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ORGANIC CHEMISTRY—
A PERSPECTIVE VIEW

*Inaugural Lecture of the Professor of Organic Chemistry
delivered at the University College of Swansea
on December 5, 1972*

by
PROFESSOR A. PELTER, B.Sc., Ph.D.

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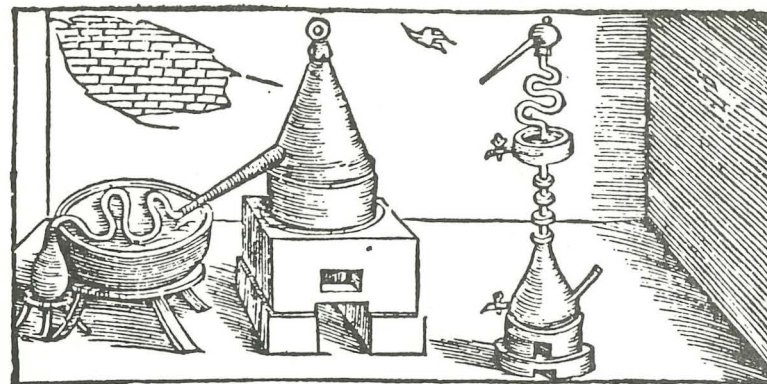
PROFESSOR A. PELTER, B.Sc., Ph.D.

ORGANIC CHEMISTRY—A PERSPECTIVE VIEW

Before giving any account of my own work and aspirations, I have chosen to give a lengthy preamble which deals with organic chemistry in a general way, and attempts to place it in its context with regard both to chemistry and society. I feel that this is particularly necessary in the present climate in which the pure and applied sciences do not receive particularly favourable publicity. Indeed, many young people do not feel that they are "relevant" inasmuch as they do not deal directly with the social and personal aims of human beings. I hope to show, however, that in the case of organic chemistry such a view is particularly mistaken.

As is the case for all sciences, the origins of organic chemistry are lost. It is clear that a large corpus of empirical chemical knowledge was available to many early societies and indeed became the characteristic distinguishing features of those ages known as the bronze and iron. We can feel sure also that very early on vegetable and mineral pigments were used for ornamentation purposes. Indeed the investigation of colouring matter is a continual theme of organic chemistry (the area of which I will later define).

Of course, the potent combination of biochemistry and chemistry must have been utilised for many ages by those interested in the practical aspects of fermentation. On Fig. 1 we can see a late development of this interest—the still developed by the great Arabic chemists, the first to put chemistry on more than a practical footing and the condenser, a European contribution. This is quite a useful piece of apparatus with a reflux head and a take-off not dissimilar to many pieces of modern apparatus. It was not used only for distilling alcohol—a substance introduced by the way during late mediaeval times as a potent prophylactic against plague giving rise to the name 'aqua vita'—but also for the purification of mercury, a substance that played a vital role in alchemical theory. When I look at and taste one product of such a



Still with *canale serpentium* or *serpentes* condensing tube. From V. Biringuccio, *Pirotechnia*, Venice, 1558 (1st edn. 1540).

Fig. 1

biochemical-chemical combination, a delightful bottle of white wine, it would seem that the process that produced it must be taken as having a civilising influence. On the other hand (Fig. 2), we see a different viewpoint taken by Hogarth of the effects of strong liquor. Here are portrayed all the degradations and humiliations open to people who cannot control their intake of this organic chemical. Obviously, the truth of the matter must lie between the extremes, but here already we have an example of the profound interactions between the products of organic chemistry and society and a rather mild illustration of the dilemmas presented by this science.

In common with other sciences, the rate of output of products is rising. In the case of organic chemistry, the rise is very rapid, and hence the number of potent chemicals produced must be expected to rise. I use the word "potent" to mean "physiologically active" and possibly may narrow this even further to mean those compounds that have a measurable effect on human beings. This is of course the nub of the matter—the products of organic chemistry do not only affect us indirectly by affecting our environment, but can affect us

