

Why Natural Products?

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In the fall of 1951 I spent several days in Los Angeles with the eminent physical organic chemist, the late Saul Winstein. At the end of a very stimulating visit, during which we discussed the past, present and future of organic chemistry, he asked me in his typical candid fashion: »Why do you waste your time working on natural products?« I was deeply shocked by his question because I believed that the elucidation of the structure of natural products was the most important objective of organic chemistry, besides being intellectually rewarding.

Rudolf Lukeš, my mentor and friend at the Czech Institute of Technology in Prague, where I studied and later worked for my doctoral thesis, was fascinated by the then seemingly bizarre structures of alkaloids, such as quinine, morphine, and strychnine. Our chemical hero at that time was Robert Robinson whose work on natural products we so much admired. During the following period 1929—1941, when I worked in Prague and Zagreb, my great ambition was to contribute something to this area of research. When I joined Leopold Ružička in 1942, Zürich was considered the Mecca of natural product chemistry. The foundation for that reputation was laid by Richard Willstätter, who was from 1906 to 1912 Professor of Chemistry at the Federal Institute of Technology (ETH). He transferred from Germany to Switzerland the inspiring tradition of Emil Fischer, one of the greatest natural product chemists of all times. When Willstätter's student and coworker Arthur Stoll later became research chemist and industrial manager in Basel he demonstrated how research in the field of natural products could be rewarding for the pharmaceutical industry. At the same time, by their achievements in the field of natural fragrances, hormones and vitamins Richard Kuhn, Leopold Ružička, and Tadeusz Reichstein at the Federal Institute of Technology and Paul Karrer at the University of Zürich contributed not only to pure chemistry but also to the economic prosperity of the chemical industry. Thus, before I met Winstein it never had occurred to me that I was wasting my time by working on natural products but since then I have often asked myself: Why natural products?

The answer was not always the same. *Fons et origo* of the natural product chemistry were pharmacy and medicine and to a lesser extent certain crafts such as dyeing and food processing. The practical value for industries supplying these professions was and still is one of the main sources of motivation for their investigation. In addition to that, before and during the second world war the structure determination of complex natural products, particularly of those possessing interesting biological activity, was considered the most prestigious task because much knowledge, experience, good luck and

also sometimes the touch of a poet was necessary to arrive at correct conclusions. However, soon after the war the tedious and sometimes unreliable chemical methods for structure determination were replaced more and more by physical ones: X-ray analysis and molecular spectroscopy. Together with progress in isolation and identification methods, this development changed dramatically not only the style but also the scope and limits of natural product chemistry. In this process, the structure determination lost somewhat of its high prestige and became in many cases a routine, which allowed one to deal with a great number and variety of compounds. The thrill of it lessened, and several excellent chemists abandoned the field altogether.

Most of them, however, remained faithful to natural compounds and profited from the new methods, whose great advantage was that they could be adapted for working with small samples of material. This made many new sources of natural products available, which either had been not easily accessible or which were present only in very low concentrations. Until this time the term »natural compounds« had been used by and large for secondary metabolites such as terpenoids, flavonoids, alkaloids and related groups of compounds. Important constituents of living matter such as proteins (enzymes), nucleic acids and many others were *de facto* »off limits«, because their structures could not be elucidated by the available methods. This attitude changed first slowly and then faster and faster as new techniques were developed.

The isolation and structural elucidation of the penicillins was a major achievement which strongly enhanced the interest in microbial cultures as sources of natural products. As their extensive investigation was being facilitated by new methods, a great number of microbial metabolites with highly interesting biological properties were discovered and their often unprecedented exotic structures were elucidated. The short reproduction times of microorganisms and their susceptibility to mutations and genetic manipulations made them also favourite tools for biotechnical production and transformation of natural and other products. The techniques developed on microbial cultures were recently adapted for cell and tissue cultures, a development which is certain to play an important role in pure and applied natural product chemistry.

Microbial as well as cell and tissue cultures are also being successfully used for elucidation of biogenesis, surely one of the most interesting common tasks of natural product chemistry and biochemistry.

Of the other sources, one could mention: marine animals, insects, snakes and frogs, and pathological single organs of higher animals. Besides, numerous constituents of highly complex mixtures such as natural fragrances and flavours or fossile materials can be separated and their structures determined.

Every natural product, which has appeared sometime during the 3 billion years of evolution and survived, carries in its structure a message and many of them have a yet unrevealed function. To decipher the message, and to find out their function will remain for a long time one of the most challenging tasks of chemistry.

The impact of all accumulated knowledge about natural compounds on pure and applied chemistry can hardly be overestimated. Let us mention only

a few of them. The imagination and creativity of synthetic chemists was always stimulated either by usefulness, or by unusual structural and stereochemical subtleties. These features mobilized a great army of chemists who devote their knowledge of chemical reactivity, their combinatorial talents and their experimental skill in order to synthesize natural compounds with particularly challenging structures. Other synthetic chemists devote their efforts to improve selective methods, which are often *conditio sine qua non* for obtaining the desired products with acceptable yields. Some of them successfully use »biomimetic« methods in imitation of biogenesis. At the same time chemists with an interest in »prebiotic« chemistry are concentrating their efforts to find out how some of the most important complex natural products were synthesized under prebiotic conditions from simple precursors.

The fundamental concepts of stereochemistry — configuration and conformation — were conceived in the course of studies of carbohydrates, amino acids, terpenoids and related compounds. Carbonium ion chemistry, for many years a favourite of physical organic chemists, was discovered and to a great part investigated with bicyclic terpenes. A further example is the synthesis and use of macrocyclic crown ethers and related complexing agents as selective inophores for which microbial metabolites served as models. Stereoelectronic effects, such as preservation of molecular orbital symmetry and the anomeric effect, were uncovered in the course of studies of natural products. The variety of constitutions and geometry of natural products and their analogues makes them also very suitable substrates for studies of relationship between structure and reactivity. Well known here are the studies of photochemical and other reactions on terpenoids and steroids.

One of the successful contributors to the last mentioned field of research is Professor Mihailo Lj. Mihailović, whose former pupils and collaborators, Professors Lj. Lorenc and M. Gašić, together with Dr. M. Eckert-Maksić, took the responsible task of editing this issue of *Croatica Chemica Acta*. From the very beginning of his scientific career Mihailović has been interested in the dependence of reaction regiospecificity and stereospecificity on structural details of organic compounds. After spending some time in the Laboratory of Organic Chemistry of the Federal Institute of Technology, Zürich, where he worked on natural compounds, he started in Beograd to use the steroids with a variety of known structures for his studies of reactivity. These investigations led to numerous novel steroid derivatives containing 10-membered and recently also 14-membered rings with interesting chemical and biological properties. By these achievements he has demonstrated once more that by studying reactivity of a particular group of natural compounds one can arrive at results of very general interest.