

CLOSING ADDRESS BY LORD TODD

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Sixteen years ago to the very month the first International Symposium on Natural Products, under the auspices of the International Union of Pure and Applied Chemistry, was held in Australia. I had the honour to be President of the Symposium but despite that handicap the Symposium was a success - so much so that these Symposia have become a regular biennial feature of the work of I.U.P.A.C. for chemistry. One of the privileges, or should I say, the vices of the elderly, is reminiscence, and I confess that the return of the Symposium to Australasia, a thing I have long looked forward to, has brought back memories of 1960 to me. Perhaps this is the more so because of my sadness at the recent death of Professor L.H. Briggs of Auckland, Bob to his friends, who, as Sir Malcolm Burns reminded us at the Opening Ceremony, did so much to promote natural product chemistry in New Zealand. Bob Briggs occupies a prominent place in my recollections of the Australian meeting. I can still see him on the expedition which a number of us made under Australian Government auspices to New Guinea. Dressed in an aged and derelict pair of khaki shorts with a torn shirt to match and with his slightly bowed legs terminating in a pair of old walking boots, he was always at the head of the column carrying a machete. Every five minutes or so he would dash off into the bush and hack off a piece of bark or some leaves or berries. On these he would immediately perform his first and invariable step in studying a new natural product; he would chew a portion thoughtfully, spit it out and make a few colourful comments on what it was likely to contain. Also prominent in my mind is the enthusiasm of the young Australasian chemists, an enthusiasm which I am delighted to see burns as strongly here in Dunedin this week.

It would be presumptuous of me, as well as tedious, to attempt to summarise or review critically the fine plenary lectures and scientific papers we have had this week and I shall not do so. Rather, I will make some more general remarks arising in part from our proceedings, but which are essentially reflections on the field of natural product chemistry as manifested over the period covered by all ten symposia of this character. In thinking about what I should say, I recalled that in Australia in 1960 our late colleague and my very dear teacher and friend Sir Robert Robinson had the privilege as grand old man of the party to give the closing address in the Great Hall of the University of Sydney. As I, however unworthily, have been cast by the organisers to fulfil that same role here in New Zealand, it seemed appropriate to look at what he said then.

In his remarks Sir Robert surveyed much of the work presented at the Symposium emphasising as a dominant theme the structural elucidation of natural products. One of the four-sections of the Australian meeting was devoted to physical methods, in particular infra-red spectroscopy, optical rotatory dispersion, and X-ray diffraction analysis. Sir Robert expressed some alarm about the growing number and power of these new physical methods from the standpoint of extending experimental organic chemistry. His thesis was that extension of our chemical skills and the depth of our chemical knowledge could be adversely affected if the main weight in structural determination passed to the use of a few physical techniques. He cited the case of indigo as a natural product whose structural elucidation had involved or had led to the development of a whole field of chemistry. Would this have happened, he asked, if it had been possible simply to isolate indigo and read off its structure on a machine?

If such a possibility had existed at the time of Baeyer's work, the answer might well have been no, and Sir Robert's fears would at that time have been fully justified. But our position to-day is very different; we have a vast

background of knowledge and the structural elucidation of a natural product is no longer, or only rarely, an end in itself. To this point I shall return later. While much of our basic knowledge was in the past derived from degradative studies its extension to-day rests primarily, and I believe adequately, on the synthesis of natural products and their analogues and their chemical modification for a variety of purposes. This comes out very clearly from a glance at the main topics discussed in previous Symposia. Apart from the continuing saga of the ever more complex and brilliant work on total synthesis by Woodward, there are many other examples in all nine Symposia and again in this, the 10th; accompanying them we find a variety of contributions on modification or analogue synthesis of steroids antibiotics and other natural products. Surely no one can doubt the contribution such work makes and will continue to make to our general store of chemical knowledge, and not merely in its experimental but also in its theoretical aspects. Witness the origin of the Woodward-Hoffmann rules of orbital symmetry conservation, our growing understanding of stereospecificity and last but not least the revolutionary impact of conformational analysis originated by our President Sir Derek Barton; all these and many other advances stem from work of the types I have been discussing.

