Vitreous phases or glasses formed by shock also have many unique properties; they have not been studied by such methods as thermoluminescence, electron spin resonance, low-angle x-ray diffraction, or infrared spectroscopy. Shock-fused glass of high density needs to be studied in detail in carefully controlled laboratory conditions.

Experimental shock-wave studies of the equation-of-state of single minerals and mineral assemblages, under carefully controlled conditions, must precede estimates of peak pressures and peak and residual temperatures of shocked natural mineral assemblages. Detailed petrographic and mineralogic studies, however, have provided useful and definitive criteria for characterization of impact events. Such data should be of paramount importance in the study of samples brought back from Moon.

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Biosynthesis of Polyketides and Related Compounds

A. J. Birch

In 1907 Collie (*1*) suggested that orsellinic acid (I), a common lichen constituent, originates from two molecules of acetoacetic acid, as shown. This was part of a general suggestion that fatty acids, terpenes, and carbohydrates arise from acetic acid. He appears to have had the underlying idea that such compounds are polymers of ketene ($CH_2=C=O$) and called them first "polyketenes" and then "polyketides"; a close analogue is the later "isoprene" hypothesis for terpenes. Collie had some experimental evidence favoring his orsellinic acid hypothesis, since he had obtained this compound from "dehydracetic acid" (II), itself obtained from two molecules of acetoacetic ester. He implied that other natural phenols could be included in the scheme, but did not discuss examples; the hypothesis seems to have been largely forgotten, as was his related (correct) hypothesis for terpene biogenesis, and his (incorrect) hypothesis for carbohydrate biogenesis, on which he expended most of his effort.

There are a few bare mentions in the literature of the original hypothesis (for example, *2*) but the extent of its neglect is shown by the fact that the topics most affected—mold products (*3*), lichen products (*4*), and flavonoids and related plant products (*5*)—were completely unaffected as late as 1952. Robinson published for the first time in 1955 (*6*) an extrapolation of Collie's theory, but meanwhile we had considered the topic (*7*), starting from a different origin and with experimental support.

Collie's hypothesis was based on the biosynthetic use of organic-reaction mechanisms of the Claisen type (reactions involving an ester group and an activated CH_2, leading to β-polyketoesters or β-polyketones; for example, III) and aldol condensations involving a reactive methylene and a carbonyl (for example, reactions of the type leading from III to IV). He recognized the similarity, but did not identify them, except in the case of I, with natural products; hence he was led to the hypothesis. He was in essence postulating a relation between certain laboratory and biosynthetic processes on the implicit but unstated assumption that chemical mechanisms should be recognizable in biosynthetic processes, even though enzymes and coenzymes are clearly important. Great superficial differences in fact existed between laboratory conditions (for example, the necessary use of powdered sodium metal to produce ethyl acetoacetate from ethyl acetate) and any conceivable processes compatible with biological environments. Collie was nevertheless basically cor-

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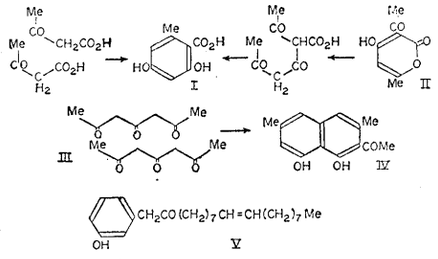
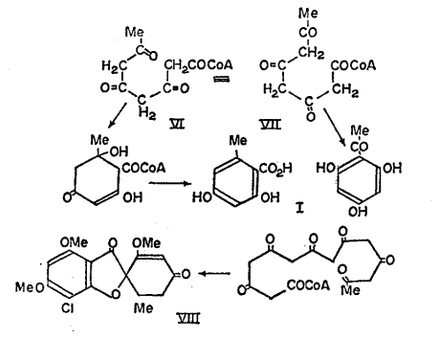
rect in his general assumption, which was later exemplified with great ingenuity by Robinson in the alkaloid field.



