STUDIES IN ORGANIC CHEMISTRY 17

# CHEMISTRY AND BIOTECHNOLOGY OF BIOLOGICALLY ACTIVE NATURAL PRODUCTS

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PROCEEDINGS OF THE SECOND INTERNATIONAL CONFERENCE
BUDAPEST, 15—19 AUGUST 1983

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# PREFACE

A new series of conferences on the Chemistry and Biotechnology of Biologically Active Natural Products was initiated in Varna, Bulgaria. The second conference took place in Budapest, Hungary, 15-19 August, 1983. Connections between the two subjects, chemistry and biotechnology, are becoming increasingly important. It thus seemed an attractive idea to combine them in the framework of one meeting.

Our expectations were well rewarded by the high standard and comprehensive character of the lectures delivered by the twenty-three speakers at the conference. These papers are all included in this proceedings volume and have been arranged in the order they were presented at the meeting. Examples of elegant syntheses and biosyntheses of compounds of different kinds are contained in the lectures by W. Bartmann, I. Tömösközi (prostanoids), J. Rokach (leukotrienes), Ch. Tamm (mould metabolites), S.D. Géro (aminocyclitols), E. Winterfeldt, E. Wenkert, R. Vlahov (alkaloids), L. Kisfaludy (peptides), F. Arcamone (antibiotics), I. Vincze (steroids) and L. Novotny (sesquiterpenoids).

The use of enzymes as agents in asymmetric syntheses was the main subject of the lecture given by M. Schneider. Isolation and structure elucidations were the topics of papers by B. Lindberg (polysaccharides), L. Merlini (perylenequinones), H. Musso (betalain pigments), D.G. Strauss (pigments from microorganisms), J. ApSimon (saponins), I. Popov (monoterpenes), and W. Kraus (compounds from Meliaceae). Real biotechnology was

presented in the lectures delivered by R. Manfredini and E. Pungor.

The talks were followed by lively discussions in the presence of an audience of about 300 scientists. A large number of interesting posters were shown during the week.

The conference was the second in what promises to be a continuing and healthy series of international meetings on the above topics.

We are pleased to have been able to foster the meeting through our efforts and those of our colleagues, whose enthusiasm made the conference a success.

*Cs. Szántay*

# OPENING ADDRESS

by

Dr. rer. nat. WOLFGANG FRITSCHE, C. Chem. FRSC
General Secretary of Gesellschaft Deutscher Chemiker,
Secretary of the Federation of European Chemical Societies (FECS)

*Mr Chairman,*
*Ladies and Gentlemen,*

It is a great honour and pleasure for me to open the "Second International Conference on the Chemistry and Biotechnology of Biologically Active Natural Products" here in this beautiful and charming city of Budapest, and I should like to thank you, Mr. Chairman, and the organizing committee very much indeed, for inviting me and giving me the opportunity to speak on behalf of the Federation of European Chemical Societies at this opening ceremony.

The present organizers have built upon a sound basis when they decided to take over the task of organizing this conference, because the first meeting in Varna, Bulgaria, in September 1981 proved to be an event of a high scientific level, also in retrospect. That conference started the international discussion and the exchange of experience in a field of chemistry that has gained more and more importance in recent years. years.

I am therefore convinced that this second meeting will follow a path shown by the first conference in Varna, and that it will establish a regular series of such conferences leading to a permanent transfer of knowledge.

Under these aspects it was, of course, easy for the Advisory Board of the Federation of European Chemical Societies unanimously to grant an FECS sponsorship to this second conference, as it did to the first one.

In my opening address at the first conference in Varna, I devoted some thoughts to the transfer of science and technology,

which is the major task of Chemical Societies, and I said that this challenge for the Chemical Societies refers not only to the transfer of knowledge among chemists, but also to the information of the general public about the impact and effects of chemical activities, at an adapted and appropriate level.

For both his activity as a professional chemist and his contacts with human society, the chemist most certainly needs a thorough background of scientific knowledge which, at the beginning, is provided by university education, and which must continuously be adapted to the progress of science and the requirements of the time by a continuing education. This can be achieved by in-service training courses, and of course by congresses, symposia and conferences like this one.

However, to provide scientific capability cannot be the ultimate and only goal of university chemical education. The big problems facing mankind, such as overpopulation, depletion of resources, environmental contamination, ecological imbalance, etc., demand an awareness of the contributions which could be made to the solution of these problems by application of the natural sciences. This requires adequate and good professional attitudes with regard to the impact which scientific work may have on these issues and on the human society in general. A good professional attitude requires a readiness to seriously consider safety aspects also. Chemical education for the future, therefore, means not only scientific training, but also the forming of attitudes and awareness. The realization of this may be different in different countries, because education, including education in chemistry, will always constitute a part of the culture and historical development of the educational system of each individual country. It is the task of national Chemical Societies to take care of this aspect of chemical education, too, in close communication with the relevant authorities in their countries. There will be no general recipe for transfer of science education systems from one country to the other. Everybody will, however, benefit from a frank exchange of views and experience, and from mutual assistance. So there is an opening for international communication also in the field

of chemical education, and this communication should by all means be initiated by the Chemical Societies.