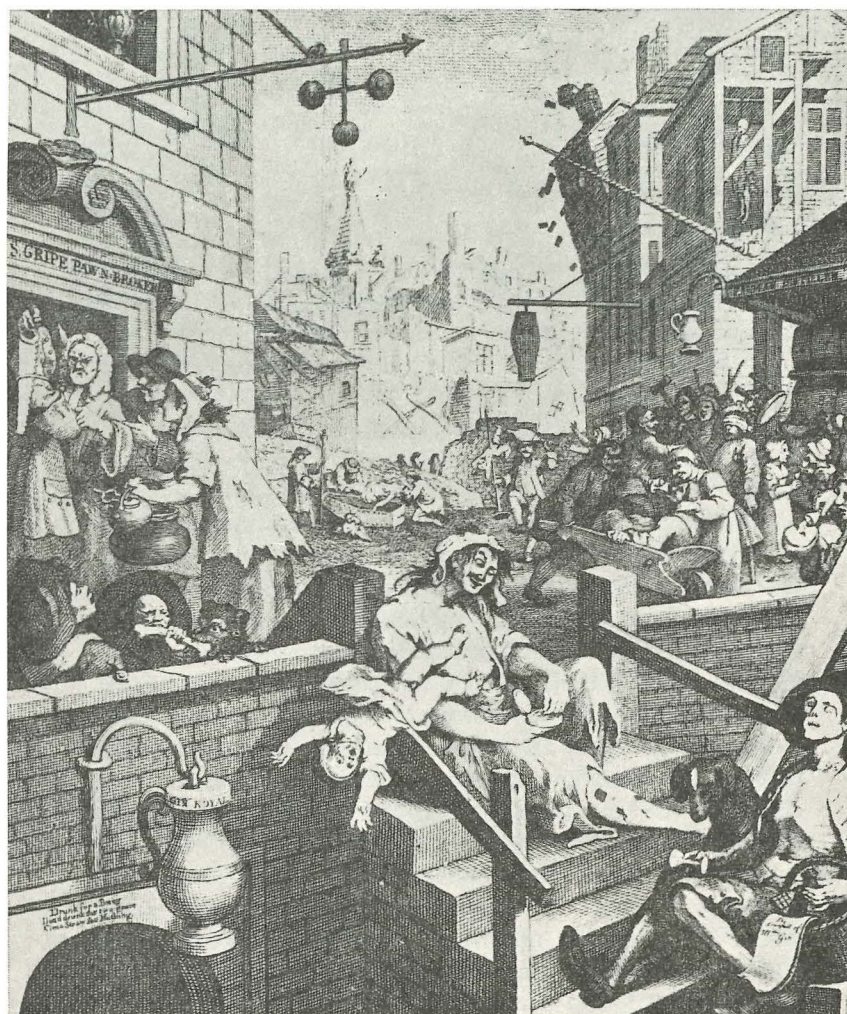


Fig. 2

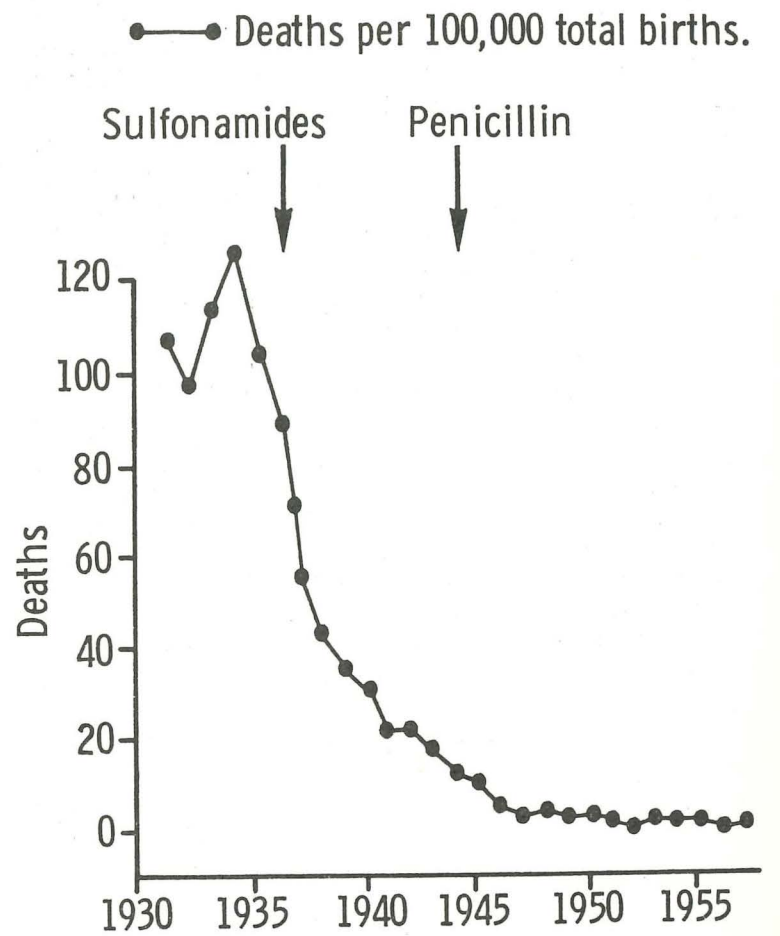
profoundly by a direct, primary action. From this arise the many problems and hopes on which I will touch.

Throughout its history, chemistry as a whole has always interacted with medicine, this being particularly true of organic chemistry. Nevertheless, due to the relatively late development of a unifying theory of chemistry, and particularly of organic chemistry, the medical situation late last century and the early part of this may be summed up by a quotation from "Buddenbrooks" by Thomas Mann. "As for treatment, preparations of iodine, potash, quinine, and antipyrin are indicated—with a diet as light and nourishing as possible, for the patient's stomach and bowels are profoundly attacked by the disease. He will treat the consuming fever by means of frequent baths into which the patient will often be put every three hours, day and night, cooling them gradually from the foot end of the tub and always after each bath administering them something stimulating like brandy or champagne.

But all these remedies he uses entirely at random, in the hope that they may be of some use in the case ; ignorant whether any one will have the slightest effect."