My conclusion is then that there need be no fears of the type Sir Robert expressed sixteen years ago. The natural product chemist will take in his stride new techniques as they appear, whether they be aids to structure determination or synthesis. New techniques simply open new vistas and research is able to move forward into areas it could not previously penetrate. There is much to be said for the German saying "Jeder Fortschritt der Wissenschaft ist ein Fortschritt der Technik".

In my Presidential Address at Canberra in 1960 (Pure and Applied Chemistry, 1961 2 359) I used the same German quotation with regard to the growing number of physical techniques of analysis which were being developed. This I did in connection with my main thesis, that natural product studies once confined largely to the study of structure, were moving in the direction of structure in relation to function and that the appearance of these new techniques would accelerate this and would at the same time have the desirable effect of bringing biochemistry and organic chemistry into a closer relationship with one another. To-day, looking back over these sixteen years, I feel that my arguments and predictions have been in general justified by events. Let me quote from that Address given sixteen years ago. On the subject of natural product chemistry whose historical development I had been discussing, I said:

"But what of its significance to-day? Is it still a developing field and will it retain its importance? My own answer to both questions is yes; the changing pattern of natural product chemistry is to be expected, but the importance of the subject remains. I have already suggested that the older type of structural study applied to isolated plant products is no longer a spearhead in the advancement of the science, but this does not mean that it has everywhere lost its importance from a practical standpoint. We have seen in recent years the medical value and industrial stimulus provided by such a natural alkaloid as reserpine, isolated from plant material for long used in oriental folk-medicine. It is likely that still other substances with significant and valuable pharmacological properties remain to be isolated from plant materials, and that, incidentally, clues to some of them may still be found in the folk-medicine of primitive people. In particular, the rich and comparatively uninvestigated flora of South-East Asia and the Australian continent still require careful study, and it is gratifying to see that this is now being undertaken on a collaborative basis following the excellent start already made by Australian chemists. The spectacular success of some antibiotics should not blind us to the possibility that interesting materials may still be found in the higher plants as well as in the fungi and bacteria.

I believe, however, that now and in the future, the real spearhead of the subject will lie in studies closely associated with biological investigations, in studies where questions of structure and function are closely linked. Difficult problems abound, many of them of economic importance, and all fascinating from the scientific standpoint. In the animal kingdom, the arthropoda have been relatively little studied by the chemist, partly because of their small size and the trouble associated with collection of material. But they differ in many ways from other types of animal, and, even from our present scanty knowledge of hormones and their

pigments, it is clear that a rich field of investigation lies waiting here. The whole problem of parasitism in plants and animals also lies open. Already, from investigations with nematodes of the *Heterodera* genus, with which I have myself been concerned, it is clear that the factors which make a parasite specific to one type of host are chemical in nature and, in some cases at least, of relatively low molecular weight. Clarification of such problems in parasitology could be of considerable importance in agriculture and forestry as well as in veterinary and human medicine, and they warrant the most serious attention.

It would be possible to provide many examples of such unexplored or partially explored fields, but I would mention here only the natural macromolecules as a further field - a field which includes as its most interesting members the carbohydrates, proteins and nucleic acids. For these macro-molecular substances are the very stuff of life, and ultimately it is on progress in their chemical study that a real understanding of enzymology, of immuno-chemistry, of virology, and of the chemical basis of heredity will depend. These materials present a tremendous challenge to the organic chemist as well as to the biophysicist. For, without in any sense underestimating the vital importance of physical and physicochemical properties in determining the way in which molecules such as those of the nucleic acids behave in the cell, I believe that the chemist still has his contribution to make if we are to solve the problems of the self-replicating molecule and the information code, which seem to reside in the natural nucleic acids and which in some way controls the synthesis of specific proteins. But work in these fields is difficult, and it will demand the development of still more refined techniques of experimentation and probably the inclusion of others, hitherto more common in the biochemical field. The new techniques necessary will be found - of that I am sure - and, using them, the future natural products chemist will go forward into these new and exciting fields".

