can plan and execute the synthesis of even the most intricate structures with a confidence that goes far beyond our present experience.) We can then imagine, for example, that a femtogram or attogram of Chanel No. 5, injected one evening into a 22nd-century appropriately instructed universal desktop analyzer/synthesizer, could result in the production of a neatly labeled ounce of the perfume, indistinguishable from the original product, by the next morning. For anyone interested in the details of the *process* as well as in

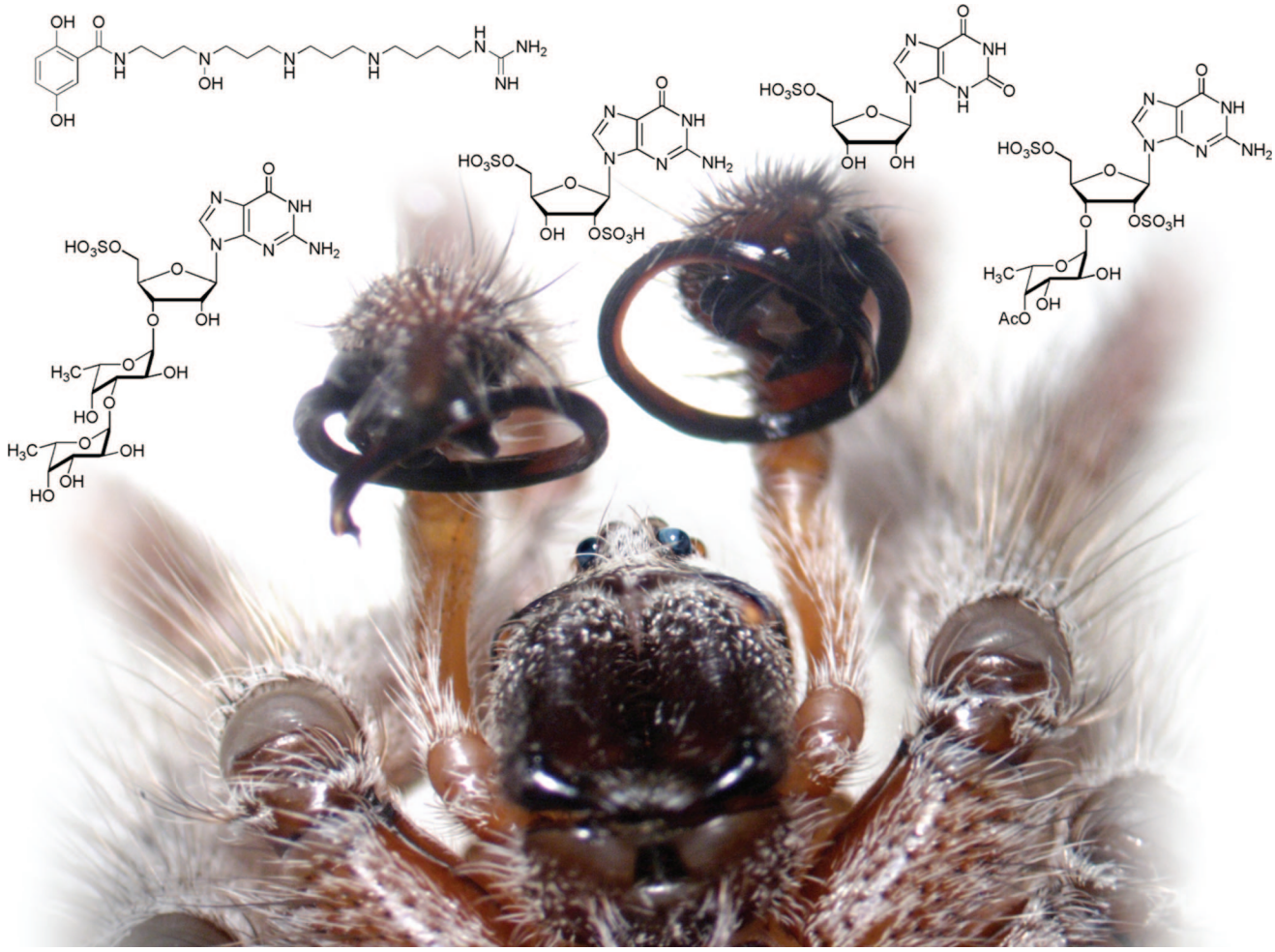


FIGURE 8. Funnelweb spider (*Agelenopsis* sp., family Agelenidae). Sulfated nucleosides and acylated polyamines occur frequently as major components in the venom of spiders from the Agelenidae.

the final *product*, the logic by which all the components' structures had been determined, the relative amounts of each component, and the synthetic schemes used to produce each constituent could be displayed in full detail.

