Laszlo describes a "true renaissance man" ("a Romantic polymath") and makes the case that he might have won a Nobel Prize were he not an industrial chemist. Here I will disclose that Pierre was my Ph.D. advisor at Princeton University and that we have remained in touch ever since. A fascinating portrait is provided of grandparents and parents producing a gifted only child (*L'enfant unique*) with extraordinary ability in languages, knowledge of music. His father, steering him from a lineage of Chesapeake fisherman, met his youngster's scientific interest by building the twelve-year-old a small laboratory. As an undergraduate at MIT, he chose chemistry over math and physics, performing his senior research with John D. Roberts and continuing with him for his Ph.D. He completed his Ph.D. in two and one half years. One research project, largely developed and carried out by Simmons employed ^{14}C-labelled benzene to implicate the existence of benzyne. Published in 1953, this research remains in advanced organic chemistry textbooks as an illustration of a technique for probing mechanisms. Other JACS papers with Roberts and Arthur C. Cope were published not long afterward. Although encouraged by J. D. Roberts to join him at Caltech, Simmons was successfully recruited by Ted Cairns to join the Central Research Department at DuPont in Wilmington, Delaware, not far from his aging parents in Norfolk, Virginia. At DuPont, had an amazing career, not only of originating and collaborating on original science but assembling formidable teams of scientists. His work was far-ranging. Interested in assembling the platonic solid molecule dodecahedrane, independently of R. B. Woodward, he conceptualized triquinacene dimerization. Then he hired Woodward's co-worker Fukunaga Tadamichi to work on triquinacene among other projects. Although dodecahedrane did not emerge from this work, interesting studies of homoconjugation did and further research on spiroconjugation both theoretical and experimental were published. With Ron G. Smith, the Simmons-Smith reaction, a safe and convenient method for generating methylene was developed. Also in the late 1960s, with Chung-Ho Park, Simmons synthesized macrobicyclic amines that exhibited a new conformational isomerism—in-out amines. This was an early contribution to host-guest chemistry. Laszlo concludes by summing up many traits of this fascinating polymath. An Appendix includes internal DuPont correspondence dated 1956 detailing Simmons' concepts toward synthesis of triquinacene and dimerization to dodecahedrane.

Slightly apologetically, this reviewer admits this is a longish review. But aside from describing the monograph's fascinating look at individual cases, it is a fascinating meta study of the history, criteria, politics and personalities behind the Nobel Prize headlines. It is highly recommended for institutional libraries and for those individuals who wish to better understand the humanistic endeavor we call science.

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Classical Methods in Structure Elucidation of Natural Products, Reinhard W. Hoffmann, Wiley-VHCA, Zürich, Switzerland, 2018, 265+viii pp, ISBN 978-3-906-39073-4 (ePDF *-79-6), $165 (e-Book $132.99).

Rightfully, scientists' focus is forward-looking. It is the nature of scientific research to scan the horizon and rush toward the rainbows. It is all too easy to take for granted the foundations upon which research is conducted. Scientists often have little awareness of the types of struggles that previous generations of scientists encountered. Bringing the history of science to the scientist is a joint responsibility of historians of science, of scientist-historians, and of scientists themselves. The book reviewed herein describes one scientist's historical documentation, a single-volume gift to the organic chemical community and an archival treasure for the history of chemistry.

Now 85 years old and officially retired as professor of organic chemistry at Philipps Universität in Marburg, Germany (1970 to 2001), Reinhard W. Hoffmann has published a unique book in the annals of chemistry publication. And I emphasize "unique." Singularity by itself is noteworthy in a world rather awash with chemistry books. Simply put, there is no other book whose goal is to teach the *Classical Methods in Structure Elucidation of Natural Products*. In this beautifully produced 273-page volume, Hoffmann's true achievement goes far beyond the title of his volume. He literally places the reader into

Table 1. Compounds whose structure determinations are discussed in this volume.

Compounds with only oxygen functionalities	**Compounds with nitrogen and oxygen functionalities**	**Compounds with additional functionalities**
Ascorbic acid	Pyridoxine	Biotin
Hinokitiol	Muscarine	Thiamine
Cantharidin	Lupinine	Griseofulvin
Camphor	Lysergic acid	
α-Terpineol	Riboflavin	**Compounds without heteroatom-functionalities**
Lactaroviolin	Cocaine	Decacyclene
Santonin	Quinine	Carotene
Estrone	Luciferin	
α-Tocopherol	Strychnine	**Can you do it yourself?**
		Penicillin

the blindfolded abyss that was organic chemistry in its pre-instrumental, pre-spectroscopic era. Hoffmann then challenges the reader to determine the structures of compounds such as quinine, strychnine, and penicillin using only the tools and chemical knowledge of the times in which chemists did just that.

