Further Perspectives in Organic Chemistry
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Further Perspectives in Organic Chemistry

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Chairman’s opening remarks

G. W. KENNER

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Although this symposium commemorates Sir Robert Robinson and his researches, I shall not give a biographical introduction in view of the splendid memoir by Lord Todd and Sir John Cornforth (1976) and Sir Robert’s own Memoirs of a Minor Prophet. Nevertheless I cannot resist mentioning his connection with Liverpool, where he occupied the newly created Heath Harrison Chair of Organic Chemistry from 1915 to 1920. It was in this period that he achieved his synthesis of tropinone. Our institute is named after him, and the photograph, which he gave us, is a constant, salutary reminder of the standard expected from the Robert Robinson Laboratories.

The title of this symposium—Further Perspectives in Organic Chemistry—was a stroke of inspiration by Professor Battersby, alluding to the famous Perspectives in Organic Chemistry, which Lord Todd edited (1956) in commemoration of Sir Robert’s 70th birthday. The money raised by the sale of that book was used to establish the Robert Robinson Lectureship of the Chemical Society. I am delighted that six of the contributors to the earlier printed symposium are at this meeting and also that we have a ‘full house’ of Robert Robinson Lecturers.

The stimulus to hold this symposium arose partly from my concern about the fragmentation of organic chemistry through the formation of specialized groups, dealing with nucleotides, carbohydrates, reaction mechanisms and so forth. In themselves these groups are most useful to the specialists concerned, but this development seems to me to be contrary to Sir Robert’s outlook: he was interested in so many things; for instance, Todd & Cornforth’s biographical memoir mentions 11 different areas of work. His contributions to the development and application of electronic theory were comparable in importance to his contributions to synthesis. By splitting into groups, we may be in danger of missing the unity of organic chemistry. I hope that this symposium may counter that danger to some extent.
The topics in this symposium do not represent accurately in emphasis Sir Robert's own work. In particular we shall lay greater emphasis on biosynthesis and less on synthesis; that is not inappropriate, because his speculations about biosynthesis set out in the Weizmann Lectures (delivered 1953, published 1955) were so fruitful and stimulating. Structural analysis by classical chemical degradation is, of course, missing, and there must be some regret over the loss of this source of new reactions, despite the enormous advantages conferred by spectroscopic and crystallographic methods. I believe that the papers to be presented reflect the interests which he would have had in the current era of organic chemistry.

References

ROBINSON, SIR ROBERT (1955) *The Structural Relations of Natural Products*, Oxford University Press, London
Introduction

LORD TODD

Christ's College, Cambridge

This symposium had its origins in some discussions Professor Kenner had with me and subsequently with the late Sir David Martin. Professor Kenner reminded me that it is now 21 years since I produced *Perspectives in Organic Chemistry* to mark Sir Robert Robinson's 70th birthday. *Perspectives* contained a series of essays by pupils and friends of Sir Robert on the current position in a variety of fields, and Professor Kenner suggested that now might be a proper time to look at some of these fields afresh by bringing together not only Sir Robert's associates but also younger workers for informal discussions. The outcome of these early talks and especially of the hard work and enthusiasm of Professor Kenner is to be seen in the programme of this symposium. Our membership covers a wide span of activities and ages; we range from specimens like Professor Prelog and myself who reach back almost to the medieval period of organic chemistry down to young men to whom Sir Robert was known only by name. Only a few of us — Professor Birch, Professor Dewar, Sir John Cornforth and myself — actually worked in the laboratory with Sir Robert, but everyone here has been influenced in one way or another by Sir Robert's work. By coming together for this symposium we seek to stimulate further progress in the various fields of organic chemistry we represent. Published under the title *Further Perspectives in Organic Chemistry* we hope that it may provide an appropriate successor to *Perspectives* and a worthy tribute to the memory of a great chemist.

Topics to be discussed in our symposium include synthetic methods, biomimetic studies and biogenesis, biosynthesis and theoretical organic chemistry—a wide range of subjects in all of which Sir Robert was interested. It would be difficult to find a single basis for the variety of individual research topics he pursued, but one of the things about his work which he himself often stressed to me and which many who did not know him personally seldom realize is that
a passionate interest in colour in organic compounds, stimulated perhaps by his early work on brazilin, played a large part in his selection of research topics throughout his career.