Our own approach, begun in 1951, was first discussed in early 1952 (*8*). Its origin was in the then-known involvement of acetyl coenzyme A in biosynthesis of fatty acids and steroids; it was initially an inquiry as to what could result (on paper) from chemically acceptable cyclizations of fatty acid chains in which the β-ketone groups remained instead of being serially removed as in biosynthesis of fat. It was stimulated by then-current structural work on some natural phenolic and enolic compounds (*9*) which finally turned out to be somewhat complex examples. The first substance in which a polyketide origin was recognized was campnospermonol (V), the critical factor being the recognizable "oleic acid" side chain, as far as the carbonyl group, leading to further inquiry as to whether the rest of the system could arise by continuation of the fatty acid synthesis with C_2 units. When one took the simplest examples, a pencil and paper rapidly revealed that the idea would explain not only V (further discussed below) but also many other natural products.

The basic schemes are shown below for the simplest case which involves four acetate units and two chemically acceptable types of ring-closure: aldol (VI) and C-acylation (Claisen) (VII). The latter process is similar to that which built up the chain itself.



The literature was then searched for natural phenols to which the same idea could apply, possibly with complications caused by larger numbers of units and additional processes. The reason for considering phenols (or enols) was not that the hypothesis was expected to apply only to them, but that the type of structure-analysis involved depends on the relative positions of ring-closures and of oxygen attached to the skeleton; the pattern is less likely to be obscured by reduction processes than in aliphatic or alicyclic compounds. At this stage we were made aware of Collie's work by P. Maitland, who had known him personally.

General Characteristics of Polyketides

Molecules produced in this way tend, if cyclic, to have six-membered carbon rings, and to have oxygens attached β- to each other or to positions of ring-closure, because of the β-positioning of the reactive carbonyl groups and methylene groups in the original chains. Several obvious examples (*7*) are shown above: griseofulvin (VIII) (seven units) and emodin (eight units) (IX).

In order to include within the scope of the hypothesis a number of compounds that seemed good candidates, one had to introduce four further ideas:

1) A chain can start with a coenzyme-A ester other than acetyl coenzyme A: examples involve branched-chain fatty acids (probably related to amino acid biosynthesis), nicotinic acid, benzoic acids, and, notably, cinnamic acids. The last case permitted explanation for the first time of flavonoid and anthocyanin biosynthesis and is discussed below. In contrast with the units in the chain, where only "acetate" (now known to be malonyl coenzyme A) and occasionally "propionate" (methylmalonyl coenzyme A) are implicated, there is little reason to doubt that examples may be found of initiation of the chain by almost any acyl coenzyme A found in nature (*10*).

2) Oxygen is frequently missing from expected positions. The example of methylsalicylic acid (X), a common fungal product, shows that this absence could result from reduction of a carbonyl in an open-chain or cyclic, but nonaromatic, precursor, aromatization being accomplished by dehydration rather than by enolization. Methylsalicylic acid from *Penicillium griseofulvum* was in fact the first polyketide whose origin was confirmed by tracer experiments (*11*). The genetics of *Dahlia*, in connection with the origin of the chalcone butein, can be explained (*12*) by postulation that the gene Y controls the production of an enzyme specific for the reduction of one carbonyl group in a ring-open intermediate. This loss of oxygen is closely analogous to that involved in biosynthesis of fatty acids.

In view of the origin of our hypothesis, it is interesting that Lamberton (*13*) has shown that the precursor of campnospermonol (V), an artifact, is the optically active XI, the ring-closed, reduced, dehydrated, and decarboxylated (β-keto acid type) but not aromatized β-polyketide.