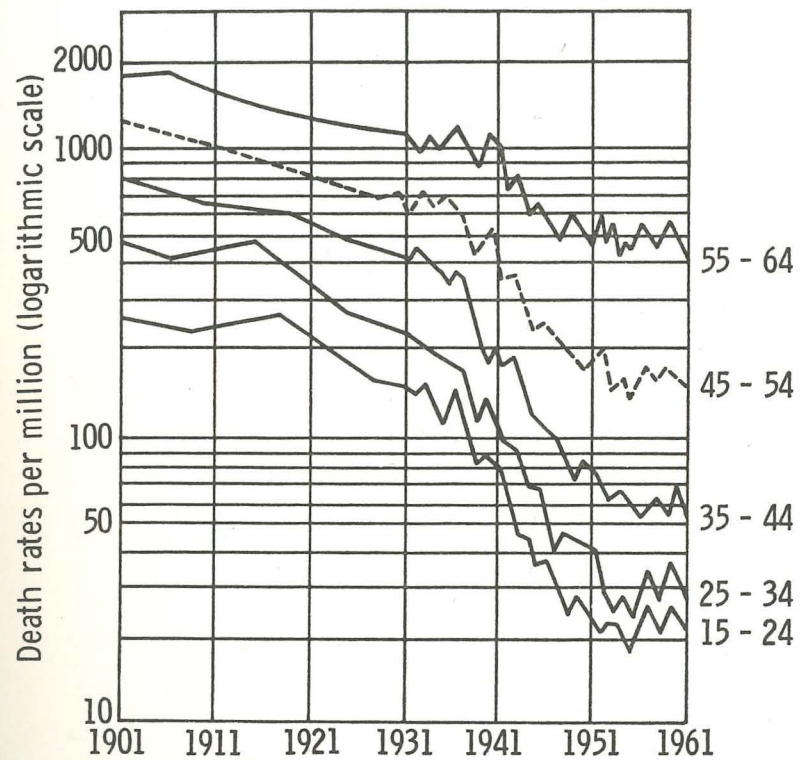
The hopelessness implicit in the passage with regard to the possibilities of a cure is characteristic of all previous generations, but completely at odds with our own feelings on the matter. Indeed we feel bewildered and resentful if a disease does not respond to one or other of the numerous treatments available. Nevertheless, the first effective treatment for bacterial diseases was only introduced in the early '30s as a bi-product of the dyestuffs industry. The situation at the time was one of pessimism with regard to chemotherapeutic agents and this undoubtedly accounts for the lack of interest shown in Fleming's announcement of penicillin in 1929. Only when it was realised that a systemic chemotherapy of diseases of bacterial origin was possible, were the antibiotics reinvestigated.

The dramatic effects can be seen in Figures 3 and 4. Immediately after the introduction of the sulphonamides in 1935, the death rate from puerperal fever due to haemolytic streptococcus fell enormously—this being a



Infection During Childbirth and Puerperium.

Fig. 3



Standardised Death Rates from Pneumonia in
England and Wales.

Fig. 4

condition that had not responded previously to immunotherapy and hygienic methods. Again with pneumonia, we can see that with the introduction of sulphapyridine in 1938, there was a saving of life which was particularly noticeable in the younger age groups. It has been calculated that 350,000 people now alive in this country alone would have died from this one disease if the sulphonamides had not been discovered. Nor must we only consider our own country—the introduction of effective anti-malarial drugs and agents to control sleeping sickness, trypanosomiasis has released millions of people not just from death, but also from the debilitation that is the companion of endemic disease.

The overall change in the picture is quite astounding in such a small space of time and it must be remembered that the drugs stem directly from the efforts of organic chemists. I think that we would generally agree that the preservation of human life is a worthy project to which we are morally committed. However, the increase in the number of effective therapeutic reagents has undoubtedly been a major cause of the great increase in population which has brought with it such enormous and obvious problems. Indeed there may be subtler problems to do with the make-up of the populations which should also give rise to anxiety. Here once again, but on a vaster scale, we see the usual dilemma facing organic chemists. We are, for all the right reasons, replacing one problem with another which may be even more intractable. It is worth mentioning that together with the invention of drugs went the development of insecticides. I do not have time to discuss these in detail, but it is true that a price has had to be paid for each advance. Contamination by, say, DDT is something we find intolerable. However, we must beware of the accusation that we, relatively healthy and prosperous, are selfishly thinking of ourselves alone. To poorer tropical countries, the use of DDT may well be a necessity and may greatly increase the life expectancy of the indigeneous populations. Thus the life expectancy of an inhabitant of Ceylon has doubled since

the great DDT campaigns of the '40s. To them the pollution that accompanies its use may seem a minor matter and our deep concern only a self-indulgence. The answer must be either the development by organic chemists of new efficacious compounds without the drawbacks of the current products, or else the development of non-chemical methods of control which neither lead to pollution problems nor upset the natural balance in a disastrous fashion.

There are indeed an ever-increasing number of points at which organic chemistry makes contact with the lives of us all. A more recent example is the production of oral contraceptives. I find this a particularly interesting story as it shows the deep interaction of academic and industrial knowledge which has been used so profitably in the U.S. The interaction was such that when a decision was made to expand research on this topic, Professor Djerassi took leave of absence from his University to act as vice-president in charge of research. My own Professor at Manchester, Arthur Birch, made great contributions to the synthetic methods used and Professor Sondheimer, now at University College, London, was employed by Syntex. The collaboration was fruitful (if that is the word) and a possible solution to population growth is presented to us. At least we can say that the combination of chemotherapy and controlled birth presents a humane alternative solution to the problem of human population when compared with the ancient one of disease and famine. Moreover, the population resulting is a healthy, energetic one rather than a sick and listless mass. Once again, however, the effect of the organic chemist on society is more profound than anticipated. It is quite clear that the introduction of these chemicals affects our society at all levels. The psychological effects of intercourse without the necessity of childbirth have yet to be plumbed, but it is already safe to say that the status and outlook of women has been profoundly affected and many of the basic assumptions of our civilisation will therefore be called into question. It may be that these

chemicals will have more effect on social mores than all the philosophical tracts produced in the last century.

I have used these few examples to show the direct interaction of organic chemistry with society. Of course there are other more light-hearted situations. The fact that we can choose among a wide variety of colours for our clothes creates a pleasant psychological environment in which to swim. It is indeed gratifying when walking on the campus here on a summer's day to realise that the bright colours worn by students of both sexes originate from the knowledge of the spectroscopic properties of organic chemicals and the know-how of the synthetic chemist. Nor is the creation of a genial atmosphere unimportant to us all. And, indeed, the very materials we use, the cottons, wools, plastics, synthetic fibres, etc. are organic chemicals.