The structural elucidation of natural products and synthesis as a confirmation of structure—these were the essence of the work of chemists of Sir Robert's generation, and his theoretical interests stemmed from them. And yet it has always seemed to me that he was more interested in the development of new methods than in the aesthetics of synthesis on the grand scale; in this he differed from Professor Woodward. He never enjoyed the hard slog of a lengthy synthesis; he preferred to do a few experiments on one reaction and move on to another. That is why his name is far more frequently associated with synthetic methods than with complete syntheses of complex natural products.

To me one of the striking things about his work on structural determination—and one which I learnt from him—is his use of analogue synthesis as a tool to be used as an adjunct and in part a replacement for classical degradative studies. A good example of this is to be found in his anthocyanin and anthoxanthin studies. True, analogue synthesis could be a dangerous weapon in the hands of the unwary, but despite his impetuosity nobody could seriously apply the adjective 'unwary' to Sir Robert.

It is, I think, difficult for the young chemist of today to appreciate fully Sir Robert's achievements; we always underestimate the achievements of our predecessors. I am sure that most students when they read, as I did, about Körner's orientation of substituents in the benzene ring must feel, mistakenly, that it was easy to make one's name in his day. Sir Robert was an organic chemist in the classical mould and structures were determined by him using the simplest equipment and without any of the physical aids we take for granted today. There was no n.m.r. and indeed scarcely any spectroscopy at all, no chromatography and little or no X-ray analysis during almost his entire career. Against that background his achievements were prodigious and his influence on all of us here perhaps greater than we realize.
Abstract  Classical approaches to structure determinations of natural molecules can be assisted by biosynthetic considerations. Application of these needs some structural evidence, based on degradations and spectra, as to biogenetic type. This evidence can be effectively supplemented by incorporations of precursors labelled with $^{14}$C, $^{13}$C or $^{15}$N, as appropriate, with examinations of the distributions of label in the product. Several examples of both classical and incorporation techniques are reviewed.

Some uses of structure–biosynthetic relations have recently been summarized (Birch 1976). One use is to suggest possible structures of natural molecules, on the basis of incomplete evidence from other sources. Historically, the isoprene rule has been one of the most critical factors in determining terpene structures. I shall consider some individual cases in relation to various types of available evidence and ways of thinking. These examples are from my own work, partly because authors of papers often neglect to record the mental steps which lead them to a final result.

A CONGENER RELATION: ACORIC ACID

Congeners may be rationally derivable in many instances from common precursors, although the usefulness of this in structure determination depends on how far back in biosynthetic sequences the routes diverge.

A simple example is acoric acid (1) (Birch et al. 1964a). Chemical degradations suggested (1) or (2) as alternative structures but could not distinguish between them. As acoric acid occurs with achorone (3) in Acorus calamus L., the structure (2) is almost certainly correct, derivable from (3) by oxidation. This assumption was confirmed initially by partial synthesis from (3) and eventually by total synthesis (Birch et al. 1972a). The steric configuration suggested by (3) is also correct.
RELATIONS BASED ON CARBONIUM ION MECHANISMS

