CHIRALITY 14:98–109 (2002)

Ernest L. Eliel: A Life of Purpose, Determination, and Integrity

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ABSTRACT A concise biography of Ernest L. Eliel is presented. The highlights of Eliel's scientific achievements are described, beginning with his Ph.D. thesis research performed under the supervision of Professor Harold Snyder (University of Illinois) and continuing as a faculty member at Notre Dame (synthesis of nonracemic $C_6H_5CHDCH_3$; kinetic method of conformational analysis; equilibrium and NMR methods of conformational analysis); and at the University of North Carolina (conformational analysis of heterocyclic compounds; enantioselective synthesis). Eliel's professional career as a teacher, textbook author, and major figure in the American Chemical Society are discussed. His philosophies of life, science, and chemistry are described by a series of poignant quotations. *Chirality 14:98–109, 2002.* © 2002 Wiley-Liss, Inc.

KEY WORDS: Eliel; biography; stereochemistry; conformational analysis; enantioselective synthesis; Notre Dame; University of North Carolina; American Chemical Society; Priestley medal; textbook

Käsenstrasse 28, Köln, Germany. It was my first visit to this ancient city. It was a bright spring afternoon, 1 year ago. I stood before this house, taking in its physical structure as well as the street and peaceful square across the way. I closed my eyes to imagine what it might have been like, inside Käsenstrasse 28, in 1935. Known as Ludwig as a youth, Ernest L. Eliel was 13 in 1935. Along with his parents and two brothers, he lived in this stately house.[a] By 1938, they had all departed, blown by the gusts of upheaval, to lands and languages foreign and unanticipated. For Ernest, 2 years in Scotland, a forced transfer and internment in a Canadian camp, the war years and college in Havana, Cuba, and then emigration: The United States, The University of Illinois, graduate school!

The pictures I saw were clearly mine, romanticized and fictionalized by my own understandings of history. I was trying to understand better how this young boy, forced by circumstances to begin a most circuitous route to his adult life of family and profession, prospered beyond anticipation. Like a participant in a childhood game, I was trying to connect the dots. I knew how it was in 2001, for that is now. Eliel had become an internationally famous scientist and author, a member of the US National Academy of Sciences, a recipient of the Priestley Award, and a past President of the American Chemical Society (ACS). How and why did Ernest flourish? Was it in spite of his experiences as a youth, or because of it? Did Ernest's quiet determination and selfless generosity result from these adversities, like muscles from heavy weight training? Or did these personality characteristics and others remain, in spite of such experiences?

Eliel[2,3] was born into a highly educated and financially successful family in Cologne, Germany, in 1921. He was the youngest of three brothers. Ernest's intellectual propensities were apparent early. His love for chemistry began at the age of 11, when his parents gave him a chemistry set and he began experiments at home and also in a cousin's basement chemistry laboratory. By the age of 15 he had chosen chemistry as his life's intellectual and professional pursuit.

"My father, Oskar, influenced me strongly, intellectually and morally,"[b] Ernest told me recently. "He was a real intellectual. A vociferous reader of philosophy, he was versed in music and literature. He had a spirit of learning. He was a strong role model for me. Morally, he was very strict, we had to do 'the right things.' When I was 12, I had to decide between a high school curriculum that involved study of Latin and Greek and an alternative curriculum that focused on modern languages. Because of the Nazis, I knew that I would eventually leave Germany, so I chose the modern language option. When I told my father, he was not in the least bit surprised but he acted unhappy. 'Why?' I asked him. 'An educated person should know Greek,' he responded, continuing 'If you are a scientist,

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[a] By a remarkable coincidence, Federico A. Lehmann G.'s mother lived "around the corner from Ernest Eliel and his family" in Köln. [1]Lehmann, Russell E. Marker, and Emeric Somlo were the three founders of Syntex. The involvement of Eliel with George Rosenkranz in Cuba and Rosenkranz's subsequent career with Syntex in Mexico will be related later.
[b]Double quotation marks indicate direct quotes from Ernest L. Eliel. In most instances, these derive from interviews given by ELE to the author in February, March, and April 2001. In other cases, a reference is provided.
Received for publication 20 June 2001; Accepted 10 August 2001

DOI 10.1002/Chir.10055

Fig. 1 Oskar Eliel, Cologne, ca. 1930.

Fig. 2 Ernest Eliel, in a pharmaceutical laboratory in Havana, taking an extension course in organic analysis and synthesis, Summer of 1945.

you need to know the Greek alphabet, you ought to know the Greek roots of our vocabulary.' 'Would you teach me?' I requested. He did, and I learned enough to make him happy. Later, I turned the tables on him and asked if he had learned calculus. Having gone to a humanistic high school, he had not. I said to him, 'I think an educated person ought to know calculus.' He could have become angry, but instead, he said, 'How about teaching me calculus on Sundays?' I did. He treated me fairly and I did not resent his authority (Fig. 1).

"Life is chaotic. Events cannot be predicted because the causes change. We don't have everything under control. When we have to make a decision, we have to take into consider all the factors that we can identify. Some factors you cannot control. We are all subject to uncertainty and luck. We have our principles. We have our fundamental guidelines, but where they get us is still uncertain. Why do the best synthetic chemists have such big groups? Because they can't control everything, they must try multiple approaches, backtracking sometimes. The more factors you can take into account, the better you can succeed. The other thing that distinguishes the great from the mediocre is the importance of the problems they choose to solve."