We must consider seriously the future impact of this science on us all. The creation of potent drugs with intense psychic effects and possible medical use creates obvious problems. The elucidation of the structure of DNA, the genetic material, together with the breaking of the genetic code provides interesting food for thought. In the last two or three years, organic chemists have devised means for producing simple analogues of DNA in the laboratory and work is proceeding apace. The possible production of artificial foodstuffs or the modification of existing materials is another basic topic. It is clear that the direct effect on all of us of organic chemistry is only beginning and the implications of future developments will have to be seriously considered by people qualified to judge—a very good reason for training as many young people as possible in the potentialities of this science.

What then is the definition of organic chemistry? It is of course only a branch of the great science of chemistry. This very statement is an interesting one. Last century the chemist Wöhler carried out the experiment of heating ammonium isocyanate (Fig. 5). An interesting rearrangement occurred and urea resulted. Urea is a



Ammonium isocyanate

Urea

Fig. 5

compound undoubtedly characteristic of many living systems whereas ammonium isocyanate is unequivocally derived from non-living inorganic systems. This classic experiment, for some reason much overlooked by science historians, indicated the unity of the chemistry of living and non-living matter and was the basis for as important an advance in human thinking as the later evolution theory. Above all, it ended for ever the vitalistic theories that had pervaded scientific thought throughout the ages. Like Darwin, Wöhler was worried about the implications of such a discovery and kept it to himself for many years before being prevailed on to release it to the scientific world. It was particularly important in this case as the known chemistry of organic matter did not fit in with the then evolving theories of chemistry, and the cleavage had seemed to give a foundation for the old distinctions.

In Figure 6 we see a list of the elements arranged in such a way that similar types of element are close together, and more exactly those with similar electronic configurations form easily recognised groups. Chemistry deals with the properties of these elements, their methods of combining and the properties of the compounds formed by such combinations. It is a unique science with an enormous range which forms a bridge between physical and biological studies. At Swansea, for example, we have people engaged on theoretical studies of quantum mechanical interactions, others studying the ways that molecules interact in the gas, liquid, or solid phase. By this I mean the ways they line up to react, the energetics and timing of the interactions, the number of molecules involved in the collisions and the results in terms of bond-making and

ATOMIC NUMBER		SYMBOL FOR ELEMENT		OUTER ELECTRON	
SHORT PERIODS					
I	1	H	1s		
II	4	Be	2s		
III	5	B	2p		
IV	6	C	2p		
	3	Li	2s		
	4	Be	2s		
	5	B	2p		
	6	C	2p		
	11	Na	3s		
	12	Mg	3s		
	13	Al	3p		
	14	Si	3p		
LONG PERIODS					
	19	K	4s		
	20	Ca	4s		
	21	Sc	4s		
	22	Ti	4s		
	23	V	4s		
	24	Cr	4s		
	25	Mn	4s		
	26	Fe	4s		
	27	Co	4s		
	28	Ni	4s		
	29	Cu	4s		
	30	Zn	4s		
	31	Ga	4s		
	32	Ge	4s		
	33	As	4p		
	34	Se	4p		
	35	Br	4p		
	36	Kr	4p		
	37	Rb	5s		
	38	Sr	5s		
	39	Y	5s		
	40	Zr	5s		
	41	Nb	5s		
	42	Mo	5s		
	43	Tc	5s		
	44	Ru	5s		
	45	Rh	5s		
	46	Pd	5s		
	47	Ag	5s		
	48	Cd	5s		
	49	In	5p		
	50	Sn	5p		
	51	Sb	5p		
	52	Te	5p		
	53	I	5p		
	54	Xe	5p		
	55	Cs	6s		
	56	Ba	6s		
	57*	La	6s		
	57*	Hf	6s		
	73	Ta	6s		
	74	W	6s		
	75	Re	6s		
	76	Os	6s		
	77	Ir	6s		
	78	Pt	6s		
	79	Au	6s		
	80	Hg	6s		
	81	Tl	6p		
	82	Pb	6p		
	83	Bi	6p		
	84	Po	6p		
	85	At	6p		
	86	Rn	6p		
	87	Fr	7s		
	88	Ra	7s		
	89	Ac	7s		
	90	Th	7s		
	91	Pa	7s		
	92	U	7s		
RARE EARTHS					
	58	Ce	4f		
	59	Pr	4f		
	60	Nd	4f		
	61	Pm	4f		
	62	Sm	4f		
	63	Eu	4f		
	64	Gd	4f		
	65	Tb	4f		
	66	Dy	4f		
	67	Ho	4f		
	68	Er	4f		
	69	Tm	4f		
	70	Yb	4f		
	71	Lu	4f		