*Neocembrene-A*

This trail substance of the termite *Nasutitermes* (Birch et al. 1972b) is an oil, which cannot be examined by X-ray crystallography, and 2 mg was obtained from 20 kg of termites. It was accordingly examined chiefly by spectroscopic methods (mass and n.m.r. spectroscopy), its only chemical reactions being hydrogenation and degradation by microozonolysis combined with gas chromatography which showed that the molecule, C\textsubscript{20}H\textsubscript{32}, had four double bonds and gave rise to 1 mol of formaldehyde and 2 mol of laevulinaldehyde CH\textsubscript{3}CO.CH\textsubscript{2}.CHO. Spectra showed it to contain \(-\text{CMe}=\text{CH}_{2}\), \(-\text{CH}=\text{CMe}\) and to be monocyclic with four double bonds. The C\textsubscript{20} formula, the degree of unsaturation found and the spectroscopic evidence suggested that it has an isoprenoid skeleton. The biogenetic key to the structure seemed to be the MeC=CH\textsubscript{2} group. Limonene (5) results from the cyclization of the terpene chain (4); a similar cyclization to a six-membered ring from the C\textsubscript{20}-precursor geranylgeranyl pyrophosphate would not yield this group, since the resulting double bond would be trisubstituted. However, if not a six- but a 14-membered ring were formed as shown, the structure (6) would contain naturally this grouping.
The suggestion of such a ring was supported by the fact that the n.m.r. shifts of protons in the \(-\text{CH}=\text{CMe}-\) groups are slightly different to those in similar six-membered-ring analogues. Formula (6) having been suggested, it was easy to show that it is correct because key degradation reactions became immediately apparent. All these operations consumed 1.4 mg of the 2 mg of material available.

**Pleuromutilin**

To apply biogenetic ideas we must have some clues about biosynthetic type, even as little as the isoprenoid formula \([\text{C}_2\text{H}_4]_n\) above. In other cases usually some degradation evidence is available. We decided in several cases as an adjunct to, or a substitute for, degradation to use tracer incorporation from known simple biogenetic precursors as evidence. This would have the dual purpose of showing what units are present and possibly, by specific labelling and degradation, how the units are related to each other. The first example I shall discuss is pleuromutilin.

![Scheme 1](image-url)
This mould product is a glycollate of an alcohol $\text{C}_{20}\text{H}_{22}\text{O}_{3}$ (Birch et al. 1963, 1966), the formula alone suggesting a terpenoid origin. Infra-red spectra, supported by n.m.r. spectra when these later became available, strongly suggested the presence of a CH=CH$_2$ group. This was initially the only structural evidence available besides i.r. evidence for an OH group and a cyclopentanone ring. The group MeC-CH=CH$_2$ was known to be characteristic of several diterpenes generated by carbonium ion cyclizations of terpene chains as originally suggested by Wenkert and by Stork.

Using [1-$^{14}$C]acetate or [2-$^{14}$C]mevalonate (7) as precursors, we found the skeletal labelling and biogenetic processes outlined in Scheme 1.

We had not long previously confirmed for the first time the predicted tricyclic and tetracyclic diterpene route (Birch et al. 1959) using incorporations of labelled acetate and mevalonate into gibberellic acid and rosenonolactone, finding the expected labelling of MeC-CH=CH$_2$.

The group CH$_{14}$CH$_2$ in material derived from CH$_3$. 14COOH should on this picture contain one eighth of the radioactivity of the molecule. This was found to be true for pleuromutilin by ozonolysis to formaldehyde. Also, the terpene precursor [2-$^{14}$C]mevalonate was well incorporated, although we did not degrade the product. Therefore, we were sure that it is a terpene and that biogenetic ideas valid for that area can be used. It was clear from the beginning that the picture cannot be as simple as that shown above, because of the five-membered ring deduced to be present.

A favourite general degradation is based on the fact, that, as nuclear CH$_3$-C groups can be isolated by Kuhn–Roth oxidation to acetic acid from most molecules containing them, the radioactivity of these two carbon atoms can be examined readily. All the CH$_3$ groups from the material prepared from [1-$^{14}$C]-acetate should normally yield CH$_3$.14COOH with the carboxy group containing one eighth of the molar activity in each acetate produced. In fact, in the acetic acid from pleuromutilin the carboxy group had only about 75% of the expected radioactivity. From this it can be deduced that one CH$_3$ has moved during biosynthesis as the result of a carbonium ion rearrangement, as shown in Scheme 1 for (11) and (13), resulting in attachment of this CH$_3$ to an unlabelled carbon atom. One reaction which we did not do, which would have been critical for the structural elucidation, was Kuhn–Roth oxidation of the compound originally derived from [2-$^{14}$C]mevalonate.

To our initial astonishment, no doubt, the resulting CH$_3$.COOH would have been inactive.