Safety in connection with chemical activities either in the laboratory or in an industrial plant has become of increasing importance. The advancement of analytical methods makes us more aware of the presence of manmade chemicals, even in the remotest places of our planet. Of course, the concentrations are very low indeed in most cases. But on the other hand, we all have become cautious, maybe even overcautious, concerning the effects which chemicals may have on the human population and its natural environment.

If there is any hazard involved in dealing with chemicals, then of course, it is the chemist, his co-workers in the institutes, the workmen in chemical plants, and students of chemistry, who are the most endangered persons. On the other hand, it is again the chemist who has not only to care for his own personal security, but who is also responsible for the prevention of risks to others originating from his work. It is therefore absolutely necessary to begin with safety training at the same moment as one starts to work actively with chemicals. This idea is as old as chemistry. Universities have always dealt with safe laboratory practices beginning at the start of the first laboratory course. But the more our knowledge in chemistry, biology, medicine, toxicology increases, the more difficult it becomes even to decide where safety ends and negligence begins. In this field it is also the Chemical Societies which are challenged to establish a rational and fruitful communication on a national and international basis.

To conclude, please, permit me to devote some thoughts to some basic principles which I consider important for international communication, also in the light of communication in chemistry.

International cooperation, in general, should always follow certain major normative concepts which, while respecting the diversity of value systems measured against certain universally recognized moral criteria, would therefore be acceptable to the international community at large. Thus there should be no discrimination in education, in line with the principle

of the equality of all men and all women and of all peoples, as recognized in the Preamble of the Constitution of UNESCO. International cooperation should also contribute to the flow of ideas and information, the exchange of opinions, the checking of theories against experience, the assimilation of the findings of research, and the general advancement of knowledge, all of which we refer to as intellectual action. The activities in the fields of science, culture, education and information should also be aimed at assisting the countries which are the least endowed with resources, to strengthen their educational, scientific or cultural capacities.

These courses of action proceed from a basic principle of international life, according to which a lasting peace is possible only if it is based on respect for dignity, identity and freely expressed will of all nations, and is posited on the establishment of new relations between nations that allow them, each in its own way, to follow a path of development suited to their needs and aspirations. It is in this context that the principle of endogenous development, development in harmony with each people's cultural identity and allowing scope for manifold forms of regional and international solidarity, should acquire a predominant place in the whole concept of international cooperation.

And even though chemistry has no direct political role to play in the family of international organizations, it must help to create the conditions for an equal welfare for the whole world as a prerequisite for a lasting peace among the different nations.

There must be a place for solidarity, for while cultural and scientific indentity and cultural and scientific specificity are fundamental features of our age, another factor must also be taken into account: with modern modes of technology and communication, the world is ceasing to be infinite and is rapidly becoming finite. This *de facto* interdependence of nations and peoples is a major fact of our times of which the simultaneous avilability of information we observe today is a reflection; no people, no nation lives in isolation at present; a problem that arises in one nation is relayed around the world

through the mass media; no people can any longer withdraw into itself or be unaware of the existence of other peoples of the world, or the situation which they live in. We are accordingly witnessing a dual, apparently contradictory trend: on the one hand, a strengthening of cultural identity and, on the other, a growing degree of interdependence, particularly with regard to the achievements of science and technology, among the different nations of the world. This raises the problem of whether such interdependence must of necessity lead to standardization. As I see it, the fact remains that most peoples want to preserve what constitutes their identity at its deepest level, their own culture.

All man's aspirations and needs, including his intellectual and spiritual ones, must be taken into account. However, international development clearly must also enable all peoples to reap the benefits of modern science and technology. It should be made understood that there is no contradiction between that requirement and the promotion of cultural identity. The fact is that neither science nor technology is neutral, they bring in their train modes of organization and patterns of thought which could vitally affect the life of any people that failed to integrate the benefits of modern science and technology into its culture in a purposeful way.

I should like to emphasize that scientists the world over are conscious of the need to place science and technology at the service of all peoples. Unfortunately, science and technology are a privilege enjoyed in a part of the world where the will to contribute to the scientific and technological development of the poorest countries is not always present; but all of us should endeavour to strengthen international scientific cooperation. We do have responsibility for scientific progress and world-wide intellectual cooperation in the domains represented by us.

Scientific and technological development also presupposes the circulation of scientific and technical information, and Chemical Societies and their international organizations should continue to promote the development of the transfer of knowledge in different parts of the world. All developing and in-

dustrialized countries should be given access to the scientific and technical information available in the world, and chemical societies are obliged to provide this communication in as optimal a manner as possible.

