NATURAL PRODUCT CHEMISTRY—RETROSPECT AND PROSPECT

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As a part of this Symposium, with its specialist lectures and scientific communications in which the latest results in natural product research are being reported, it is my task—and a rather difficult one—to attempt a broad review of the field, to consider its development and its present status, and to attempt an estimate of its future. Natural product chemistry is essentially a part of organic chemistry, itself one of the most remarkable of all the sciences, and one which is usually regarded by the layman as one of the most abstruse and remote from everyday life and thought. This view, is, perhaps, based on its content of jargon and its use of abbreviated molecular formulae as a kind of hieroglyphic script. It is hard to believe, however, that a science can properly be described as abstruse which permeates almost every material aspect of modern civilization, which stands as the bridge linking the physical with the biological sciences, and which is perhaps the biggest of the sciences in its factual content and in the number of its adherents. Organic chemistry is, I believe, the most logical of the sciences, and in its history of little more than a hundred and fifty years it has suffered fewer theoretical upsets than other science. It is a remarkable fact that the whole towering edifice of modern organic chemistry rests essentially on three basic concepts propounded in the third quarter of the nineteenth century—the concept of fixed combining power or valence due to Frankland, the Kekulé–Couper theory of the tetravalency of carbon and the capacity of carbon atoms to join together into chains and rings, and the van't Hoff–Le Bel tetrahedral carbon atom which gave us stereochemistry. All of these concepts were purely empirical, but they have stood the test of time and, on them, the whole of the science rests; advances in theory have certainly occurred since they were enunciated, but these advances have been essentially refinements giving more precise meaning to them, and have in no way upset or destroyed their essential validity. I doubt whether the same could be said of any other science.

There have been two definitions of organic chemistry. Historically the first, due to Berzelius, was " the chemistry of substances found in living matter ". The second, commonly ascribed to Gmelin, first appeared about fifty years later, when more was known about the peculiarities of substances found in living matter, and was quite simply " the chemistry of the carbon compounds ". Each of these definitions has some validity, but neither is wholly satisfactory, since the first is too restricted and the second, in certain respects, too general. A very large number of the carbon compounds known today are of purely synthetic origin and do not, as far as we are aware, occur in living matter. But it is undoubtedly true that the study of substances which are found in living organisms has provided most of the major stimuli to the advance of organic chemistry throughout its history, and there is every reason to believe that it will continue to do so. After all, it was Pasteur's work on the tartaric acids that paved the way for the theory of van't Hoff and Le Bel; the anthraquinone dyes stem from the work of Graebe and Liebermann on alizarin from madder root (and let us not forget that Perkin's famous mauve dye resulted from an attempt to synthesize quinine); and work on polymerization and plastic materials goes back to the work of Harries on natural rubber. Many other examples might be quoted: in current organic chemical literature one is struck by the prominence of the ideas associated with conformational analysis, developed notably by Hassel and Barton. It could be argued that this concept goes back to the theoretical work of Hückel on the fused-ring system of the decalins, and Hückel received the stimulus to that work from the studies of Windaus on isomerism among the sterols. The direct study of substances found in living matter or, more briefly, of natural products, is as old as chemistry itself. It has been evident in organic chemistry throughout its history, although it has only become a dominant feature of the science during the present century. Its rise to a position of dominance was relatively sudden, and it is interesting to consider why this was so.