The reason why this would have been so significant is that the C-2 atom of mevalonate should label only one terminal methyl group of a terpene chain or one only of the gem-dimethyl groups in a skeleton derived from it, e. g. as in
(11) and (13). The experiment that we did not do would have shown that no such labelled methyl group is present and, therefore, that the methyl group must have disappeared in a biosynthetic step. This could have been as the result of oxidation, but it was known by then from the chemistry that no primary alcohol or ester was present in the molecule.

The biosynthesis in Scheme 2 was demonstrated by later work. Although lacking this vital clue, we were considering formula (14) amongst several others on both chemical and biosynthetic grounds when Arigoni (1962) published it, having ascertained it on the basis of extensive chemical degradations.

We were able to limit the carbonyl group to one of four positions related to the original biosynthetic chain by examining the label of the carbon atom of C=O. It was converted into MeC–OH by methylmagnesium iodide, followed by Kuhn–Roth oxidation to CH₃-COOH. This acetic acid was radioactive when derived from material biosynthesized from [2-¹⁴C]mevalonate material but not when derived from [1-¹⁴C]acetate material. The carbon atom, therefore, arises from the C-2 of mevalonate, and is therefore limited to at most four and probably three positions related to the initial chain. The formula (14) agrees with this conclusion. This approach to limiting situations of groupings in terpenoid and steroid molecules, particularly in mould metabolites where tracer incorporation is easy, could be used more widely, especially with the advent of ¹³C n.m.r. spectroscopy.

![Scheme 2](image)

**Scheme 2**

**RELATIONS BASED ON SPECTROSCOPIC AND DEGRADATION EVIDENCE COMBINED WITH TRACER INCORPORATIONS**

**Echinulin**

When we began work on it, this mould product had been assigned the partial
formula (15) (Quilico et al. 1958) on the basis of chemical evidence. Biosynthetic considerations led us to the full structure (16) (Birch et al. 1961a; Birch & Farrar 1963). This was based on probable origin from tryptophan and alanine and three introduced C₂-terpene units, and needed revision of the original empirical formula by addition of CH₃. Incorporation of ¹⁴C confirmed the expected origin. Formula (16) was independently shown to be correct on chemical grounds (Casnati et al. 1962). When this work was done, mass spectra were not available and only a few n.m.r. spectra, of key compounds only, were available—with difficulty.

![Chemical structures](image)

**Brevianamide-A**

This metabolite of *Penicillium brevicompactum* (Birch & Wright 1969) was available only in mg quantities and seemed, from analyses and spectra, to represent a new type of molecular skeleton. The presence of a 3-indolinone structure was established by spectroscopy and reactions. I.r. spectra also suggested a diketopiperazine ring; that could be derived from two amino acids but, as no amino acid was released by hydrolysis, subsequent changes probably involving formation of new C–C bonds may have occurred. One amino acid might be tryptophan. From the formula C₂₁H₂₂N₃O₃, six rings should be present, including one benzenoid, since no other double bonds could be traced, chemically or spectroscopically. The n.m.r. spectrum indicated a CMe₂ group and the mass spectrum showed a major loss of C₅H₉, which may originate as a C₅-terpene unit, as in echinulin. If this assumption is correct, the second amino acid must lack a methyl group, but should contain a ring to assist in providing the six rings
BIOSYNTHESIS AND STRUCTURE DETERMINATION

needed. The prime candidate, fitting the molecular formula, is proline. Up to this stage, all the considerations about possible skeletons were pure speculations. The biosynthetic units involved were, therefore, examined by tracer incorporations which confirmed our speculations about tryptophan, proline and mevalonate. The lack of characteristic diketopiperazine CH signals in the n.m.r. spectrum and the necessity for loss of a double bond in the C₅ unit together with requirements for two more rings suggested the structure (17). Somewhat to our astonishment, this was later confirmed.

\[ \text{Figure 17 and 16a} \]

The structure we suggested explained the ¹H n.m.r. spectrum and the mass spectrum (for details see Birch & Wright 1970). The pertinent point here is that the spectra were too complex for us to derive a structure from them. For example, the loss of C₅H₉ in the mass spectrum involves the fission of three C–C bonds, which is readily understood from the structure of (17) but which was not suggested by it. Apart from destructive ozonolysis of the benzene ring, no meaningful chemical degradations of brevianamide-A have been done.