When the Nazis came to power in 1933, economic, social, and cultural life for Germany's Jews deteriorated suddenly and dramatically. By 1938, the Eliel family had separated: his parents had emigrated to what was then officially named Palestine; one of his brothers to Holland, the other to England, and Ernest to Scotland, where he was awarded a stipend for 4 years of university studies. Just as he was completing his first year at the University of Edinburgh, Germany invaded Holland and Belgium on May 10, 1940. Two days later, Eliel, 'as an enemy alien,' was taken to an internment camp.

France soon thereafter fell and in July, 1940, Eliel was put on a ship and "told that its destination was a military secret. Thus I left Europe for good. The ship went to Canada." Following 10 months in a Canadian internment camp, Eliel traveled via Trinidad and Venezuela to Havana, where he lived for 5 years until July 1946 and emigration to the United States.

Fig 3. At the Notre Dame Post Office, 1960. "It might be claimed, probably false, that what I am carrying is part of the *Stereochemistry* manuscript."

In the preceding 8 years he had traveled far, intellectually and emotionally. Eliel learned English and Spanish, earned an undergraduate degree from the University of Havana, and conducted research in the laboratory of the then-largest Cuban pharmaceutical firm under George Rosenkranz (Fig. 2). As recounted by Rosenkranz, "three outstanding and brilliant pupils emerged from these days" in Havana,[4] Eliel, Fausto Ramirez (later Professor of Chemistry at the State University in New York in Stony Brook), and John Weisburger of the American Health Foundation. Eliel also published two articles and submitted his undergraduate thesis "El Aldehido Homoverátrico, Intermediario para la Síntesis de Homoveratrilamina y Acido Homoverátrico" to the Universidad de la Habana in June 1946. It was dedicated "A mis Padres."

Eliel was now ready to begin his Ph.D. studies. His professional life parallels those of other Jewish or part-Jewish scientist-émigrés from Europe. Rosenkranz was to move in June 1945 to join F. Lehmann and E. Somlo at Syntex in Mexico City and eventually become its president (as well as an internationally famous bridge player). Carl Djerassi, another European refugee, was to join forces with Syntex in Mexico City and participate in the most creative era of steroid research. [5,6] P. Lehmann, the son of F. Lehmann, has described some of these events. [1]

"I come from a secure family. That certainly made a big difference, and that feeling of security transmits itself to the children. I am not given to phobias and fears. I try to think about the future by having some kind of idea as to what is likely to happen. Not too often was I subjected to fearful experiences that I had not anticipated. Maybe I learned that in Germany. Had we better anticipated what the Nazis were doing, we certainly would have left earlier.

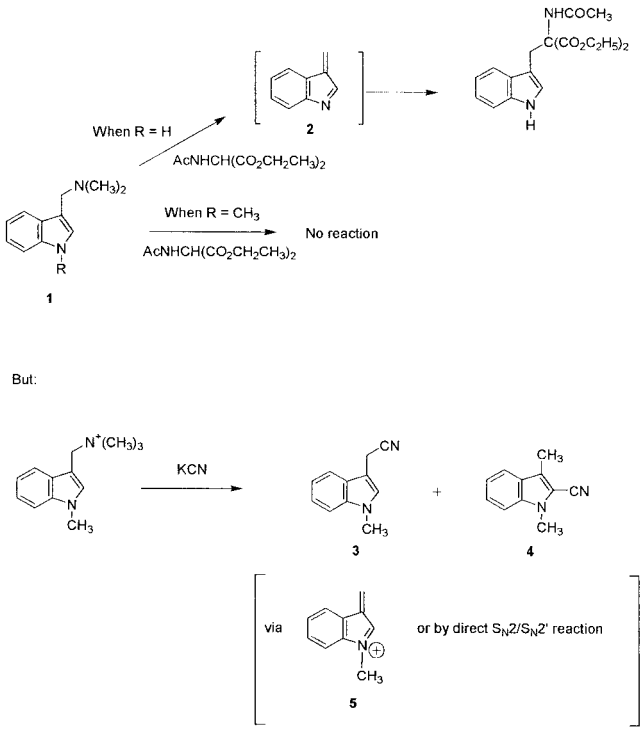
"When people understand what we went through, they are astonished. But for me, I am not. It was part of my life and that is the way it was. I am happy that I survived. No member of my immediate family was killed. It was just luck; I was fortunate. I never feared for my life, no. Neither did my father, I don't think so. My parents were very protective of me when it came to nasty things. They tried to keep bad news away from me. One of the relatively few lasting effects of my experiences of the 1930s and 1940s is that I would never live in Europe, certainly not in Germany, again. Once you feel you are not wanted, you don't want to go back. Eva [Ernest's wife, who was also born in Germany] and I have been very happy living in the United States, still the land of unlimited opportunities.

"I am not a philosophical person. I consider myself a pragmatist. My father was a humanist. He lived in a world of ideas. The practicality of what he was thinking was far from evident. He had some view of the world that was based on his philosophy, and the way he behaved must have been related to his philosophy, derived from his vast reading. I am much more interested in observations, what is happening in my experiments."

At the University of Illinois, Eliel chose Harold Snyder for his Ph.D. advisor, who asked the young graduate student to study carbon alkylation of indole Mannich bases **1** (Scheme 1).[7,8] The objective was to determine the fate of the reaction when the putative imine intermediate **2** was unavailable due to N-methyl substitution. The free amine in the methyl homolog did not react but the quaternary salt did, to give two products, which Eliel established to be **3** and **4** by an early use of infrared spectroscopy. "Professor Snyder suggested the use of IR but would never have been satisfied with that alone! I then had to prepare a sample of the authentic material **4** by chemical synthesis. I was intrigued by the fact that I might have observed an S_N2' reaction. Professor Snyder was more interested in the possibility of obtaining 1-methyltryptophan, which I later did prepare."[9] Eliel completed his Ph.D. thesis work, which resulted in eight publications, in 2 years.