The periodic classification of elements

Fig. 6

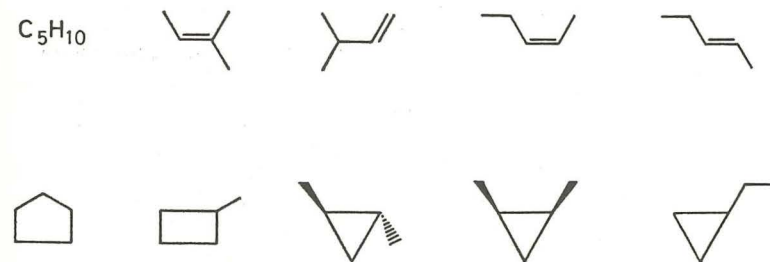
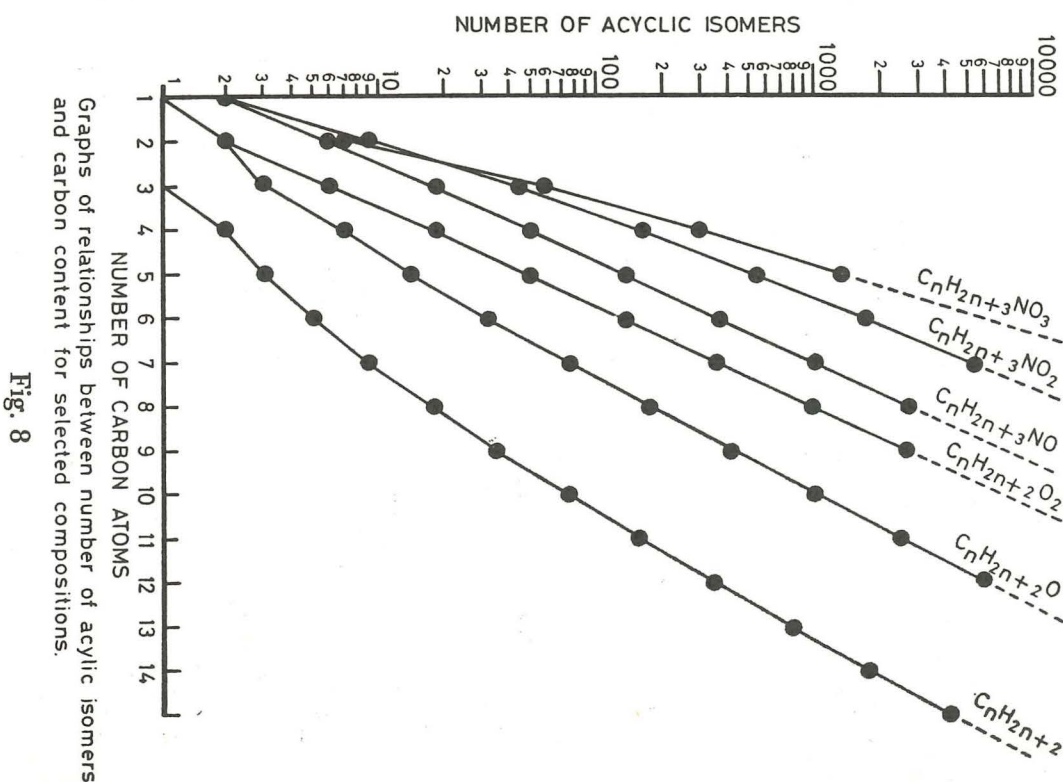


Fig. 7

breaking. Advanced methods of analysis, of interest theoretically and practically, for example to try to trace food chains in the oceans, are studied. Other people are looking at new synthetic reagents and yet others are attempting to produce small proteins by new methods. Attempts to set up crude chemical systems that imitate aspects of living ones are well in hand.

With this breadth of subject, it is natural that some divisions based both on history and teaching necessities are set up, although the boundaries are happily rather fuzzy. The accepted divisions are Physical, Inorganic, and Organic, whilst more recently Biochemistry dealing specifically with living systems has taken its place as a separate discipline. A physical chemist will attempt to reduce a complex system to its simplest terms and to approximate in mathematical-physical symbols to the processes going on. He will derive principles fundamental to the other branches of the science. Organic chemistry simply studies the chemistry of essentially one element, carbon, in combination with a rather small range of other elements, and inorganic chemistry the rest. This makes organic chemistry seem a rather restricted science, but if one turns to Chemical Abstracts, a typical formula index (1969) lists references to organic compounds taking 1118 pages and to the rest 67 pages. In fact the majority of known compounds are organic due to the ability of carbon to bond with itself a seemingly infinite number of times. A simple formula, C_5H_{10} , can represent many compounds (fig. 7). Figures 8 and 9 show a rough



14

The Number of Aliphatic Isomers of $C_8H_{16}O_2$ Separated by Functional Groups

No.	Functional group name	No. of isomers of $C_8H_{16}O_2$	Contained subgraph(s)
1	Acid	39	$-\text{COOH}$
2	Ester	105	$-\text{COO}-$
3	Keto ether and aldehyde ether	329	$\succ \text{COC} \leftarrow$ and $-\text{CO}-$
4	Hydroxy ketone and hydroxyaldehyde	458	$\succ \text{COH}$ and $\succ \text{CCO}-$
5	Diether (excluding enol ether)	183	$(\succ \text{COC} \leftarrow)_2$
6	Hydroxy ether	783	$\succ \text{COC} \leftarrow$ and $\succ \text{COH}$
7	Enol and ether	305	$\succ \text{COC} \leftarrow$ and $\succ \text{C}=\overset{\text{OH}}{\text{C}}$
8	Hydroxy enol ether	497	$\succ \text{COH}$ and $\succ \text{C}=\overset{\text{COH}}{\text{C}} \leftarrow$
9	Unconjugated acetal	102	$\begin{array}{c} \text{OC} \leftarrow \\ \\ \succ \text{CC} \\ \\ \text{OC} \leftarrow \\ \\ \text{OC} \leftarrow \end{array}$
10	Conjugated acetal	46	$\begin{array}{c} \text{OC} \leftarrow \\ \\ \succ \text{CC} \\ \\ \text{OC}=\text{C} \leftarrow \end{array}$
11	Acyloin enol ether	48	$\succ \text{COC}=\text{COC} \leftarrow$
12	<i>gem</i> -Diol	262	$\begin{array}{c} \text{OH} \\ \\ \succ \text{CC} \\ \\ \text{OH} \end{array}$
13	Diol (excluding <i>gem</i> -diol and enol)	32	$(\succ \text{CCOH})_2$
14	Unconjugated peroxide	197	$\succ \text{COOC} \leftarrow$
15	Unconjugated hydroperoxide	306	$\succ \text{COOH}$