With this sort of chemical capability in hand, it is reasonable to expect that, along with very many other natural product structures, the structures of the pheromones and interspecies signaling agents of most species of direct interest to man will have been determined and that these compounds will be made readily available via synthesis for a wide range of applications in agriculture, forestry, aquaculture, medicine, and public health. At the same time, the chemical activities of the presently largely unculturable soil microbes will surely be elucidated, giving us not only deeper insight into the vastly complex area of soil chemical ecology but also providing us with novel compounds which will satisfy our need for medicinal agents such as antibiotics with which to combat multidrug-resistant, pathogenic bacteria.[48]

Perhaps the ultimate challenge will be to determine the structures, biosynthetic and degradative pathways, functions, and mechanisms of action of all of the signaling agents that are involved in cell-to-cell communication in the human brain. Ideally, we should be able to measure by noninvasive techniques and with good spacial resolution, in real time, the changes in metabolite concentrations occurring in any part of the central nervous system. Fundamental spatial and temporal chemical knowledge of this sort, along with the ability to deliver relevant neurochemical agents to specific sites within the brain, will transform the practice of psychiatry, while at the same time providing a molecular understanding of how the brain manages to do the absolutely remarkable job that it does.

Once we reach this level of insight and capability, what might the role of future organic chemists be? Of course, they will be essential to bring about the above-described advances. In addition, they may be occupied with improving our ability to manipulate very small samples of materials without physical loss. Or with the design of new catalysts for bringing about novel, stereocontrolled reactions, and the elucidation of detailed reaction mechanisms. It seems certain, however, that by the time that most of the problems concerning the analysis and synthesis of *small molecules* are solved, *large molecules* will have captured center stage. It is already apparent that the interactions of small molecules with proteins are largely responsible for their biological effects. Our ability to predict macromolecular folding, or to design and synthesize macromolecular catalysts, receptors, or channels is rapidly progressing, but still has a very long way to go. In addition, the design and synthesis of large molecules for the performance of a wide variety of mechanical and electronic functions is likely to be a major concern of 22nd century organic chemists. Finally, it seems inevitable that we will have burned up most of the earth's petroleum and natural gas by the time of our second Centennial. We are already

seeking new sources of energy, and we certainly will require new starting materials for the synthesis of both small and large molecules a century from now. On a somewhat different front, the potential of engineering heterologous microbes to synthesize pharmaceuticals such as artemisinin[5] is likely to give rise to entirely new biology-based industries. A detailed understanding of nature's biosynthetic machinery will be needed to realize these objectives, and research at the interface between chemistry and microbiology will surely be a highly productive occupation for organic chemists throughout the 21st century.

In bringing this Perspective to a close, I want to trace the influence of a number of teachers, co-workers, friends, and colleagues who have played particularly crucial roles in my own scientific development. To start with, there is Michael P. Cava, fellow Brooklynite and for many years a summer Long Island beach neighbor, who introduced me to the wonders of the chemical world before we were teenagers. Mike's father was a physician, and Mike would bring his father's biochemistry text to the beach to show me colorful photos of crystalline hemin along with a description of how one could isolate this beautiful compound in the laboratory! We soon found ourselves broadening our chemical interests and reading books on chemical subjects ranging from fireworks to synthetic dyes. We began putting on fireworks shows for our neighbors on the beach. During the academic year, we would make regular trips to New York's magnificent 42nd Street Public Library (just around the corner from the Cornell Club of New York, where I am writing this paragraph) to hand-copy (since the ubiquitous Xerox machine had not yet been invented) laboratory procedures for the synthesis of such fascinating compounds as Methyl Orange, Malachite Green, and Congo Red. Almost every Saturday, Mike would take the subway to my house, and we would do laboratory work all day. When a procedure required several hours of refluxing, we would usually withdraw to a large room adjacent to our converted kitchen/laboratory, where we would either present lectures to one another on chemical subjects, such as how to identify organic chemical unknowns, or else play skeletal versions (top and bottom voices only) of assorted orchestral suites, *concerti grossi,* or sonatas by baroque masters such as Bach, Handel, Vivaldi, and Corelli, on flute and trombone. While we each developed a deep feeling for music independently, it was certainly Mike's passion for organic chemistry that set me on my lifelong career path.