Later, a minor product of the mould was shown to be (16a) which is more closely related to echinulin (16) and which is also closely related to the classically expected biogenetic precursor of (16) (Birch & Russell 1972). Incorporation of cyclo(L-tryptophyl-L-proline) into brevianamide-A was later demonstrated (Birch et al. 1974).

**Phomazarin**

The polyketide hypothesis has proved to be extremely useful in limiting the number of possible formulae for natural products of its class and is thus, in ways, reminiscent of the use of the isoprene rule. The first practical use of this hypothesis was to correct the formula of eleutherinol from (18) to (19) (Birch & Donovan 1953).

\[ \text{Figure 18 and 19} \]
Phomazarin had been extensively examined chemically (Kögl et al. 1945) and Kögl formulated it as (20), in which the orientation of the pyridine ring relative to the substituted benzene ring could not be defined. Our attention was first attracted by this ambiguity, since it appeared to be a polyketide molecule, and a property of the polyketide hypothesis is to assist the placing of the substitution in one ring, relative to a more distant ring, as in the example of eleutherinol (19). We first showed that the molecule arises from either eight or nine acetate units and that the COOH was originally the methyl group of acetate (Birch et al. 1961b, 1964b). In the course of this work it became necessary for chemical and spectroscopic reasons to question Kögl's formulation of the pyridine ring and to alter it to the substitution shown in the pyridone (21). Since this formula can be derived by complete head-to-tail linkage of acetate units, it was considered more probable than the alternative with the pyridone inverted. Later, after re-examination of further anomalies in Kögl's results, we had to modify the substitution of the benzene ring to that shown in (22) (Effenberger 1973).

![Chemical structures](image)

After these alterations, we favoured the structure (23) on the basis of polyketide origin over the alternative with the inverse orientation of the end rings. A problem, however, was that interpretations of i. r. spectra based on interactions of the quinone carbonyl with the neighbouring OH and NH seemed to favour this inverted alternative. This conclusion, however, depended on some structural assumptions, notably that the pyridone ring is in the normally expected form rather than existing as the isomeric pyridol. Because of this contradiction between biosynthetic assumptions and spectroscopic interpretations, the question was further examined.

Studies of $^{13}$C n.m.r. spectra suggested that phomazarin exists as the pyridol form (24) (Birch et al. 1976). To examine this point further and also to explore the relationship of the heterocyclic ring to the rest of the molecule, we used...
biosynthetically incorporated $^{15}$N as a probe. We did this by using labelled sodium nitrate as the sole source of nitrogen in a buffer replacing the original culture solution. In its n.m.r. spectrum, the di-0-methylphomazarin methyl ester we obtained showed a low-field exchangeable proton at $-3.23 \tau$ with no $^{15}$N–H coupling (typically 93 Hz) and hence it was present in OH rather than NH: that is formula (24) rather than (23). This conclusion was confirmed by further n.m.r. studies.

The relative ring orientation was also studied in the same $^{15}$N-enriched material. Couplings with the carbonyl carbon atoms support the pyridol structure (24) rather than the structure with the pyridol ring reversed.

The use of doubly labelled $[^{13}\text{C}_2]$acetate is now standard for examination not only of polyketide origin but of the exact dispositions of the C$_2$ units. This application depends on the fact that the enriched molecules of product are mixtures containing acetate units with either two $^{13}$C or two $^{13}$C-enriched carbons, in positions restricted by the origin of the chain, which can be examined by n.m.r. spectra. Studies with doubly or singly labelled acetate supplement spectroscopic studies on material with a natural $^{13}$C abundance. Simpson (1975) has reviewed the methods.

If phomazarin is (24), it must arise either from two chains or, more likely, by fission of an anthraquinonoid precursor of the type (25) with considerable uncertainty about the stages of introduction of ‘extra’ OH and whether R is Me.