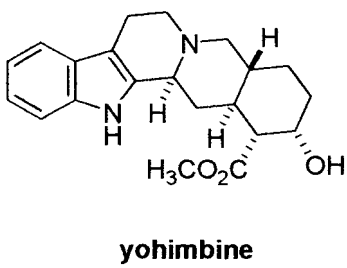
Fig 4. With Samuel Wilen and Lew Mander, Honolulu, Hawaii, December 1989.

"What are my principles of life? One very important thing, you ought to know what you want or what you are aiming for. You want to be clear about that. The German word is 'Zielbewusst.' 'Ziel' is 'target' and 'bewusst' is 'conscious of.' You must be conscious of your target."



Scheme 1.

In the spring of 1948, at a time when academic jobs were scarce, Eliel was offered a tenure-track position at the University of Notre Dame by Charles C. Price, who had just become head of chemistry after some years as a professor at Illinois. Eliel's early research at Notre Dame involved the synthesis of nonracemic $C_6H_5CHDCH_3$ (**6**), establishing that the optical activity in **6** was due to the deuterium. The key step was the reaction of optically active α-phenethyl chloride with lithium aluminum deuteride, which proceeded with inversion of configuration. Lithium aluminum hydride was a novel reagent at the time, and the successful preparation of **6** "provided impetus for important work elsewhere." Eliel studied the mechanisms of hydride reduction of halides and also worked on a (never completed, and perhaps overly ambitious for the young chemist) synthesis of yohimbine (Scheme 2). While the first 4 years at Notre Dame did not result in other important scientific publications, Eliel was granted tenure. During this time he became aware of D.H.R. Barton's pioneering studies on conformational analysis and interacted



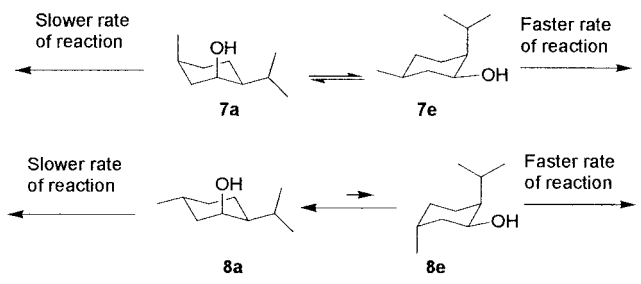
Scheme 2.

also with Michael Dewar and Vladimir Prelog, who visited Notre Dame as Reilly lecturers in the very early 1950s. (Barton visited only for a day at that time; he was a Reilly lecturer only much later.) Eliel's career was poised to take off.

"Another of my fundamental values is 'persistence.' In science, even the best laid-out ideas frequently don't work out. You have to find out how to get around the difficulties. If you give up right away, you won't get anywhere. On the other extreme, you must know when to give up, when the approach is unfruitful. You must then change your approach. How do you know when that time is? It's judgment. Your record demonstrates your success, and it's a hard thing to rationalize. How can you make judgment a more rational process? Think about it, try to come up with some conclusion. Whatever you do, you must discuss it with your students to see what they are thinking. You then try to weigh the factors and make a decision: is the student capable, are there pitfalls to the approach which you haven't thought of, is there a better way of doing it? Years ago, one of my colleagues said that I was a bulldog. The story of my travails in Cuba shows how I came to be one."

Perhaps the description "bulldog" characterized Ernest's ability and willingness to engage a significant problem without letting up. "I do not let go, once I have bitten into something important," Ernest summarized recently. While he is usually quite mild in both character and manner, when he feels strongly about something he can become both outspoken and insistent. The rarity of such occasions makes their nature ever so remarkable. For example, we will be in the midst of a discussion, like one preparing for writing this article. Ernest and I are 'traveling together' along an intellectual discourse, like on a pleasant Sunday ride in the country. And then, bang. The car stops suddenly. Ernest says, "No, I don't want to discuss that further." I hurriedly take a few reassuring steps backwards. His dander then falls, as precipitously as it rose. Perhaps our long friendship prevents a more serious diversion; perhaps it's my rapid, immediate capitulation. And I remind myself that this otherwise gentle soul can, indeed, be quite determined as well as resolute!

During a 1952 summer sabbatical at Ohio State University, Eliel's attention focused sharply on the reactivity of conformationally mobile systems. He interacted intensely with Melvin S. Newman and Herbert C. Brown. Eliel continued his correspondence with Albert Burgstahler, one of Eliel's first undergraduate research assistants and later a graduate student at Harvard who had attended Derek H.R. Barton's original Harvard lectures, which covered what would be his Nobel Prize discoveries. Eliel himself had earlier (in 1950) heard, first hand, Barton present his tenets of conformational analysis "in an electrifying lecture" at Notre Dame. Eliel subsequently "was intrigued by an article by Read concerning the nitrobenzoylation of the four diastereomeric menthols and especially by the fact that neoisomenthol (**7**) reacted faster than neomenthol (**8**) (see Scheme 3)." Thereafter, Eliel began to apply the concepts of conformational analysis to this and related chemistry.



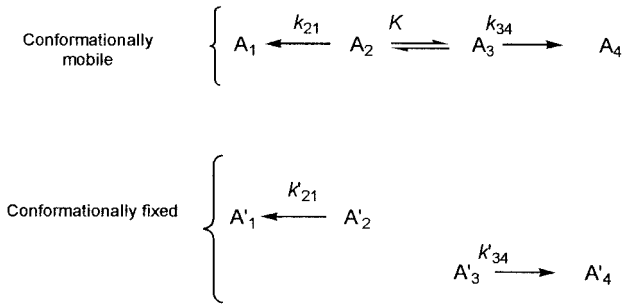
Scheme 3.