Hoffmann's self-created endeavor was no easy task to write, nor was it easy to obtain permissions to use all the photographs that adorn this volume. And his book is not an easy read. Indeed, Hoffmann's book is not a read at all, nor is it a study manual, a textbook, or a resource. In a sense, the book comprises a series of mini-adventures, each like climbing the face of a sheer mountain cliff, many stories high. With the climb, and only with the climb, does the learning and appreciation of each structure determination occur. This book is an immersion into another era.

Those of us who entered organic chemistry more recently than 1960, that is, most of us younger than about 80, cannot—without a book such as Hoffmann's—have any idea of the darkness in which those pioneering chemists wandered in pursuit of structure determinations. Nonetheless, chemists from the middle of the 19th century until the advent of the instrumental era (middle of the 20th century) were unbelievably successful in the determination of structure through exceedingly slow yet deliberate steps. Hoffmann's book reveals these painfully slow steps, and the revelations come not so much from reading his book but from experiencing it.

Table 1 lists 24 natural products that Hoffmann discusses, one per chapter. These compounds represent a wide range of chemical structure, complexity, and time period of experimentation. Ultimately, "structure determination" comes in three stages of increasing complexity: constitution, relative configuration of all stereogenic centers (a term that was not proposed until decades after the recognition of the phenomenon), and absolute configuration. Often, as illustrated in most of the 24 cases, there were years, if not decades, of experimentation between the determinations of constitution and the determinations of absolute configuration.

The book is filled with relevant and wisely chosen photographs. There are photographs of the chemists who played key roles in the structure determinations along with detailed biographical captions. There are photographs related to the properties of the compounds of interest. For example, a photograph of a person with signs of scurvy, the disease that occurs in individuals who lack ascorbic acid, vitamin C, is the first compound whose structure is discussed in the book. There are photographs of the natural products themselves, e.g., *colchicum autumnale* in flower, the source of colchicine; and the seeds of the *Strychnos nux-vomica* tree, the source of strychnine.

In the 19th century structure determinations were frustrated by chemists' primitive understanding of atoms and bonding, not to mention a near ignorance of stereochemistry, absolute configuration, and of course, total ignorance of reaction mechanism. Recall that the tetravalency of carbon awaited Kekule (in 1865), the relationship between the tetrahedral carbon and chirality awaited van't Hoff and le Bel (in 1874), modern organic

synthesis awaited Woodward (in 1944), conformational analysis awaited Barton (in 1951), and the synergy of theory and experiment awaited Woodward and Hoffmann (Roald Hoffmann, not the author of this book, in 1965). Jack Roberts spoke of his early days as a chemist in the late 1930s and early 1940s when he said, "All that chemists had at their disposal were simple glassware, a balance, a Bunsen burner, and a few thermometers."

Hoffmann makes us feel those early structural chemists' bewilderment and angst, as well as their fortitude and pioneering spirit. They were courageous, as if they did not know how much they did not know. (Perhaps that is the nature of all scientists.)

In the words of the author,

> this treatise does not give the history of structure elucidation of particular natural products. Rather, the results from historic experiments are combined to derive a line of evidence for the structures that are accepted as "established" today. The line of evidence may follow the path put forward by the original contributors. In some instances, however, the experimental facts have been combined to another, hopefully shorter, line of evidence. Eventually, it is the aim to put the reader into a position to trace the "facts behind the established structure assignments" of some important natural products.

Those early chemists did have a shared *modus operandi* and the book literally takes us right there. Each chapter follows the same format, just as each structure was determined following the same general approach. Hoffmann first presents a historical and even botanical overview of that chapter's structurally-unknown natural product. A photograph of the tree or nuts or whatever natural source is included along with photographs of the chemists who led each particular structure determination, along with concise yet detailed biographical information.

Invariably, the first sentence of the second paragraph begins with the empirical formula of the unknown based on combustion analysis; and, if the compound is crystalline, its melting point is revealed, allowing the chemist to determine if it were a known compound. Two investigative pathways then followed: chemical degradations to known compounds or to simpler compounds whose structures could then be determined; and functional group analyses. By performing a wide range of reactions, chemists hoped to gather a package of hints, ideas, structural information and especially negative results such that a correct structure could be put forward. For each structure determination in his book, Hoffmann leads us down both paths. Ultimately the chemists were able to piece together structures that uniquely explained all the experimental data. These were exercises that demanded great mental flexibility, experimental expertise, patience and precise record keeping.