The only negative consequence of this early chemical experience was that subsequent high school and even introductory college chemistry courses had little to offer. At Stuyvesant High School in New York City, the chemistry course was certainly more than adequate, but it was really my math courses that were the most fascinating. (In fact, I would have seriously considered a career in mathematics, but I had no idea of what a mathematician actually did.) The other high school activities I especially enjoyed were the glassblowing course and the concert band, orchestra, and woodwind quintet in which I played. Freshman chemistry at Brooklyn College (where I spent one semester) was unexciting, although Organic Chemistry at Queens College, where I studied for one year, served to pull together what I had already learned in a rather disorganized fashion on my own. It was at this point in my academic career that I turned eighteen, and I was almost immediately drafted into military service. Fortunately for me, the U.S. Navy had a pressing need for Electronics Technicians, and if one could pass a test in elementary math, physics, and electronics, it was possible even for a nearsighted, underweight, and overly shy teenager to enter the Navy rather than the Army. On emerging from the Navy eighteen months later (by which time World War II was over), I had the good fortune to be able to continue my undergraduate education at the University of Chicago. I was particularly attracted to Chicago's broad and deep undergraduate curriculum, as well as by the absence of a physical education requirement. The G.I. Bill took care of most of my college expenses. The intellectual and musical opportunities at the University of Chicago were outstanding, and it was there that I was able to take Advanced Organic Chemistry with Professor George Wheland.[49] It was through this course that I gained a genuinely rich appreciation of the molecular world. Wheland's accounts of the evolution of our understanding of molecular rearrangement mechanisms, of resonance theory, and of stereochemistry, in particular, enhanced by readings from the original literature, were a true inspiration. They provided an incomparable foundation for much of my own subsequent teaching and research.

When the time came to think about graduate schools, it was again Mike Cava who pointed me toward R. B. Woodward as the ideal mentor, and this advice was reinforced by Professor Wheland. I was overjoyed when I was able to enter Harvard (where I had not been admitted as an undergraduate) for graduate work. I greatly enjoyed my experiences as a teaching assistant. I joined the Woodward group as soon as possible. One great mistake I made was not taking Paul D. Bartlett's first year graduate course in physical organic chemistry, which stressed reaction mechanisms much more than George Wheland had done. Nevertheless, during my three and a half-years as a graduate student, I came to realize what a truly broad subject chemistry actually is. In Professor Woodward I saw a model of scholarship and deep analytical thinking, an incredibly detailed knowledge of the literature, and unlimited perseverance in pursuing scientific goals, all combined with a brilliance in lecturing (including the exquisite rendering of molecular structures in colored chalk!) that has remained unique in my experience.

Two other distinct influences on my education as a chemist were Franz Sondheimer, a star postdoctoral in the Woodward group, and Gilbert Stork, then a young Assistant Professor. Franz was a laboratory mate with whom I spent countless hours discussing both chemistry and music. Although he had not quite come around to enjoying Béla Bartók's string quartets, his love of Beethoven's quartets and Schubert's Lieder further strengthened our friendship. Franz's incomparable synthetic skills were central to the Woodward group's successful synthesis of the saturated steroids and provided the basis for his subsequent, independent investigations both of natural product synthesis and of annulene chemistry at Syntex, the Weizman Institute, Cambridge, and London. His early death while on leave in California cut short a brilliant career.

Gilbert Stork's office was just next door to the laboratory I shared with Franz and several other distinguished members of the Woodward group. Gilbert's door was always open. If a chemical question came up, he was always ready to discuss it, whatever the time of day or night. I remember clearly his summoning me into his office one night to "consult" with me about a grand plan he had just developed for a highly imaginative synthesis of morphine. His natural tact in treating an inexperienced graduate student like a peer did wonders for my self-confidence. Gilbert's deep knowledge and love of

FIGURE 9. The author (with Baroque flute) and Thomas Eisner (at the harpsichord) enjoying a moment of musical collaboration.

organic synthesis, his chemical playfulness, and his ability to foresee molecular behavior were wonders to behold. Gilbert, without question, is one of the most generous persons I have ever known, and it was he who told me that there was a faculty opening at Cornell University for which he thought I should apply.