Eliel concluded that neoisomenthol (**7**) reacted via the conformation **7e**, in which the bulky isopropyl group is axial.[10] Conformation **7e** is reactive because the hydroxyl group is equatorial. On the other hand, neomenthol (**8**) exists primarily in the less reactive conformation **8a**; the proportion of **8e** present is very small and the overall reaction rate is thus low (Scheme 3).[11]

Eliel subsequently published the general principle, called the "kinetic method of conformational analysis".[12,13] The observed rate constant k_{obs} for a conformationally mobile reacting system is the sum of the specific rate of the contributing conformations weighted by their respective mole fractions, n_i (see Scheme 4) for the general system and Scheme 5 for a specific example). Discussions with David Y. Curtin and William G. Dauben clarified these conclusions. (Saul Winstein independently came to the same conclusions, although formulated differently, as shown in Scheme 4.[14]) Eliel also confirmed the consistency of this thinking with then recently proposed Curtin–Hammett principle.[14,15] In the kinetic method of conformational analysis, conformationally fixed systems are used as models for conformationally mobile systems. In Scheme 5, the equilibrium distribution constant K for a conformationally mobile system is estimated based on the determination of the reaction rate constants for two model conformationally fixed systems, i.e., one experimentally determines k_{obs}, k'_{21} and k'_{34}, assumes that $k_{21} = k'_{21}$ and $k_{34} = k'_{34}$, and calculates K as shown in Scheme 4. "The kinetic method of conformational analysis has been much criticized and is not really very good because reaction rate is very sensitive to deformations and to long-range effects of biasing groups, such as tert-butyl."

Eliel then proceeded to develop a second method, the so-called equilibrium method (Scheme 6) for determining conformational equilibrium constants.[16] This method was superior to the kinetic method of conformational analysis because it did not require the use of model systems. As summarized below, the equilibrium method has been used to great advantage in many systems. This technique is one of the methods of choice for determining conformational equilibria (now known for many cyclohexyl substituents) when the locked model systems can be chemically equilibrated.

In 1958, Eliel's sabbatical year was divided between Harvard and Caltech. Both proved to be "immensely stimulating in a variety of ways." At Harvard, Eliel learned



k_{ij} = reaction rate constant for the reaction of conformation "i" to product "j"

The rate of formation of products = $k_{observed} \times \{[A_2] + [A_3]\}$,
where $k_{observed}$ = empirical reaction rate constate of the substrate,
$[A_i]$ = concentration of conformation A_i,
and n_i is the mole fraction of conformation "i" .

Winstein and Holness

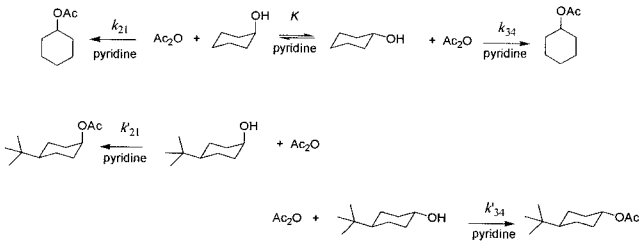
$$k_{obs} = n_2k_{21} + n_3k_{34}$$

Eliel, Ro, and Lukach:

$$K = \frac{k_{21} - k_{obs}}{k_{obs} - k_{34}}$$

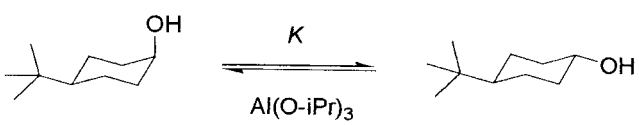
$$\text{and } k_{obs} = \frac{k_{21} + Kk_{34}}{K + 1}$$

Scheme 4.



Scheme 5.

new experimental techniques in Paul D. Bartlett's laboratory; "perhaps more importantly, within the first week of my stay, I gained the respect of Robert B. Woodward, by giving an almost impromptu lecture about my, by then quite extensive, aluminum hydride research."[17] At Caltech, in Jack Roberts' laboratory, Eliel learned the principles and practice of NMR. He realized that conformational equilibria could also be determined by NMR, using model



Scheme 6.

Observed average shift δ_{OBS}

Observed axial shift δ_a Observed equatorial shift δ_e

$$\delta_{obs} = n_e\delta_e + n_a\delta_a \text{ where } K = n_e/n_a$$

Scheme 7.

compounds to ascertain the chemical shifts of the contributing conformations (Scheme 7).[18] This was the first time that NMR had been applied to the determination of conformational equilibria.

"When I was on sabbatical in Zurich in 1967–1968, I learned the German word 'Dünnbrettbohrer.' 'Dünn' means 'thin,' 'Brett' means 'board,' and 'Bohrer' means 'one who drills holes.' Hence, 'Dünnbrettbohrer' means an individual who picks easy problems and solves them successfully and then tries for, and sometimes gets, credit. A great scientist is not of that ilk. On the other hand, you need to be aware of your own limitations. You need to be at the limit of your ability to solve the problem, but not pick a board so thick that you have no chance of getting through it! That is an interesting balance, to challenge yourself to the maximum. But what is maximum is a very personal decision."