Since I wrote that, progress has indeed been made in all these directions. True there has been less in the area of obligate parasitism than I expected and perhaps more in the chemistry of the arthropoda and in the study of marine organisms. But work on carbohydrates, proteins and nucleic acids - the elucidation of the genetic code and the nature and function of enzymes - have come marvellously to the fore. In our Dunedin meetings we have had many examples of this, and I think especially of the brilliant work on sequence determination in nucleic acids and proteins described to us by Dr Sanger and Dr Niall and Professor Battersby's biosynthetic work, part of which he reviewed so brilliantly on Monday in his plenary lecture.

In his opening address, our President Sir Derek Barton, referred briefly to the relation between organic chemistry and molecular biology and to his vision of 100% yield reactions. I am sure he will not mind if I use them as a basis for a few general remarks which touch upon them.

It has always seemed to me that the essential difference between the various branches of science is the state of aggregation (if that be the right word) which they accept as their base-line. Physics operates from the sub-atomic level and probes back to the ultimate particles and energy itself. Chemistry begins at the atom with the protons and electrons involved in the combination of atoms. Biology, as we knew it in the past, took the living cell as its base and did not probe into the chemical composition of the cell constituents. It was inevitable that as time passed and science advanced, people would probe further into the nature of living cells and seek an explanation of their behaviour in molecular terms. One could say that this is the origin of molecular biology; but although the expression is relatively new and only really came to the fore with the development of genetic studies, in the light of our knowledge of D.N.A. it was there already in, for example, the work of Dale on the function of acetylcholine in nervous transmission, half a century ago. Viewed in this way molecular biology is simply an endeavour to explain the phenomena of life in terms of molecular structure and function and not only organic chemistry (although it is necessarily a major component) but most of the natural sciences - with the exception of astronomy and geology - are components. Our own subject of organic chemistry or natural product chemistry if you will, is by its own definition, the chemistry of substances in living matter, so much involved that it cannot set barrier lines on molecular weight or any other basis.

Especially is this true when one comes to consider 100% yield reactions, since to the best of my knowledge none can really be claimed apart from those brought about in living cells through the intervention of enzyme systems involving macromolecules. Surely there can be little doubt that the macromolecular nature of the enzymes has a profound influence on the efficiency, as well as the ease, with which reactions in the living cell proceed. I find it hard to explain the apparent precision and the ordered complexity of life unless it be that by using these huge macromolecules reactants are taken out of normal solution and brought into close proximity with one another under conditions entirely different from and more favourable to interaction than those existing in dilute solution. But, of course, we do not yet know whether in life under these conditions reactions really proceed with 100% efficiency. The efficiency must be very high but it is possible that the scavenging procedures of the cell eliminate unwanted by-products. There is indeed, one theory of the ageing process which postulates exactly this; that errors are made in replication processes and that although most can be eliminated by metabolic scavenging, some are not, and so the cell mechanism over the years slowly becomes inefficient before it ultimately ceases to function and life terminates.

Be that as it may, Sir Derek was right, in my view, to point to the 100% yield reaction as one of the goals of synthesis. Listening to some of the papers given at this Symposium on synthesis, I was struck by the remarkable advances which have been made since 1960. The isolation and characterisation of ever more complex natural products has been matched by a tremendous increase in the power of synthesis. New and highly specific reagents, stereochemical control and more precise control of reaction conditions have all played their part. They have perhaps brought us nearer to that goal of 100% but I feel that to go much further there will have to be big advances in our knowledge of enzymes, and their experimental use, perhaps in modified form, or perhaps merely stabilised. I am confident that these advances will be made by the natural products chemist. This I expect to be one of the consequences of inter alia biosynthetic studies.

In short, I see the outlook for the natural product chemist as bright as ever. It is only sad to think that I am now too old to participate in the fascinating problems that lie ahead. In all countries to-day we hear the cry about the need for "relevance" in research. Just what is meant by "relevance" is not very clear, but if it means that the understanding of life and the practical application of science to the advance of human welfare should be promoted, then the natural product chemist has nothing to fear.