On behalf of the Federation of European Chemical Societies I should like to thank the organizing committee under the chairmanship of Professor Szántay very much indeed for preparing such an attractive programme of a high scientific level. I am convinced that this conference will largely contribute to the progress of its special field and of chemistry as a whole. It will also be another contribution to international cooperation in chemistry for the benefit of human society.

Thank you very much for your attention!

# OPENING REMARKS

## THE ROLE OF BIOLOGICALLY ACTIVE NATURAL PRODUCTS IN THE PHARMACEUTICAL INDUSTRY

by

Gy. FEKETE

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*Mr. Chairman,*
*Ladies and Gentlemen,*

The use of drugs for the treatment of illness and physical wounds is as old as mankind. Yet pharmacy as an independent profession and later as a science is only about 300 years old, while the earliest pharmaceutical companies in the present sense were formed in the 19th century only.

From the beginning of his history man has used materials of natural origin, such as medicinal herbs and animal organs, as therapeutic agents. The latter had almost disappeared from the therapeutic arsenal by the 18th century according to the testimony of monographs of that period. It was almost only medicinal mixtures of plant origin that were used until the end of the 19th century, that is for more than 150 years. The rejuvenating self-experiments of Brown-Sequard with use of extracts of calf testicle started a new era of therapy during the last years of the 19th century and have led to an entirely new trend of therapy dominated again by drugs of both plant and animal origin.

An important development in the field characterized the next period: empirical compositions were replaced by products of standard biological activity, this being ascertained by biological titration of raw materials and finished products. The next obvious step was isolation of the active reagents and their production in a pure crystalline form. By the late thirties the most important natural drugs, i.e., digitalis glycosides, ergot alkaloids and most steroidal hormones, were marketed in this form. During the late forties the development of synthetic chemistry made it possible to modify the struc-

tures of the natural compounds. This was a necessary step, since most natural substances, especially the hormonal ones, had a multiple action since they were capable of regulating many specialized functions in the homeostatic mechanism of the whole body, while specific therapy demanded specific drug effects. This is the reason why many of the important natural substances such as epinephrine, serotonin, acetylcholine, natural glucocorticoids and sex hormones and many others failed to become important drugs. At the same time a great number of a new group of natural products, the antibiotics, were discovered and they largely replaced the chemotherapeutic agents produced by organic synthesis. The fifties brought the advent of peptide chemistry making it possible to produce peptide hormones by total synthesis as well. And it is the major development of the present that genetic engineering has permitted the production of molecules, the isolation or synthesis of which had not been realizable on an industrial scale before, such as human insulin, human growth hormone, urokinase, etc.

In the past 100 years it has been the pharmaceutical industry that has served as the engine of these important developments. Today drugs of natural origin in the broader sense fall into five categories.

1) - Products of natural origin and natural sources, such as ergot, vinca and catharanthus alkaloids, morphine, digitalis glycosides, heparin, most of the insulins, gonadotropins, different enzymes, etc.

2) - Natural compounds derived from other cheaper or more readily available natural sources by partial synthesis, such as some natural steroidal compounds as hydrocortisone, testosterone, progesterone, these being synthesized today from diosgenine, solasodine, sitosterol, stigmasterol or hecogenine.

3) - Natural products produced by total synthesis, such as the major part of contraceptive steroids, oxytocin, vasopressin, ACTH peptides, prostanoids, vincamine and most vitamins.

4) - Derivatives of natural substances, such as some contraceptive steroids, the super glucocorticoids, ergot

alkaloid derivatives, semisynthetic digitalis preparations, vinpocetine, rifampicin, prostaglandin derivatives, etc., semi-synthetic penicillins and cephalosporines.

5) - Drugs produced by fermentation, such as most antibiotics, steroids, ergot alkaloids, vitamin B-12, calcium gluconate, just to mention the most important ones.

This list, although it is far from being complete, clearly shows the importance of drugs of natural origin and their derivatives from the viewpoint of present therapy and, consequently, from the aspects of drug research and the pharmaceutical industry. To underline this importance by concrete figures, I should like to mention here that my company, the Chemical Works of Gedeon Richter, has always attached great importance to this group of therapeutic agents and at present about almost 50% of our total output belongs to this group, in spite of the fact that production of antibiotics does not belong to our profile. Figures of the total world market are also very impressive. Sales in this category amount to about US $ 10 billion.

In my remarks I wanted to emphasize briefly the importance of this conference from the viewpoint of drug research and production. I am firmly convinced that the pharmaceutical industry all over the world is keeping an eager eye on the developments in the field of isolation and synthesis of biologically active natural substances and their even more potent and selective derivatives. On behalf of the Hungarian Pharmaceutical Industry, I wish the conference much success from the aspect of both theoretical and practical results and thank you for your attention.

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