Eliel had found what was to be his area of scientific excellence: conformational analysis. Organic chemistry was rapidly advancing. The topic of stereochemistry in the broadest sense drove the science along with major developments in analytical instrumentation. The new spectroscopic methods of NMR and IR were making their mark. Instrumental techniques such as gas chromatography were becoming standard. Because much of organic chemistry involves conformationally mobile systems, an understanding of the three-dimensional nature of molecules, their shapes, and their conformational preferences is required.

Eliel provided many seminal research publications in the areas of stereochemistry in general and conformational analysis in particular, including numerous determinations of conformational equilibria by low-temperature ^{13}C NMR, both in substituted carbocyclic and heterocyclic saturated six-membered rings. However, some have concluded that his greatest gifts to science are his books. The book *Stereochemistry of Carbon Compounds*[15] was begun at Caltech and completed at Notre Dame. It sold over 40,000 copies and was translated into Japanese, German, Czech, and Russian. "I have met hundreds of chemists all over the world who have told me that they learned stereochemistry from my book," Eliel told me recently. "They told me that

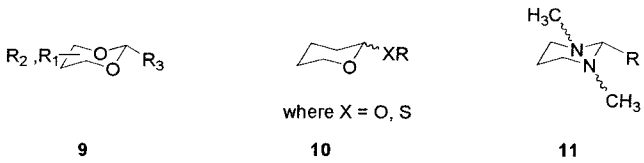
they had considered stereochemistry a mysterious subject until my book helped make it clear to them. Just this past Sunday, I was at a reception for award ceremony for graduate students at UNC, and a professor in the Pharmacy School mentioned that she had always been grateful that she had learned stereochemistry from my book. I have estimated that some 100,000 chemists have studied from that book (Fig. 3)."

I am certainly one of those 100,000 chemists. I marvel that perhaps the singularly most important text I studied for my Ph.D. exams at Berkeley was written by the gentleman about whom I am now writing, 35 years later! Indeed, Ernest's teaching has, of course, extended to both the classroom and to graduate students. He has won three teaching awards: the American Chemical Society's George C. Pimentel Award in Chemical Education; the Manufacturing Chemists' Association (now American Chemical Council's) College Chemistry Teacher's Award; and an AMOCO teaching award at the University of North Carolina. An honorary doctorate from the University of Notre Dame in 1990 particularly pleased Eliel, "because I believe that it was given not just for scientific achievement and public service, but also as a recognition that I did contribute to the Notre Dame Chemistry Department in my 24 years there."

Eliel continued, "We now have the 1994 book [*Stereochemistry of Organic Compounds*[19]] that I wrote with the late Sam Wilen (with a chapter by Lew Mander, see Figure 4). Mike Doyle and I have recently written an abbreviated version, *Basic Organic Stereochemistry*[20] for classroom use." Eliel is most certainly a thorough and exact person and scientist. It is therefore not surprising that the 1994 Eliel–Wilen book is more of an encyclopedia than a second edition of the 1962 textbook, given the incredible development that stereochemistry has experienced since that time and the authors' desire to be comprehensive. I am very proud that some of my own research is found in these books. I am looking forward to seeing the new Eliel/Doyle arrival, most likely to be a hit (and following a special pedagogical tradition)!

Recently, I was telling Ernest about some of my carbohydrate pyrolysis research and my conclusion that furans form during the pyrolysis of D-glucose because of the kinetic preference to form five-membered rings over six-membered rings. "Where in your book is that kinetic preference covered," I asked. "Chapter 11" was his immediate response. I have witnessed many other demonstrations of his wonderful memory, to include being able to pinpoint information, even dates of events decades earlier.

Eliel's next major scientific contributions were to the conformational analysis of saturated heterocyclic compounds. The conformational preferences of dioxanes **9** were studied (Scheme 8).[21,22] Conformational equilibria of 2-alkoxy- and 2-alkylthiooxans (**10**) were investigated because of their importance with regard to the anomeric effect seen in sugars.[23] Analogous studies with N,N′-dialkyl-1,3-diazanes (e.g., **11**) were also undertaken.[24,25] The funnickname "rabbit ear effect" was rapidly replaced by a thorough understanding of the controlling factors which

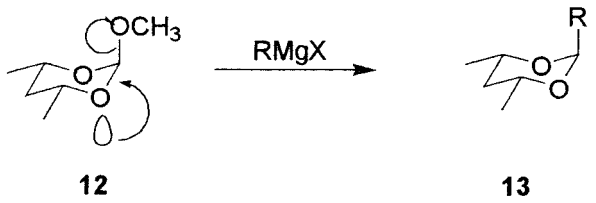


9 **10** **11**

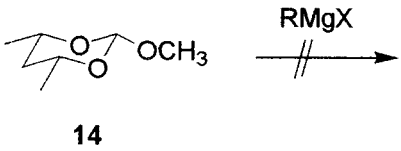
Scheme 8.

determine conformational preferences: dipole interactions and n–σ^* bond overlap, or double-bond–no-bond resonance, topics of paramount importance in carbohydrate chemistry.

Studies on the reactivities of these conformationally



12 **13**



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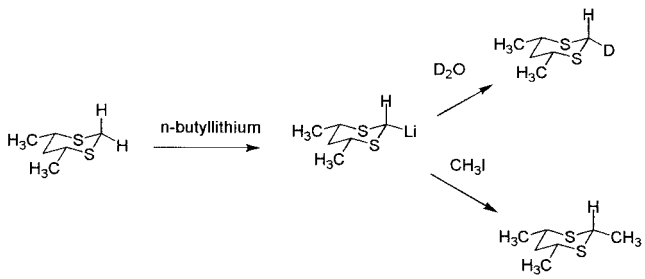
Scheme 9.

mobile systems then followed. In experiments with conformationally fixed ortho esters with Grignard reagents (Scheme 8), the axially substituted **12** reacts smoothly to form mostly the axially substituted **13**, while the equatorially substituted isomer **14** reacts slowly, if at all. Eliel and his students explained this result on the basis of the anomeric effect and conformational analysis (Scheme 9).[26,27]

"No sooner had the preliminary account of these finding been published than an even more important discovery was made by my Ph.D. student Armando Hartmann." As shown in Scheme 10, butyllithium-mediated reactions of



Scheme 10.