As this reviewer studied each structure determination, I wondered: If a time machine could take me back to the 1890s or even to the 1940s, could I succeed? Hoffmann's book makes it very clear that I would not have an easy time of it. I would be stuck after obtaining the elemental analyses. No less than 21 functional group tests are cited by Hoffmann, ranging from several that I actually knew (e.g., Blanc's rule for the thermal behavior of α,ω-dicarboxylic acids; the iodoform test for methyl ketones) to others I did not (e.g., the Angeli-Rimini test for aldehydes; the van Urk test for indoles; and the Sakaguchi test for mono-substituted guanidines). Surely for the early 20th century chemists, there were many functional group tests that are not cited in this book. Hoffmann provides Information Boxes illustrating each of these named reactions. Appreciating that many who study this book (note, I have intentionally not called them "readers") would not proceed in numerical (chapter) order, Hoffmann thoughtfully—and the publisher apparently willingly—repeats the Information Boxes as each relevant test reaction reappeared. Thus, there are five identical Information Boxes for the Kuhn/Roth determination of methyl groups and four for the Zerewitinoff test for active hydrogen.

Numerous Comment boxes appear throughout the book. These are always pedagogically relevant, e.g., a discussion of the

> common practice to dehydrogenate compounds with alicyclic rings to the underlying aromatic compounds . . . by heating with selenium to about 300°C

or the explanation that

> certain reactions are considered diagnostic for a class of compounds with a particular functional group . . . if the occurrence of such a diagnostic reaction results in the appearance of a distinct color

or the understatement that

> In those days, the drastic conditions of the Zn-dust distillation were considered to be quite acceptable. The concern that something could go wrong under those conditions was not too prevalent.

To get a sense of the content of Hoffmann's book, to get a basic understanding of classical structure determination, and especially to get a feel for what it was like to be a natural products chemist in the late 19th century up to the late 1940s, I shall present in the Appendix an

abbreviated description of the structure determination of cocaine. I shall do this by using excerpts from Hofmann's chapter on cocaine.

It is interesting to peer behind the scenes of authoring this book, and courtesy of Reinhard Hoffmann, we can do just that. In several emails, Hoffmann explained,

> When retiring, I had a number of projects in mind to do. Eventually, after ten years, they had all been accomplished. I thus had the leisure to read this and that. I don't remember which impetus (external or internal) brought me to ponder how solid and reliable are the classical structure assignments of representative natural products. Out of curiosity and just to get a feeling I started to look up the structure elucidation papers of curcumin and of colchicine in search of a convincing line of evidence. After reaching a line of evidence, I wrote the results down. As this was a pleasant experience, I continued with further structure elucidation papers. Somewhere along these efforts it occurred to me that these vignettes might be combined into a book.

Writing a book is a very personal experience, and I questioned Hoffmann further. In a follow-up email, he wrote,

> The book is an outcome of several pleasant pastimes, which eventually developed into the present book. At the starting point were structures of representative natural products in textbooks.
>
> In the early phase, the choice of the structures addressed was focused on textbook examples, that is, structures considered as important for organic chemistry. But then, I got interested in the mindset of the chemists who elucidated the structures. How did they go about tackling the structure of an unknown compound? This led me to include some compounds, the structure elucidation of which I found remarkable and typical. Being concerned with the mindset of the protagonists, I became curious to see whether there are differences in a European, an Anglo-American or in a Japanese approach. Thus, two or three compounds were chosen from this vantage point. At this point, I could and should have considered Woodward's contributions such as patulin. It just didn't occur to me; a missed opportunity. In hindsight I realize that the [names of the] scientists were not at all determining my choice of compounds. It was primarily the type of compound that influenced my choice.

As special as this book is, I wish it had more. For example, with each structure determination, a coda revealing all the degradative reactions could have been presented in a logical sequence. More historical information could have been included. For example, nothing is said of the enormous controversy, even power struggle, between Sir Robert Robinson and his thiazolidine–oxazolone structure versus R. B. Woodward's and Abraham and Chain's β-lactam structure for penicillin. Woodward's role in the strychnine structure determination is almost absent. Wonderful quotes from Robinson and Woodward about the evolutionary disappearance of the classical method of structure determination could have been included. Indeed, Woodward is hardly mentioned in the text, though he was arguably the greatest chemist at structure determination in the 20th century.

Hoffmann does not focus much attention on the external influences on chemistry. Indeed the instrumental revolution, which so completely changed the nature of structure determination, finds its infusion point during and just after World War II, when developments in electronics found their way into the modern laboratory. Woodward, the real master of 20th century structure determination, was chronologically well-placed into this playground. He arrived at Harvard in 1938. Had more of Woodward, more of context, and even several examples of post-classical structure determinations been included, this book surely would have doubled in size. One could only so wish.