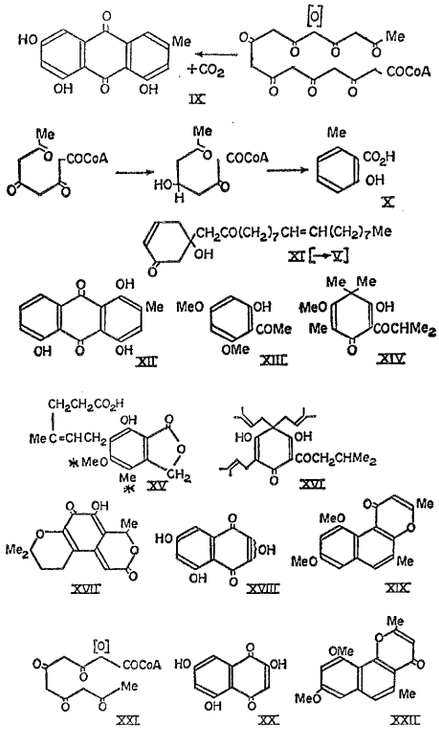
3) "Extra" oxygens occur—for example, one oxygen of the anthraquinone system (IX). There is no mechanistic difficulty and much biochemical analogy with this process. Later was added the very important subject of "phenol oxidation," chiefly as the result of the ideas of Barton and Cohen (*14*), which generates new types of ring systems; one example is the heterocyclic ring of griseofulvin (VIII), but this very large topic has been reviewed (*15*). In some instances both reductions and oxidations must have occurred, somewhat obscuring the origin (see, for example, IX and XII).

4) Groups generated by some other type of biosynthetic process are found in polyketides, apparently introduced by electrophilic attack by carbonium ions on the enolate systems. The most important are C-methylation [leading to the first suggestion (*16*) that such a process can occur from methionine] and the introduction of terpene chains. The compelling structure analysis leading to these conclusions is exemplified by the acyl phloroglucinols.

Compound XIII is clearly a classical polyketide, involving O-methylation as an additional process. Various related compounds are known, such as tasmanone (XIV) (*17*), with varying degree of C-methylation on the ring, from one to four, suggesting a series of successive processes. From synthetic work, especially that of Riedl (for example, *18*), it is well known that such C-alkylations can occur in the laboratory. Carbon-methylation into tasmanone from methionine in *Eucalyp-*

tus has recently been confirmed (*19*), although the first instance in which C-methylation was proved by ^{14}C-labeling techniques was mycophenolic acid (XV; *, ^{14}C from methionine *20*).

Analogous to C-methylation is the introduction of terpene units; compare the structures of lupulone (XVI) and tasmanone (XIV). The suggestion (*10*, *16*) of such an alkylation was later substantiated in a number of mold products, including mycophenolic acid (XV) in which the acidic side chain involves two units of mevalonic acid (*21*), and in other instances such as fuscin (XVII; *22*).



Chemical Uses of the Hypotheses

Even before the polyketide and ancillary hypotheses had been proved correct, they had practical uses in determination of structure. For this purpose they closely resembled the isoprene rule, a major factor in terpene chemistry since 1925, even though its biogenetic basis became clear only recently. Collie's ideas could, in fact, have saved a great deal of work since 1907 if anyone had had the faith to apply them. A series of possible structures for a natural molecule may be deducible by means of chemical reactions and physical methods; the structure chosen as most probable is that which agrees with a possible scheme of biosynthesis. This choice is not an academic exercise, since final proof may rest on synthesis, and much effort is saved if the correct possibility is synthesized first.

Our own use of the hypothesis with polyketides is illustrated by the first examples: flaviolin (XVIII; *23*) and eleutherinol (XIX; *24*), as the structures were then given. Structural evidence of β-polyketide origin was to be found in the β-oxygens and ring closures. Completion of this evidence for flaviolin would require structure XX, with one introduced oxygen from the chain (XXI); this structure was confirmed (*23*). Eleutherinol, written as XIX, seems wrong, since two polyketide portions do not fit; rewritten as XXII it can be derived from a complete polyketide chain, with a terminal decarboxylation. This structure also was confirmed (*24*). Many later examples of the same type are now available.

There are of course other biogenetic schemes, so some evidence of polyketide origin is required. This evidence can be structural, chemically or physically based (as I have shown), or it can be obtained directly by tracer incorporations involving ^{14}C-acetic, -propionic or -mevalonic acid. Examination of degradation products also has the advantage that the labeling can assist in assigning them to defined portions of the molecule. The subject is too complex for brief illustration, but one should note that the structure of the antibiotic nystatin has been largely defined by this means (*25*). The approach is not, of course, confined to polyketides; fungal terpenoids in particular can be examined profitably in the same way (*26*).