The original impetus to natural product chemistry—and, indeed, the move to divide chemistry into inorganic and organic sections—undoubtedly came from medicine and the use of natural drugs in its practice, and was partly scientific and partly commercial in character. Already in the eighteenth century what we may describe as scientific medicine was under way and drugs, such as extracts of *Digitalis* and *Cinchona* were being used rationally; again in connection with medical work, the animal product cholesterol was isolated and described by Poulletier in 1780. First the pharmacists and then the chemists, actuated by curiosity or by the prospect of financial reward, began to busy themselves with the extraction and purification of natural drugs known to be of value, and to study their chemistry. But this turned out to be far from easy, and indeed the decision to put all such things into a separate section of the science to be called organic chemistry was little more than a confession that the natural products were different from, and much more complicated than, the inorganic substances of the mineral world. One thing soon became clear: the natural products were all compounds of carbon and contained few other elements beyond hydrogen, oxygen, and nitrogen; and until a lot more was known about carbon chemistry, both theoretically and practically, little progress was likely to be made. So it was that the nineteenth century saw relatively little progress in the natural products field, such progress as there was being largely confined to the last two decades of the century. First the general theory of organic chemistry was developed, and then the experimental methods necessary for structural elucidation and synthesis of organic compounds, these latter stemming in part from the development of the organic chemical industry, notably in Germany, towards the end of the nineteenth century. But let us not forget that it was from work aimed at natural products in the shape of colouring matters that the dyestuffs industry developed. Nor should one forget the continuous and often unrewarding effort of the workers in the field of physiological chemistry in the second half of the nineteenth century—work which has provided a base-line for much more recent organic chemical studies, and which also gave birth to the now flourishing science of biochemistry. And here let me note in passing that organic chemistry and biochemistry are complementary, and indeed merge into one another in the natural products field, so that distinction between them is at times rather artificial.

One cannot, of course, put precise dates to changes in scientific patterns, but round about the beginning of the twentieth century natural product chemistry suddenly started to come into the forefront of organic chemistry. One reason for this was, no doubt, the appearance of some scientific giants in the field—Perkin, Willstätter, and Fischer, to mention but three. But there was, I think more to it than that. Organic chemistry had, by that time, progressed to a point where it had the experimental techniques and the background knowledge necessary to ensure real progress in the study of complex natural materials. Furthermore, the rise of the organic chemical industry and the growing outlets for new materials encouraged work on natural materials with the aim of producing synthetic analogues which might at once have their virtues and be free of their defects, just as the synthetic dyes had in many cases proved better than their natural counterparts. Finally, the steady development of scientific medicine and the opening up of tropical colonial territories by the major powers had provided a further stimulus to the search for new natural drugs and their synthetic analogues as well as to the study of bodily components, both normal and pathological. Be that as it may, the fact of the development of natural product chemistry is not in doubt and it became an increasingly prominent feature of organic chemistry during the first twenty-five or thirty years of this century. It was effectively during this period that the broad features of the essential oils were worked out by Perkin, Wallach, and others, that Willstätter's studies on chlorophyll and on the nature of enzymes were carried out, and Emil Fischer made his brilliant investigations into the proteins and carbohydrates and his preliminary foray into the realm of the nucleic acid components. Perkin and his brilliant pupils Thorpe, Simonsen, Haworth and Robinson greatly extended knowledge of terpenes, natural colouring matters, alkaloids and carbohydrates, the schools of Wieland and Windaus forged ahead in the study of steroids and bile acids, while Hans Fischer developed his monumental studies on the porphyrin pigments.