Fig. 9

representation of number of compounds versus composition, using severe selection rules and simple compositions. The scale is logarithmic and we have proceeded to no more than C_{14} . You can see that the variety of compounds is simply enormous, and when we realise that molecules associated with life may be of great bulk, it is easy to see that the complexity required is available. Unfortunately, I cannot here go into the factors that give carbon its unique properties.

The differences of structure I have mentioned are primary differences and there are many others. For example, a compound with one primary structure may fold up in many different ways to give several secondary structures, which in turn may associate with each other in various ways to give ternary structures. Such points are not academic, but vital for the structure of proteins and DNA (Fig. 10). A molecule coiled in one way may have quite different properties from a molecule coiled in another and hence we must not only know the way the atoms are joined but which one of the innumerable possible conformations open to the molecule is in fact the one adopted in a particular environment. Of course, a change of environment will alter the status quo. Our function is to first establish such structures, understand the principles underlying their mode of action, and then attempt to produce in the laboratory simplified molecules containing the necessary key points so that reactions may be efficiently carried out.

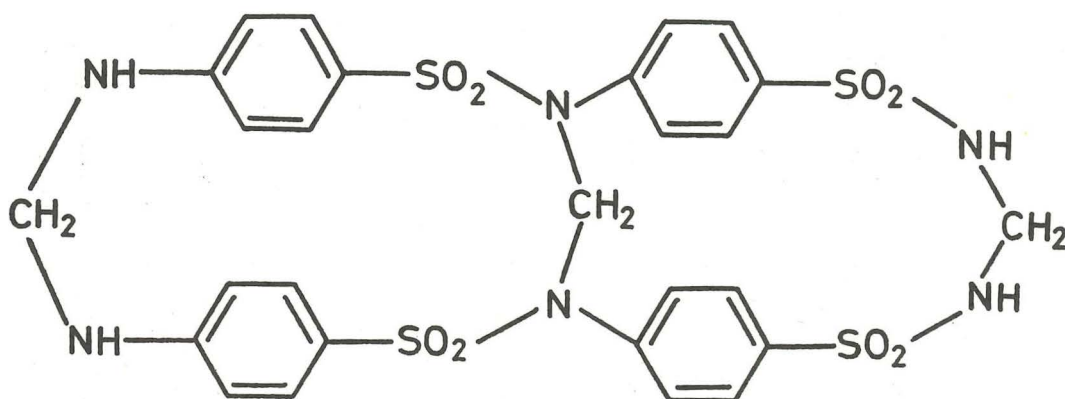
One further point is that to describe our work we cannot work only in the mathematical symbols used by the purely physical sciences, though we do use these in the appropriate circumstances. We have to describe complex molecules in three-dimensions and also their transformations. We cannot use words alone—this is far too cumbersome as you see (fig. 11). You will note that this highly symmetrical molecule has a rather fearsome name. You will not know that this is a simplified system and the author was quite delighted to have evolved such a simple name. Obviously we cannot talk and be understood in



Polypeptide chain in carboxypeptidase A. The Zn^{2+} ion at the active site is near the centre of this drawing, and the three ligands to the Zn^{2+} from the protein are shown as arrows from α -carbons of His-69, Glu-72, and His-196. The α -carbons are shown as dots, and the peptide units as line segments

Fig. 10

words alone. Hence a set of symbols have been evolved which represent transformations of molecules in the same way as a mathematician represents the transformation of functions. On the next figure (12), a synthetic sequence is described, each step being an exercise in organic logic. There are innumerable ways of going from starting material to final product and some will be clumsy and others will be elegant. In our case, the difference between an ugly and elegant process is spelt out in terms of worker time and materials and translated into industrial terms may mean the difference between a viable and non-viable synthesis. Thus theory and practise are combined and can to some extent be costed,



2, 8, 11, 15-Tetra-*p*-benza-3, 7, 10, 16-tetrathia-1, 4, 6, 9, 12, 14-hexaazabicyclo-[7, 7, 1]-heptadecaphane-3, 3, 7, 7, 10, 10, 16, 16-octaoxide.

"A very simple and concise name from which the structural formula can readily be reproduced once the rules are understood".