Fig 5. During a swimming break, at the 1980 Gordon Conference on Stereochemistry. With former students and postdoctoral fellows. Left to right: Fritz Vierhapper, Kenso Soai, William Bailey, Eliel, and Eusebio Juaristi. Photo courtesy of Kenso Soai.

the heterocyclic 1,3-dithianes lead to stereoselective equatorial protonation or alkylation.[28,29]

"You asked me, 'How do I learn new tricks?'" Eliel didn't pause a second in his response: "You must broaden the approach in your research. You must keep your eyes and ears open, know what is going on in the scientific world. It is important to distinguish new ideas from new applications of old ideas. Even though I am no longer doing research, I like to read some communication journals: *Chemical Communications* and *Organic Letters*. If I write a book, I need to know what is going on. When I talk with people or review a manuscript, I need to know what is going on. Otherwise, I am intellectually dead!"

One application of Eliel's philosophy of growth was his continuous application of advances in nuclear magnetic resonance. Scheme 7 demonstrated this with ^{1}H NMR. In the early 1970s, Eliel collaborated with both David Grant at Utah and Ernest Wenkert, then at Indiana, applying ^{13}C NMR to heterocyclic conformational analysis.[30] One of the first unexpected findings was that, in contrast to cyclohexanes, axial methyl groups resonate at lower field than equatorial ones in C-5 conformationally locked 1,3-dioxanes, an observation which eluded explanation for a long time. (One of the 12 authors of that "highly cited paper" is Bill Bailey, guest editor of this special issue of *Chirality*. See the wonderful picture of Eliel with Bailey and other former students and postdoctorals on this page (Fig. 5). Also in this photograph is Eusebio Juaristi, another contributor to this journal tribute to Ernest.)

In 1972, Eliel made another transition, from South Bend to Chapel Hill. Some of us athletically oriented folks would nod our heads, complimenting Ernest—somewhat in jest—that he was able to remain in the midst of big-time college athletics. "We took to football at Notre Dame. Eva and I both regularly and enthusiastically attended football games at Notre Dame, but somehow we didn't make the switch to basketball at UNC." Nonetheless, for several years I enjoyed an annual UNC basketball weekend as guest of the Eliel's. Ernest and I even had the good fortune to attend a UNC–Duke regular season finale. What excitement for both of us. On occasion, Ernest was yelling louder than I was, as UNC would pull ahead in the waning moments of the first half! While Ernest does not consider himself an athlete, even in his late 70s he swims 10 laps every day without stopping. I admire his determination.

The move from Notre Dame to UNC had consequences for Ernest far greater than sports. Eliel certainly responded to a new chemistry department, one that was and continues to grow in numbers and prestige. Some may argue that this was a consequence of the arrival of Eliel and—shortly thereafter—Robert Parr, both then new members of the National Academy of Sciences. While they may have a point, certainly a very important reason was the addition, in the 1960s, of a number of outstanding young faculty to the UNC chemistry department staff who began to make a reputation in the 1970s. Eliel enjoyed, and continues to enjoy, even in retirement, his move to UNC. "The chemistry department at UNC continues to grow in numbers of graduate students and in prestige. There is a great esprit-de-corps in the department—you feel this right away, not only as a faculty member but as a student and even as a casual visitor. There may be a lot of high-powered people in the department, but they realize that what is good for the department is good for its members and vice versa—a

win–win situation. That is not to say that everyone always agrees—not by any means. At faculty meetings there is often a great deal of discussion and sometimes controversy, but at the end there is almost always consensus.

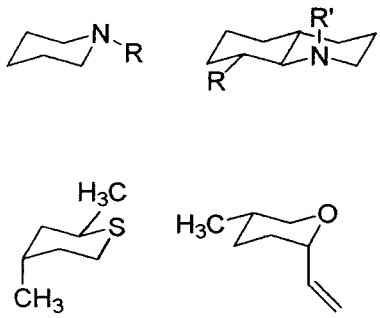
"There are certain ways of doing things which the older members know and the younger ones learn from the older. This spirit of cooperation is infectious and makes it easier for the department to attract good young faculty as well as good graduate students. Once, in interviewing a young potential faculty member, I asked him if he would accept the job if we made him an offer. He assented so quickly that I pressed him to explain his eagerness. He said—recognizing one of the hallmarks of the department—it was common knowledge that we treated our young faculty well, which was worth a great deal to him. He was right—we are very careful in whom we hire, but once they are on board, we do what we can to make it possible for them to achieve tenure (which does not come easily)."

By no means do all chemistry departments operate that way. Ernest reports having seen departments that are rife with strife and others in which the members are all primadonnas that function on their own, without any departmental cohesion and without concern for their younger colleagues. "But my principle, and this relates to my students as well as my children, is to give individuals the maximum freedom to do their thing as long as they don't harm the unit in which they work. Our department operates exactly that way—successfully so."