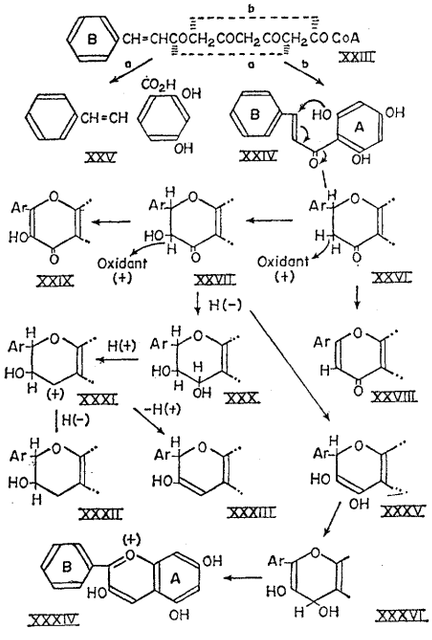
The hypotheses were largely assessed for validity by structure correlations. The most satisfying feature of the early work was, in fact, the way in which many natural products, hitherto merely a jumble of unrelated formulas, suddenly fell into well-defined patterns. The advance made can be seen by comparison of our original publication (*7*) with more or less contemporary reviews (*3–5*). One of the most interesting correlations (*7*), since confirmed by tracer experiments (*27*), was that between the plant stilbenes and flavonoids; it suggested for the first time the complete origin of both series, and the outline of probable interrelations between flavonoids, of varying degrees of oxidation, and anthocyanins. A chain of the type XXIII could arise from a cinnamoyl coenzyme-A ester and three "acetate" units, and we suggested (*7*) that simple alternative ring-closures (compare VI and VII) should lead either to the chalcone (XXIV) or to a stilbene carboxylic acid (XXV) after hydrolysis of the ester. The acid (XXV) should readily decarboxylate, and in any case several natural derivatives were known. These ring-closures appear to be genetically determined alternatives in *Eucalyptus*. On the basis of these assumptions the most primitive C_6-C_3-C_6 compound must be a chalcone (*7*).

This conclusion not only suggested the ultimate origins of the skeletal atoms; it also gave broad indications of the sequences of transformations involved (*12*).

The relevant reactivity considerations are these. Chalcones can be ring-closed very readily in the laboratory, as the result of nucleophilic attack on the $\alpha\beta$-unsaturated ketone system, to give flavanones (XXVI). We considered (*7*, *12*), therefore, that these substances are likely to be the first tricyclic flavonoids, although from the known optical activity of this series it has always been clear that the reaction is enzyme-catalyzed rather than spontaneous. The obvious next point of attack is the 3-position adjacent to the carbonyl group, requiring oxidation of the enol or enolate anion; a chemical analogy is substitution by electrophilic reagents. Such attack could entail direct addition of an oxygenated group (for example, OH) to give flavanonols (XXVII) or elimination of a proton to give flavones (XXVIII); the formation of the latter, in this view, would be a stable "dead end" alternative to the main route. The flavanonols can then lead to flavonols (XXIX) by similar oxidation, again producing very stable, aromatic products not readily susceptible to further alteration. Further steps, which can be mechanistically justified, can be written leading to catechins and anthocyanidins (*12*). In this view the flavanonols (XXVII) are key intermediates.

The importance of such speculations is that they suggest biochemical experiments. Our original hypothesis (*7*) suggested the importance of feeding experiments with ^{14}C-acetic and -cinnamic acids and their biogenetic precursors. Such experiments (for example, *27*) rapidly confirmed that the skeletal atoms arose as was suggested. The further speculations based on reactivities suggest the order in which the processes may occur; we noted in 1953 (*7*) that the first complete flavonoid must be a chalcone, and that the next

stage is very probably cyclization to a flavanone. In a difficult experimental field, results are still somewhat inconclusive (*28*) but do appear to support our overall scheme as further elaborated in 1959 (*12*). Exact details, such as the stages at which oxygens are introduced into ring B, can only be settled by biochemical experiments.