Not all of this work was crowned with success. To quote but two examples, Willstätter's work on chlorophyll and enzymes ran into acute difficulties and Fischer was halted in his protein work after a brilliant start. This was due essentially to imperfections in experimental technique. In natural product work the German saying "Jeder Fortschritt der Wissenschaft ist ein Fortschritt der Technik" applies in very large measure. It is, therefore, convenient at this point to recall how the advances of recent years have been conditioned and made possible by developments in method. The first major advance came undoubtedly through the development of reliable microanalytical methods by Pregl. The effect of Pregl's work was enormous, although it is at times rather overlooked. To be able to cut the amount of a scarce natural material needed for analysis by a factor of about twenty made possible the exploitation of fields hitherto barred to the chemist. But microanalysis was only the first of the big improvements; later came the introduction of chromatography—first by adsorption on alumina, as developed by Kuhn and Brockmann in particular, then partition chromatography on paper, ion-exchange chromatography, and finally vapour or gas-phase chromatography. Alongside these came electrophoretic separation methods and many others which in sum made the exact study of the complex natural macromolecules—the polysaccharides, proteins, and nucleic acids—possible for the first time. Just as great an impact has been made by the physical methods of analysis which have become available to us from the late nineteen-twenties onwards. First came the application of ultra-violet spectroscopy to the study of structure. One of the pioneers in this field I would mention today—Sir Ian Heilbron, a friend of many of us here and a staunch believer in the International Union of Pure and Applied Chemistry, and whose recent death we so greatly regretted. Later came the application of infra-red spectroscopy to which Dr Thompson, who has been discussing it during our Symposium, has made notable contributions; and, even more recently, the new and powerful technique of nuclear magnetic resonance. Again, the development of X-ray and electron diffraction methods in the analysis of crystal structure has been of enormous service to natural product chemistry by providing, in some instances, almost a complete answer to baffling structural problems, as in the brilliant work of Hodgkin on vitamin B_{12}. Finally, the availability of isotopes, and especially radioisotopes, has opened entirely new vistas in the study of such problems as biosynthesis.

Natural product chemistry, like science in general, has tended to advance irregularly on a broad front during this century, and during each phase of its development there were always individual investigators who stood rather apart and who broke new ground, or saw possibilities not apparent to others at the time. For this reason it is difficult, particularly with such recent events, to put precise dates to changes in scientific patterns. But, in broad terms, it seems to me that for about the first twenty-five to thirty years of the century most organic chemists dealing with natural products were preoccupied almost entirely with the structure of compounds, and paid relatively little attention to their function, which formed the main interest of the biochemists who were becoming increasingly prominent. This preoccupation with structure led, of course, to the development of a vast array of experimental methods for the structural study and for the synthesis of molecules, and our catalogue of types occurring in nature increased by leaps and bounds. This process did not, of course, stop in the nineteen-thirties—new methods still came forward and older ones were improved, so that today the organic chemist's methods of synthesis are so powerful that it might almost be said that, macromolecules apart, almost any natural product can in principle be synthesized—and, indeed, this would seem to be emphasized by the successful total synthesis of substances as complex as cholesterol and cortisone, the carotenes, strychnine, chlorophyll, and cozymase. But let us face the fact that, in the past, many people have looked to the natural products merely as suitable materials for exercising chemical ingenuity, rather in the way that one might tackle a difficult crossword puzzle. This kind of approach has doubtless increased our store of factual knowledge, but

I doubt myself whether it will nowadays lead to any major advances in science, however convenient it may remain from the standpoint of producing exercises for Ph.D. students, and whatever its commercial importance. It is certainly not in the van of progress today, and it has been dwindling in importance since about 1930.

It was about this time that a new interest began to appear, slowly at first and later with increasing rapidity—an interest in structure in relation to function among natural products. It is this which has brought organic chemistry much closer to biology than it has ever been before. Equally, of course, it has been the realization that function must increasingly be considered in relation to structure that has brought the biochemists closer to their organic chemical colleagues, to the considerable advantage of both. What brought about this change? In a sense, I believe it originated in the movement of biology, spurred on by biochemical work, away from purely taxonomic and descriptive studies. A major influence was exerted by the work on accessory food factors or vitamins. The study of nutritional problems by Eijkmann, Hopkins, McCollum, and others had reached, by the nineteen-twenties, a point at which it was realized that these mysterious vitamins could actually be isolated as chemical individuals capable of structural investigation and eventual synthesis. The opportunity was seized upon by the chemists, and with it the very similar opportunity presented by the sex hormones. Structures were worked out, and soon synthetic vitamins and, later, hormones became available. But it was inevitable that the chemists who entered this field should find themselves fascinated by the further problems which turned up: why and how do the vitamins and hormones act, and what is the secret of their specificity? And so the advancing front of the subject began to take a definite orientation towards the solution of biological problems.