Eliel's research at UNC continued to focus on conformational analysis of heterocyclic compounds. Some of the systems examined are illustrated in Scheme 11. The goal of building a comprehensive understanding of the conformational preferences of saturated six-membered ring heterocycles was the Eliel group's focus. The research can be characterized by careful experimentation, delicately selected target compounds, exquisitely written full articles, and resulted in highly educated graduate and postdoctoral students. The position of the *N*-H and *N*-CH_3 moieties in various piperidines was evaluated.[31,32] Low-temperature ^{13}C NMR was used to analyze conformational equilibria in various thianes,[33] oxanes,[34] thianium salts,[35] and piperidines and piperdinium salts.[36] This work is fundamental to the understanding of the chemistry of conformationally mobile six-membered saturated heterocyclic rings, found in many natural products as well as synthetic materials.

"I have always tried to explain things in written publications lucidly. When a paper is not clearly written, it is discouraging, annoying, and sometimes a deterrent to reading. One reason why people have read and understood my papers is that they are carefully written, in addition to whatever intrinsic interest the science possesses.

"As the research is being developed, I always think as to how it is going to be written up. This approach has both advantages and disadvantages. The advantage: it is easy to develop the paper if you think of it from the beginning. The disadvantage, of course, is that research doesn't always develop as logically as you would want. Sometimes,



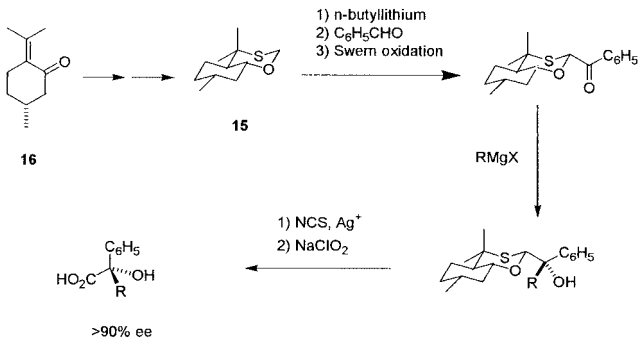
Scheme 11.

you find something you hadn't anticipated. Sometimes you cannot immediately explain the results.

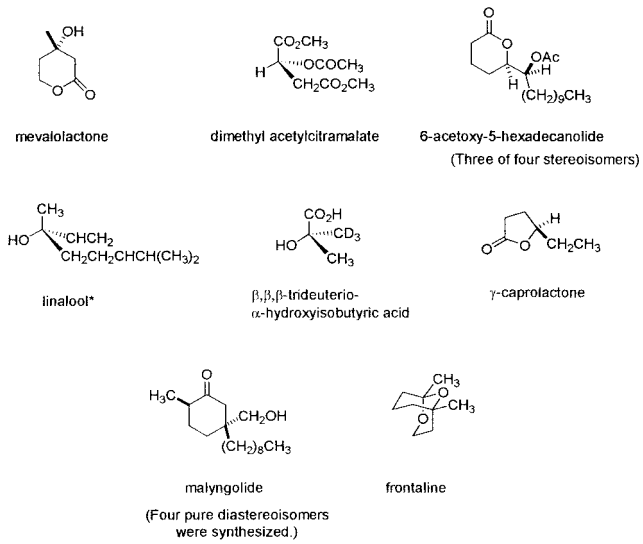
"I am an optimist, I always see the glass half full and feel that it will be filled. If you handle things right, they will come out right." Certainly it was that optimism that led Eliel back into the realm of organic synthesis.

Following the observation of high stereoselectivity in the reactions of the 1,3-dithiane reactions (Scheme 10), Eliel and his group took the logical next step: application of this fundamental research to enantioselective synthesis. The breakthrough came in the use of oxathianes.[37] Following a series of eventful advances, the goal was reached using as a key intermediate the oxathiane **15** obtainable from the commercially available enantiomerically pure natural product pulegone (**16**) (Scheme 12).[38] Eliel applied this approach to a number of important synthetic targets (Scheme 13).[39–45] The syntheses was notable at the time (the late 1970s) for the high enantiomeric excess of the products. Today, of course, innumerable such syntheses are known and catalytic enantioselective synthesis has superseded methods based, as Eliel's did, on chiral auxiliaries. One can only guess as to how his three heroes, R.B. Woodward, Vladimir Prelog, and Derek H.R. Barton, would have reacted to Eliel's becoming a synthetic chemist!

We have thus enumerated many of Eliel's contributions to his profession: his research, his teaching, and his books. He has also served the American Chemical Society well, first on various committees, then on its Board of



Scheme 12.



Scheme 13.

Directors, Chairman of the Board, and subsequently as elected President of the ACS.

"I am proud of the work I've done with the ACS. I am particularly happy that I got ACS to work more intensively in global activities. This is important for the chemical community that is getting more international, not just in the basic science but also in the industrial community. Ultimately, we need to have better relationships with the peoples from all over the world, especially from the medium well-developed countries: the countries which have the chemical capacity, in human terms, but not the infrastructure that we have, in terms of, for example, instrumentation and availability of materials. These are predominantly Latin American and Eastern European countries. Because of my knowledge of Spanish, I have been working particularly with Latin American countries, Chile, Mexico, Argentina, Venezuela, and Cuba, the land of my alma mater. We, in the ACS, have been able to arrange summer fellowships for work in the USA for some young, established investigators in some of these countries, as well as Brazil and Costa Rica. When you talk to these people, after they have worked in the United States with state-of-the-art instruments, you can see how eager they are about the collaborative arrangements we have made. After they spend time in the United States, they go home with recharged batteries, with some of their frustration gone. Such experiences make them want to continue to do research, enlivens their teaching."