Today the need for structure determinations remains, though wet chemistry in the service of structure determination has nearly disappeared. X-ray crystallography is universal (and crystalline derivatives often have to be painstakingly synthesized). But even elemental analyses now are performed routinely by high resolution mass spectrometry, not by combustion analysis. Total synthesis is no longer the gold standard for structure proof. Different skill sets are needed by today's organic chemists, including an increased emphasis on instrumentation and paper chemistry, that is, mental chemistry. Classical structure determination is now a lost art, and much knowledge otherwise gained in the required years of search for structure is unavailable. In its place is an abundance of equally time-dependent and brain-dependent achievement, the nature of which was unimaginable 75 years ago.

Fortunately we now have Reinhard Hoffmann's book to remind us and future generations about the shoulders of the giants we all stand upon and how the encyclopedia of organic structures came to be.

Appendix

This Appendix presents a few snapshots from a long-running case. First, the appendix will give a more concrete idea of the book's content and design. Second, it will place the reader right in the middle of the 19th century. And third, for the most enterprising readers, it will provide a puzzle for an amusing bit of time.

Cocaine is a modestly simple compound by today's standards and perhaps even in comparison with other compounds whose structure determinations are explained in this book (Table 1). In terms of a timeline: cocaine was first isolated in crystalline form in 1860, its constitution determined in 1898, the relative configuration of its constituents in 1954, and its absolute configuration in 1955. This represents almost 60 years from start to finish and covers an extraordinary period of advancement in science. This story also exemplifies the complexity and challenges of structure determination prior to the era of instrumentation.

In the discussion that follows, only the most pertinent chemical clues will be presented (Figure 1). These reactions were certainly neither the first nor the only reactions performed over five decades in laboratories around the world who were seeking the structure of cocaine. The chemists experienced many missteps, irreproducible experiments, misleading or conflicting observations, and experimental errors. So, what follows is more than a simplification. It is a non-trivial filtering out of irrelevant, inconsistent, and inaccurate information. To boil down a mass of data and identify the relevant information and exclude the rest is Monday morning quarterbacking in its most distinguished rendering. Indeed, to experience what the chemists of the day experienced, one would erase all of one's chemical knowledge and return to the literature of the 1860s and study—not just read—the original publications in chronological order. In the absence of such a commitment, please continue to read this Appendix for a glimpse of the intellectual past.