Biochemical Confirmations

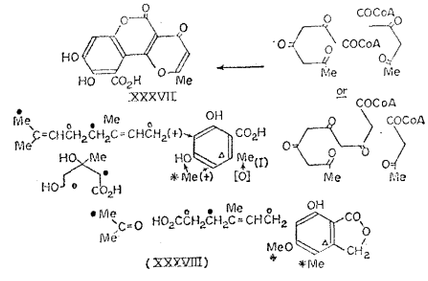
The first experimental support for the polyketide hypothesis was indirect, showing that it could correctly predict, or could correct, assigned structures (*23, 24*). This support was crucial also for publication of the hypothesis, which had previously been rejected by referees of some of the best journals. The first biochemical support entailed demonstration of the incorporation of ^{14}C-acetic acid into 6-methylsalicylic acid in *Penicillium griseofulvum*, with the correct alternate labeling pattern (*11*). Other compounds rapidly followed. A later highlight in the field was the demonstration (*29*) that ^{14}C-^{18}O-acetic acid was incorporated into orsellinic acid with retention of labels, demonstrating that the ring oxygens are, as expected from the original hypothesis, carboxyl oxygens from acetate, and that the carboxyl oxygens of the methylsalicylic acid are ^{18}O and ^{16}O, to be expected from hydrolysis of the intermediate coenzyme-A (thiol) ester by $H_2{}^{16}O$.

In view of the origin of the hypothesis (*7*), chiefly based on an extrapolation of biosynthesis of fatty acids, it is hardly surprising that the biosynthetic routes turn out to be closely parallel. With the recognition that, although acetyl coenzyme A is capable of starting the chain of a fatty acid, only malonyl coenzyme A normally acts as a building unit for the rest of the chain, it became probable that the same situation would apply in polyketides, and proof was rapid (*30, 31*). The results also explained the anomalous labeling of the Me-terminal unit in the chain, which had already been noted (*32, 33*). This differential labeling is clearly an important tool in defining how many polyketide chains are implicated in production of a branched-chain molecule (*34*). Citromycetin (XXXVII) and other compounds could arise from two chains, or from one chain with ring fission; in fact, terminal-labeling experiments demonstrate in this instance that two are involved (*35*), although there is still some doubt about the length of each.

The postulated processes of C-methylation and C-isoprenylation were based on the known chemical reactivities of phenolate and enolate anions toward cations. From biochemical work known at the time, the source of Me(+) was thought to be active methionine. We were forced to postulate some source of terpene cations, then unknown but later shown to be isopentenylpyrophosphate. The positions of alkylation were predictable from this theory, for which chemical models were available (for example, *18*) and have been borne out in practice. For example, in classical polyketides, methylation must occur on a carbon derived from acetate Me (or malonate CH_2)—not on a carboxyl carbon.

Carbon-methylation from methionine was first proved with mycophenolic acid (XXXVIII) (*20*), which conveniently contains both OMe and introduced CMe(*) with equal labeling. A similar situation exists between NMe and CMe in Terramycin (*36*), and between OMe and two types of CMe, one in a branch-chain sugar (*37*) in novobiocin (see also *38*). The fact that the origin of terpene units attached to an aromatic ring is the same as that of other terpene units was first demonstrated with mycophenolic acid (XXXVIII) by incorporation of 2-^{14}C- and 5-^{14}C-mevalonic lactone and of ^{14}C-acetic acid. By use of the first precursor, acetone, in equimolecular proportion and labeled (●) identically with that remaining in the side chain, can be detected, presumably resulting from oxidative fission of the initial terpene (C_{10}?) chain. Use of the second precursor shows two labels (○) present in the expected side-chain positions, confirming that the remains of two isoprene units are present. On examination over a period after addition of ^{14}C-acetic acid to a culture of the organism, label appears first in the ring of mycophenolic acid and later preponderantly in the side chain, emphasizing the operation of independent polyketide and terpene routes (*21*).