Ernest was also active in raising significant funds for the ACS. "Some would say the most important work I did for the ACS as Chairman of the Board was its fund-raising 'Campaign for Chemistry.' We raised $26 million. To me, it was a learning experience and I don't take as much credit as people may give me.

"The challenges for chemists today can be divided into two parts. For chemists, chemistry is still the central science, but many of the most exciting areas of chemistry have moved to the periphery of chemistry. It may be materials science, or environmental chemistry, or chemical biology. This causes a problem for chemistry departments, because in order to do cutting-edge science, a substantial proportion of their faculty's research has to be at the periphery of chemistry, yet the department has to keep the core chemistry alive. I see this at home and I see it when I visit other institutions.

"The health of a science depends on the employment opportunities of its practitioners, because people don't want to go into occupations where they cannot find jobs. The health of the chemical industry, outside of the pharmaceutical industry, in the last few years has been indifferent at best. This has reflected itself in a diminishing number of Ph.D. candidates in chemistry.

"The second and perhaps bigger problem for science in general is lack of understanding by the public, which is to some extent the fault of the scientists ourselves. Many of us neither care to teach nonscientists about our field while they are students nor explain it to them when they are adults. This is unfortunate and counterproductive. In addition, the modern development of science, for example, genetics and certain aspects of modern medicine, raises important ethical problems which society has not fully faced up to. The whole problem of energy availability, on the one hand, and the greenhouse effect, on the other, the consequence of burning fossil fuels, is very pressing. One solution that is already at hand is nuclear energy. But it has problems of safety, disposal of nuclear waste, and eventually disposal of overage reactors. Wind energy probably won't provide enough to solve the problem, but solar energy might and we need a lot of research there.

"If we learn to think in broader terms, and to apply our knowledge in broader ways, we would make quicker progress towards solution of some of these problems. Young faculty don't get tenure, don't get grants, by thinking in these broader ways, and that's unfortunate. The support problem is up to the granting agencies and I think they are making progress. Tenure is up to deans and departments, and their progress has been slow."

Eliel was awarded the American Chemical Society's highest award, the Priestley Award, in 1996. The award simply states, "…for distinguished service to chemistry." For Eliel, it honored his amazing combination of professional and personal skills and accomplishments: as a scientist and scholar, an educator, an author, an ACS volunteer, a mentor, an international science statesman and public servant, and a fine and honorable individual.

I was pleased (along with Eusebio Juaristi) to sit with Ernest, Eva, and their daughters Ruth and Carol and their husbands at the Priestley Award event. The warmth of the Eliel family is evident and welcoming. I particularly enjoy watching (and listening to) the Ernest–Eva relationship (Fig. 6). I frequently enjoy a conversation-within-a-conversation, in which I communicate with Ernest and Eva while they, in parallel, communicate with each other. I know that I will get the 'full picture' from such experiences! (For many

Fig 6. Eva and Ernest, at the 1989 Bürgenstock Conference. Photo courtesy of Jeffrey I. Seeman.

years, I experienced the same type of multiple conversation–telephone calls with Michael and Mary Dewar.)

"Eva has had a very civilizing influence on my life," Eliel recounts with pride and a smile. "She is a very cultured person, she comes from a musical family, writes very well, reads a lot, she kept me from being a 24-hour chemist. She has kept me in contact with other human endeavors. She has always been a big critic of mine, perhaps when I become a bit too arrogant or self-possessed from time to time. She plays the same role that my very much older brothers played when I was a kid, pricking my balloon.

"Above all, since I spent a great deal of time in the lab, I wasn't home enough in bringing up the children and she did a great job with them. The children have a wonderful relationship with her. She was very understanding of the fact that in order to be professionally successful, I needed a great deal of time for my work.

"Still, I was good with my children. It's probably often the little things that matter in human relationships. I taught them both how to read at the age of three or four. I taught them how to drive at the age of 15. I made a point of rarely shouting at them. I always gave them the maximum freedom that they could handle. Which, by the way, is the manner in which I treated my graduate students."

Recently, Eliel wrote a brief essay entitled "Derek Barton as 'Hidden Advisor'" in a book entitled *The Bartonian Legacy*, paying tribute to this fine scientist.[46] The essay begins:

> Most scientists, when you ask them who most influenced their early careers, will give you the names of their Ph.D. advisor, their postdoctoral supervisor, and, if they did an undergraduate thesis, perhaps their undergraduate mentor. However, the persons who have had the greatest influence on my career are two Nobel laureates with whom I was never officially associated: D.H.R. Barton and V. Prelog. But whereas I have spent considerable amounts of time with Prelog—6 weeks when he was Reilly lecturer at the University of Notre Dame in 1950 and a whole year when I was at the ETH in Zurich on a sabbatical leave in 1967–68—I have never spent more than a day at a time with Derek Barton. Nevertheless he is largely responsible for the development of the directions of my research.

I am proud to join many other chemists who today can say, 'Ernest Eliel was my hidden advisor.' I am even more pleased to say that Ernest and Eva are my friends.

ACKNOWLEDGMENTS

My many years of personal and professional relationships with Ernest and Eva Eliel have bestowed upon me the opportunity and pleasure to write this essay. I thank them both for our friendship and for their assistance in the preparation of this article. I thank Bill Bailey, guest editor of this issue of *Chirality*, for his thoughtful invitation to participate in this scientific celebration, Nina Berova for her contagious enthusiasm, and Kenso Soai and Fritz Vierhapper for the loan of photographs. I acknowledge Dr. Arnold Thackray for his passionate drive to advance the heritage of the chemical sciences.

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