Now, as I have said, one cannot put precise dates to changes in scientific patterns and, whatever effect the nutritional work on vitamins may have had in triggering off the change, the ground has been in some measure prepared by earlier events in natural product work, and had been in a sense foreshadowed by some of the ideas and interests of a few of the outstanding figures in the field. Of major significance in this respect were the ideas on biogenesis, based on the structural relationships between individual compounds in different groups of natural products. Although this attracted the attention of several workers, the greatest influence was that exerted by Sir Robert Robinson, whose rationalization of structural relations in the alkaloid field in terms of biogenesis from amino-acids, backed by his classical tropinone synthesis carried out at room temperature in dilute solution, had a profound effect on the general thinking of natural product chemists which has lasted to this day. And we should remember that it was through his interest in biogenetic considerations in the field of natural pigments that Sir Robert, in association with Lady Robinson, was drawn in the late 'twenties into genetic studies on varation in flower colour using anthocyanin pigments as his tools—another foretaste of things yet to come.

It would be difficult to exaggerate the importance of biogenetic theories in the development of structural work on natural products—especially the alkaloids, colouring matters, and the terpenoids—but it should be remembered that these theories were essentially expressions of structural relationships and were not based upon any studies of biosynthesis. Biogenesis as used by the chemist is not the same as biosynthesis, and failure to appreciate this led many biologists to pay less attention to biogenetic theories than the latter deserved. Equally, of course, it led some chemists to exaggerate their biochemical significance. The importance of the Robinson tropinone synthesis lay in its demonstration to the chemist and the biochemist that complex molecules could be built up from simple ones, using types of reaction well known to the organic chemist and under the kind of conditions which might well obtain in plants. But it has always seemed to me that the pursuit of " synthesis under physiological conditions ", which it undoubtedly stimulated, was a blind alley so long as it was not coupled closely to studies on biosynthesis. Such studies on biosynthesis were not, until quite recently, really feasible. One recalls, for example, the ingenious but unsuccessful efforts of Raistrick to elucidate biosynthetic processes in fungi. It was only when isotopes began to become available that rapid progress could be made, and we have in recent years seen enormous strides in the elucidation of biosynthetic mechanisms in micro-organisms, plants, and animals. The clarification of the biosynthesis of the terpenoids and steroids by Bloch, Cornforth, and Lynen, is one of the most beautiful pieces of work published in recent years, and it also provides a remarkable vindication of the use of biogenetic theories in considering structural relationships among natural products.

So far, I have given my picture of the development of natural product chemistry. It has, of course, been a very rough picture. It has contained very little detail and many interesting features have been omitted altogether. I have, for example, paid no attention in it to the fascinating attempts to develop a kind of chemical classification of plants according to their content of certain substances and to relate it to botanical classification. Early studies on these lines are found in the classical researches of Baker and Smith on the eucalypts here in Australia, and the investigations of Erdtman on conifer taxonomy provide a modern example of this fascinating type of study. But, despite these omissions, I think it is possible to summarize from my picture the reasons for the great importance of natural product research as a major factor both in the development of organic chemistry and of the organic chemical industry. In the first place, it has presented to chemists a stream of challenging problems, both in degradative and synthetic work; their solution has enormously enriched the range of experimental methods applicable over the whole science. Secondly, the study of natural drugs has, in turn, initiated the search for synthetic materials with similar or better medicinal value; on this has rested in large measure the spectacular development of the pharmaceutical industry. Thirdly, it has given impetus to other areas of organic chemical industry—dyes and plastics, to mention but two. And, finally, its development has brought chemistry closer and closer to biology and has, indeed, opened possible routes to the solution of many of its problems.

But what of its significance today? 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 Australia's 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 their 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 macromolecular substances are the very stuff of life, and ultimately it is on progress in their chemical study that a real understanding of enzymology, of immunochemistry, 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 seems 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 and will continue as in the past to contribute at once to the advancement of science and to the well-being of the human race.