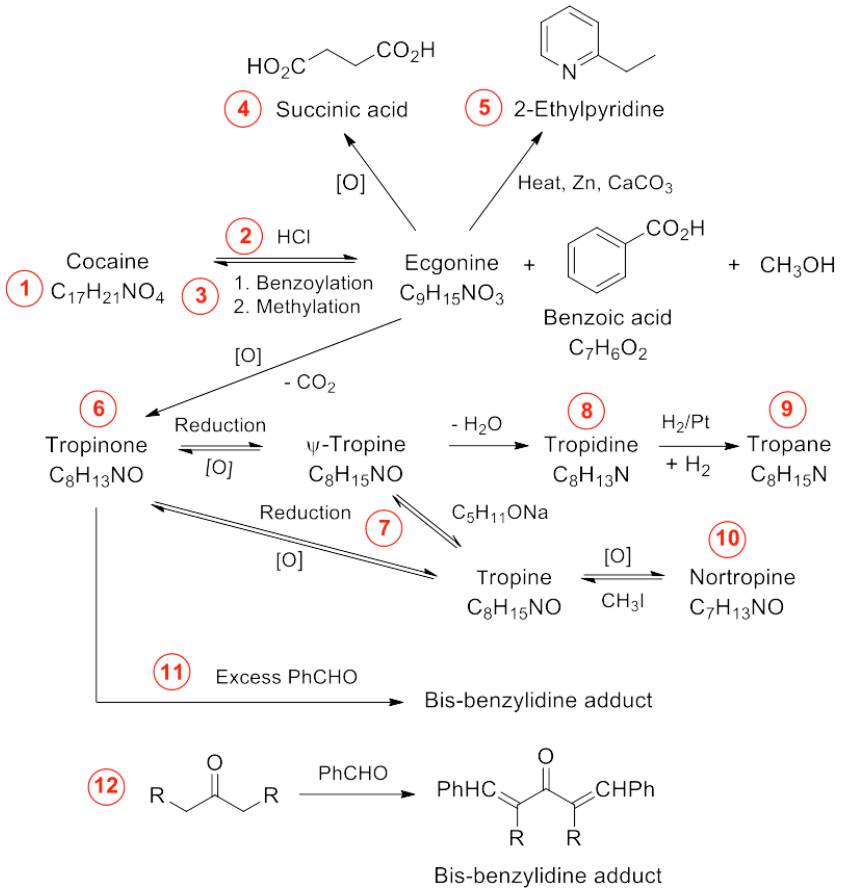


Figure 1. *Chemical transformations that allow the determination of the constitution of cocaine. See the text for the conclusions that result from the experiments performed (keyed to the encircled numbers). The structures of cocaine, ecgonine and tropinone are shown within the text. The structures of the other compounds are, of course, reported in Hoffmann's book but can also be readily found on the internet.*

The following encircled numbers refer to Figure 1.

① Cocaine was isolated in crystalline form enabling the determination of its constitution.

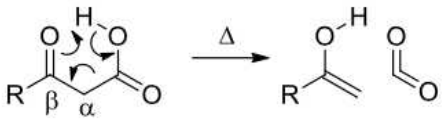
② and ③ Ecgonine is a monohydroxy carboxylic acid and cocaine is a benzoate and a methyl ester.

④ Ecgonine and cocaine have a C-CH_2-CH_2-C subunit.

⑤ The nitrogen in ecgonine and cocaine is in a six-membered ring with the CH_2-CH_2 attached to (at least) one of its nitrogen's α-carbons.

⑥ Decarboxylation indicates the intermediacy of a

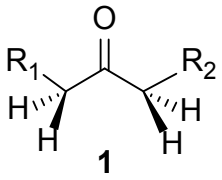
β-keto acid, thus suggesting the position of the alcohol and acid in ecgonine.



⑦ ⑧ ⑨Tropane and all the precursor substances including cocaine are bicyclic amines.

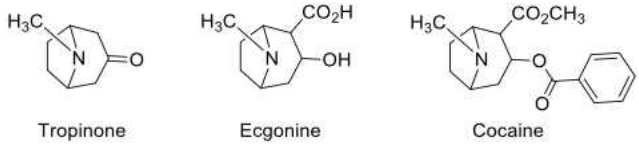
⑩ Ecognine and cocaine have a *N*-CH_3 group.

⑪ ⑫ Tropinone must have the substructure **1** as part of a cycloheptanone substructure.



1

Based on the above considerations, tropinone, ecgonine, and cocaine must have the following structures.



Tropinone Ecgonine Cocaine

Still to be determined are the relative positions of the two esters moieties in cocaine. That is, the above two-dimensional formulations are missing stereo-chemical information. In cocaine, is the methyl ester in position A or B (Figure 2)? And is the benzoate in position X or Y? These questions refer to what is called *relative configuration.* Furthermore, since cocaine is a chiral molecule, which of the two mirror image isomers, i.e., the enantiomers in Figure 2, is the natural product? This refers to what is called *absolute configuration.* These additional structural questions required another 50 years before they were answered. For more details, the reader is pointed to either the chemical literature or, more easily and especially rewarding, Reinhard Hoffmann's book.

Before this essay is concluded, one more issue will be raised. While it took 56 years from the determination of cocaine's constitution (Scheme 1) to the determination of relative configuration cocaine's two substituents (Figure 2), it took only one more year to determine cocaine's absolute configuration (Figure 2-left or Figure 2-right). The reasons for this time-collapsing chronology are worthy of another study in the history of chemistry.

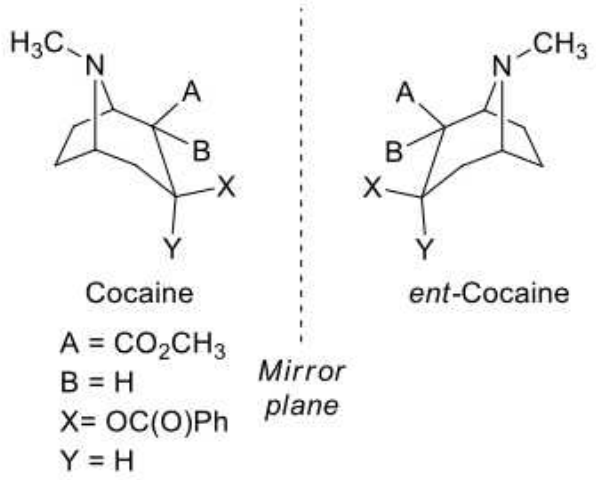


Figure 2. *Configurational issues involving cocaine and its enantiomer.*

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