Fig. 11

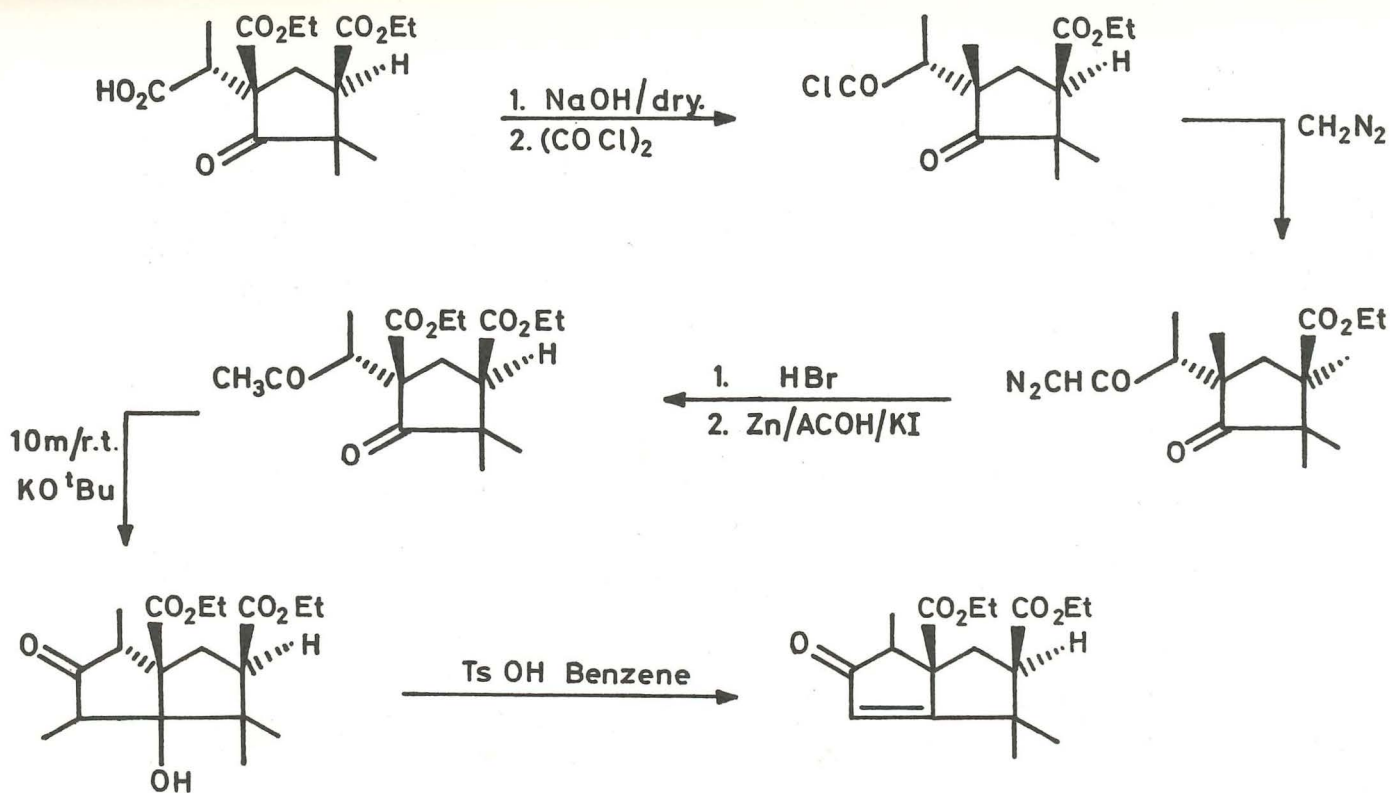


Fig. 12

exercises which we feel make a chemical training a very generally educative one.

Turning back to a synthetic sequence—very many transformations which we would like to carry out cannot be done directly because reagents or catalysts which can effect the change are not available. It is a prime aim of organic chemistry to develop as many useful reagents as possible and this is one of the purposes of my own work. For many reasons attention has focussed on derivatives of boron. Organic derivatives of boron are stable thermodynamically, that is they show no tendency to break up into their elements at room temperature and pressure, but are very reactive. Under nitrogen they are stable but in air, as you can see, they are spontaneously inflammable. They were first developed and studied by Frankland in the late 1860's at Manchester, in order to settle what was then an esoteric and fundamental argument regarding the existence of organic radicals. In view of the nature of these compounds and the primitive equipment at his disposal, it is quite amazing that Frankland and his laboratory survived at all. When the Chemistry Department at Manchester moved 8 years ago, some young lecturers decided to open one of various vials of colourless liquid left by Frankland. This was labelled zinc diethyl, a molecule of some industrial importance now, and to their profound astonishment, that was exactly the contents—beautifully sealed in vacuum and surviving after all those years! The boranes came into prominence during and after the last war, and in the U.S., Professor H. C. Brown developed their chemistry, so that now they are among the most useful of all reagents. One example of their use is shown (fig. 13)—boron has the ability to draw together the loose ends of organic molecules. If the boron could then be displaced without upsetting the cyclic structure we would have a new way of setting up cyclic systems—such systems being extremely important. We have succeeded in developing procedures for carrying out such unique transformations under mild conditions—processes graphically described as “stitching with boron

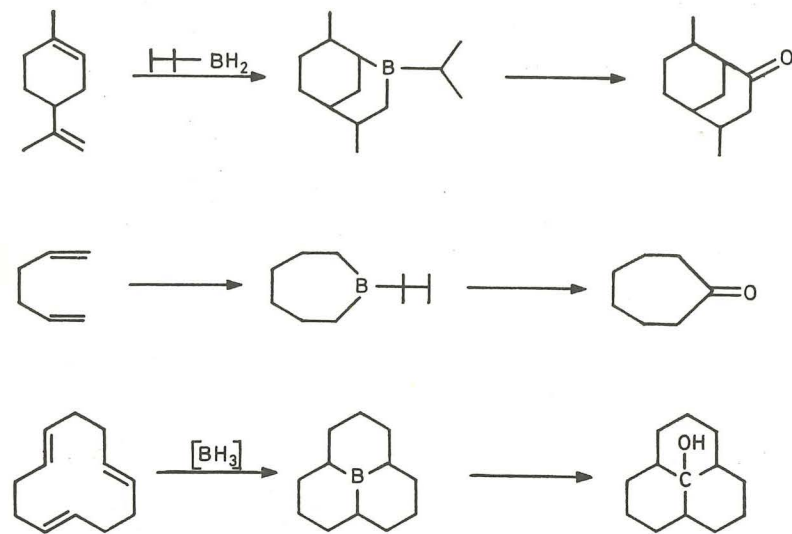
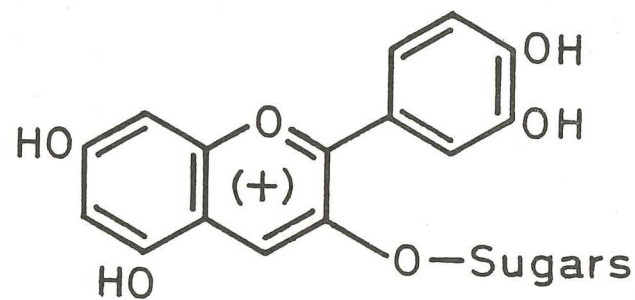