Soon after my joining the Cornell faculty (January, 1952), Yvonne Chu came to Cornell from Bryn Mawr College, where she had had a brilliant undergraduate career. I had been introduced to Yvonne while she was still at Bryn Mawr by a mutual friend, Dr. Huang Liang, who at the time was a postdoctoral fellow at Cornell with Professor A. T. Blomquist. Even before Yvonne joined the Blomquist group I was aware of her chemical talents, and she collaborated informally with me on some of my earliest research projects, including the establishment of the structure of nepetalactone. After completing her doctoral thesis, she continued to do postdoctoral research with Professor Blomquist for some time. Yvonne subsequently joined my group as a postdoctoral researcher and proved to be one of the most skilled and productive collaborators I have ever had. From synthetic chemistry to studies on insect defensive compounds and pheromone structure elucidation, Yvonne was responsible for many of the most interesting results to come from my laboratory.

Another crucial contribution that Yvonne made to my research group was her help in selecting Orville L. Chapman as my first grant-supported (thanks to the Research Corporation) research assistant. Orville had graduated from the Virginia Polytechnic Institute in 1954 with an outstanding record. He had a keen, analytical mind and thought deeply about each experiment he did. He spoke and wrote with a rare precision, setting an impressive example for his fellow graduate students. His first seminar talk as a graduate student awoke both students and faculty to the fantastic promise of NMR spectroscopy. His subsequent brilliant career as a researcher, scholar, and teacher at Iowa State University and then at UCLA reflected his uncommonly imaginative and original approach to science. (The very broad range of science pioneered by François Diederich (ETH) reflects, in no small part, the inspiration he received in Orville's laboratory.)

The first postdoctoral to join my research group was Hitosi Nozaki, who was on leave from Kyoto University. Actually, Hitosi was relayed to me by Gilbert Stork, who had many more able postdoctoral applicants than he could possibly accommodate. Hitosi worked long and hard at our effort to synthesize oxepine, although success eluded us. Nevertheless, his independent contributions to organic synthesis in Japan were outstanding. I owed my first invitations to lecture in Japan to him. Since he mentored many extraordinary students in Kyoto, I am able to claim Ryoji Noyori and Hisashi Yamamoto among my "academic grandchildren."

As I have remarked earlier, my gradual shift in emphasis from more or less traditional areas of organic chemistry to the elucidation of the chemistry underlying defense and communication mechanisms in the plant and animal world grew out of my interaction with Thomas Eisner, who came to Cornell in 1957. Tom loved insects and knew more about their natural history than anyone I have ever met. We were introduced by a mutual friend on the Cornell faculty (Howard Schneiderman) who perceived that we had potentially complementary interests. Tom and I often lunched together, and he would typically tell me a half-dozen different stories about insect behavior, several of which clearly involved some unknown chemistry as a central feature. In a short time after his arrival in Ithaca we began to collaborate on the study of many examples of insect-related chemistry, and this interaction proved so enjoyable that we still find ourselves working together over a half-century later! I should add that Tom's remarkable ability to sight-read just about any music I put in front of him at the piano led to our playing countless hours of chamber music together, cementing our friendship even more securely (Figure 9).

Paul Gassman came to Cornell from Canisius College with a burning desire to learn as much about organic chemistry as possible. He loved both synthesis and physical organic chem-

istry. Paul did the most to advance our progress in small-ring chemistry, and he guided the work of my research group while I was enjoying my first sabbatical leave at Berkeley and Stanford. Paul's sense of purpose and dedication to chemistry set an example for everyone with whom he came into contact. His subsequent highly productive, independent academic career at Ohio State University and at the University of Minnesota, as well as the leadership he showed as President of the American Chemical Society, came as no surprise. His very early premature death was a shock to us all and a blow to our community.

Koji Nakanishi and I were fellow graduate students at Harvard. Since he was a member of Professor Louis Fieser's research group, situated on another floor of the Converse Laboratory, we did not get to know one another very well at that time. However, in the early 1970s we both served as founding Research Directors of ICIPE (the International Center for Insect Physiology and Ecology) in Nairobi, Kenya.[50] We have stayed in close contact ever since. We have often found ourselves to be invited speakers at various chemistry symposia around the world, and on many of these occasions, Koji would put on a magic show for which I would provide a musical prelude on the flute. We are currently working together to try to establish a biodiversity-oriented research institute in Brazil with laboratories in São Paulo and Manaus, almost six decades after we first met!