Orsellinic acid (I) may be the first aromatic precursor of XXXVIII, since the 5-^{14}C-acid is incorporated with only partial randomization, and the terminal effect (see above) can be demonstrated with the -CH_2O- of the lactone of XXXVIII, indicating its origin from a terminal Me group. These and related topics have been further discussed (*34*).



This subject illustrates some of the aspects of the contributions that analysis of chemical structure and theories of mechanisms can make to biochemistry. The ultimate sources of the atoms in the skeletons of polyketides and related compounds are now usually fairly clear, but many details remain to be elucidated, beginning with sequences of intermediates and passing on to details of the enzymes and the processes they control. The techniques required are largely biochemical, and as organic chemists we have passed on to other areas after a most enjoyable excursion.

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Roles of the Bureau of the Budget

William D. Carey

Perspectives on the Bureau of the Budget are wondrously diverse. Experts on Presidential government see the bureau as the right arm of Presidents in the decision-making ordeal. But those left holding losers' stubs in the budgetary sweepstakes take a less generous view. A well-known scientist thinks that the budget bureau "has no place in a democratic society." A distinguished political figure recently said that, while he had learned to respect the budget bureau, he had not yet learned to love it, and that if left to itself it would "reorganize its own Mother right out of Mother's Day." From a Senate committee comes the judgment that "what we need is a stronger, not a weaker, Bureau of the Budget. They are, and must always be, the President's men."

The bureau came forth from an act of Congress in 1921, the result of years of striving for reform of federal fiscal practices. Prior to that time, federal departments were left happily to their own devices in expressing their wants to the Congress, with little or no Presidential involvement. The legend is that one Treasury Department employee had the duty of packaging up the estimates each year in the "Book of Estimates." The aim of Congress was to provide for a modern executive budget in a setting of Presidential responsibility. At first the bureau was housed in the Treasury for rations and quarters, but its chief was the President's man. General Dawes was the first Director of the Budget, a two-fisted individual who imposed a reign of terror and said, when accused of taking over policy-making authority:

> The Bureau of the Budget is not concerned with policy, for that is the province of Congress and the President. Their job is to pilot the ship of state, while we shovel coal down in the stokehole. It is a humbler place. We do not give the orders, we merely see that they are carried out. If the Congress, in its omnipotence, were to pass a law that garbage should be spread on the White House steps, it would be our duty, in a nonpartisan and nonpolitical way, to see that the largest possible amount of garbage was spread on the White House steps in the most efficient and economical manner.

In 1939 the bureau became the main staff unit of the new Executive Office of the President. This followed a study commissioned by President Roosevelt to examine the Office of the President as to its capacities for effective administration of a government vastly different from what it had been in 1921, as the result of New Deal legislation, altered philosophies of government's role in a changing society, and the threat of war abroad. The President's Committee on Administrative Management called for stronger executive management through providing the President with planning, budgeting, personnel management, and general staff arms to help him get his job done—and all this through people "with a passion for anonymity."

Since 1939, Presidents have looked to the Bureau of the Budget to help them in a number of ways:

1) As a general-purpose staff, to see to it that the far-flung Executive Branch is responsive to Presidential policies and priorities.

2) To review and critically examine expenditure proposals as to merit, costs, alternatives, and timing.

3) To appraise proposed legislation in terms of its acceptability and consistency with the program of the President.

4) To come up with proposals for reorganization of executive departments and agencies in order to improve efficiency and economy.

5) To see to the coordination of government programs and policies, as an arm of the President.

6) To keep the President informed on the performance of executive department and agencies.

7) To work for the improvement of budgeting and management throughout the government. And, finally,

8) To coordinate programs and systems of data collection and reports.

That's a large order. I would be naive to claim that the bureau is able to deliver as much as we would like, consistently and well. But what drives the staff of the bureau is its awareness of the appalling scope of a President's job, and of the expectations that crowd in on him. Our role is to supply him

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