Fig. 13

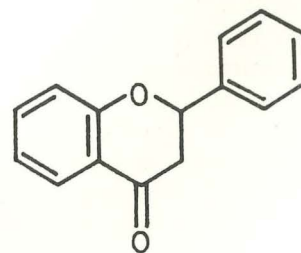


Anthocyanins

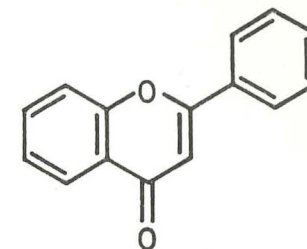
Fig. 14

and rivetting with carbon". This kind of advance is of importance both practically in that we can now carry through synthetic pathways previously unthinkable and also because the reactions concerned, which I will not detail, are themselves intrinsically interesting. Moreover, recently the first use of borane reagents in a synthesis of industrial and general importance has been published. Here we see the full, and quite normal cycle of an investigation initiated for basic scientific reasons leading eventually to technical processes of use to society.

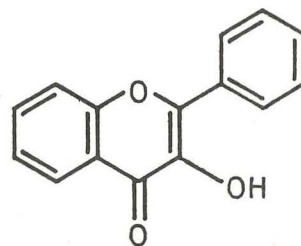
Another line of work which we are pursuing started many years ago with an interest in the colours of flowers. People have always been concerned with the incredible variety of such colours and it was something of a shock to find that nearly all of them were produced by chemicals, known as anthocyanins, all with the same basic system (fig. 14). Variations of substitution on the system, together with variations of pH across petals account for the different colours. When this was established it was realised that these compounds were examples of a general class named flavonoids (fig. 15). Here we see a few examples of such compounds, which are made by *all* plants. It is typical of the economy of nature that the same basic system will be put to a large variety of uses. Another example is that some bases, the pteridines, typical of genetic material were first characterised as the colouring matter of butterflies wings. With so many variations on the flavonoid skeleton, there were naturally very many hypotheses regarding the processes for making and interconverting them in plants. Unfortunately, each of these was a rather special case—indeed for some compounds without precedent. It occurred to me some years ago that we could invoke one process, that called phenolic oxidation, to explain the origin of all these compounds. Moreover, this process is used exclusively to build up that most characteristic molecule of woody plants, the polymer lignin. This is one of nature's bulk products and it is most unfortunate that due to its complex nature we cannot find an economic use for it. I felt that



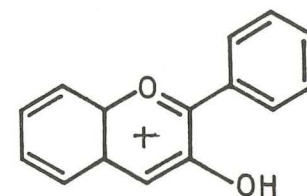
Flavanone



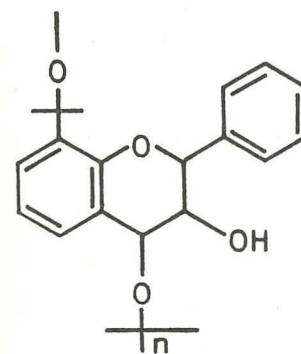
Flavone



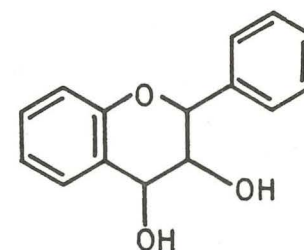
Flavonol



Anthocyanidin



Tannin



Flavan-3,4-Diol

Fig. 15

the plant could merely deflect its lignin biosynthetic machinery slightly to build up the flavonoids it required, once more economising on the number of processes needed for continued existence.

I stress that this was, and remains, a hypothesis. However, it was a greatly unifying one, as well as being satisfying, and set in train many biochemical experiments, nearly all of which gave results which are completely compatible with our theory. We set out to provide a chemical and enzymic background for the biological investigation because some of the reactions we required were very unusual. This has been a most interesting investigation in which so far we have not only achieved some of our original aims but have also been deflected into fundamental investigations of phenolic oxidations as well as initiating a new line, backed by the A.R.C., on the interactions of phenols and protein. This latter assumes increasing importance as protein derived from plants becomes more useful as foodstuff. Eventually, we hope to set up systems that genuinely mimic the enzymic reactions but this is yet some way off. Incidentally, very many other compounds are produced by phenolic oxidation processes, in particular many alkaloids of medical significance.

I have not dwelt at length on my own research, but have simply tried to place it in context in organic chemistry and in turn to give a perspective view of that science in a social framework. This may serve to illustrate both the intellectual fascination of organic chemistry and its meaningful role in our society. I feel sure that the Department here will continue to play a full part in all aspects of new developments.

Acknowledgements

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