Chemistry and music have also served to bring me together with the uniquely inventive Eiichi Nakamura (University of Tokyo) over the last twenty years or so. We have both been speakers at quite a few chemistry meetings around the world, and since we are both dedicated players of the *flauto traverso* and the recorder, we are sometimes invited to present a concert of baroque music for the attendees. The most rewarding of these events was the invitation from Pierre Potier to present a concert along with our wives Yoko (viola da gamba), and Charlotte (harpsichord) at the Ste. Clothilde church in Paris, as part of the celebration of the 70th anniversary of the founding of La Maison de la Chimie. To be able to play for our colleagues in this beautiful church (with the most flattering acoustics) at which César Franck had been organist was a memorable experience.

Lastly, I acknowledge with pleasure that one of the chief reasons that my laboratory has been able to remain productive into its sixth decade has been the expertise and the energy that Athula B. Attygalle and Frank C. Schroeder brought to it. Athula's strong background in the application of mass spectrometry to analytical problems in chemical ecology was particularly helpful in characterizing natural products that we could access only in the smallest quantities. Frank came to Cornell subsequent to earning his doctorate with the highest honors in Wittko Francke's laboratory in Hamburg. His mastery of contemporary spectroscopic and separation techniques, his skill in handling micro samples so small as to be invisible, and above all his ability to advance methodology applicable to natural products chemistry, chemical ecology, and chemical biology have allowed us to make original contributions to areas as diverse as spider venom chemistry, snake/toad chemical ecology, and plant allelochemistry. His insight into the value of employing NMR spectroscopy for the initial characterization of natural product mixtures, before subjecting them to separation techniques, is likely to bring about a quiet revolution in the methodology by which future chemists probe nature.[51] His current, independent research program ranging from studies of microbiological metabolites and of nematode signaling agents to human endocrinology promises an exciting future.

Aside from this account of associates who shaped my career, I would like to add a short, personal list of friends who I have always regarded as "superior beings," which is to say scientific heroes I have admired, knowing that their level of accomplishments and insight could never be duplicated. These include Duilio Arigoni, Albert Eschenmoser, Arthur Kornberg, John D. Roberts, Carl Sagan, Frank Westheimer, Edward O. Wilson, and Saul Winstein. To have had these outstanding individuals as friends has been a constant inspiration.

I recall being shocked many years ago when a Nobel Laureate jokingly characterized the operation of his research group during a National Organic Chemistry Symposium lecture, stating that "the spirit was willing, but the flesh was weak." The spirit, he went on to explain was his, while the flesh was that of his coworkers. My own experience has been quite different. It is my former undergraduates, graduate students, and postdoctorals who have been responsible for whatever success we have achieved in understanding molecular rearrangement mechanisms, small ring chemistry, organic photochemistry, natural products chemistry, and of course, chemical ecology. Since the number of these dedicated collaborators over the years is about 200, it is impossible to acknowledge their contributions individually. Nevertheless, I do hope that each of them realizes that I have always appreciated their collaboration and that I have considered myself privileged to be able to present the results of their efforts in publications and lectures throughout my academic career.

I thank Dr. Jeffrey Seeman for cheering me on during the writing of this Perspective. I am also indebted to Rita Pirsic, Shawn Darby, and Frank Schroeder for their invaluable help in the preparation of this paper for publication.

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Looking back, I have also realized that lecture invitations also contribute significantly to self-confidence. Having chosen rather idiosyncratic research topics throughout my career, I have always appreciated the many opportunities I have had to tell a broad range of audiences about my fields of research. It was a particular pleasure to serve twice as a Sigma Xi National Lecturer and to present talks at five ACS National Organic Chemistry Symposia, starting in 1963 in Columbus, OH, and most recently in Salt Lake City, UT, in 2005. Clearly, the invitation to speak at the August 2008 Centennial Symposium of the ACS Division of Organic Chemistry in Philadelphia, PA, belongs in this list. For these many opportunities to describe my scientific interests not from the viewpoint of "better things for better living", but rather in terms of the joy in elucidating

previously unknown chemistry, including chemistry underlying life processes, I am especially grateful.

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