Terpenoid Compounds of Mixed Biogenetic Origins

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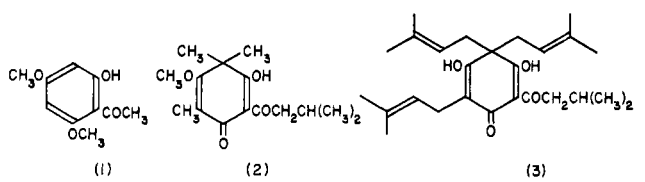
The initial biogenetic stage of the introduction of terpene units into molecules containing aromatic systems probably consists of a carbonium ion alkylation. Other processes are then involved, including oxidations, ring closures, and chain fissions. The background to the subject is reviewed and particular attention paid to the metabolites of *Penicillium brevicompactum* including mycophenolic acid and the brevianamide (indolic) pigments A to E. Work involving the incorporation of [^{14}C] precursors is described, and its utility in assisting structure determinations is discussed. Some possible applications of the biogenetic ideas to examinations of genetics in plants and molds are suggested.

The mechanistic ideas of the organic chemist have great powers of suggestion in biochemical processes, but they do not define details. The work being presented in this paper is a good illustration of these points. Our work on compounds of mixed terpenoid origins began in 1952 when it was necessary to extend our polyketide (acetate) hypothesis (Birch and Donovan, 1953) by suggesting extra steps to build certain skeletons. These were the then unknown biochemical processes of C-methylation, and the direct introduction of terpene units in hydrocarbon form by possibly mechanistically similar processes. Structure comparisons of the types leading to the postulates can be made with (**1**), (**2**), and (**3**) (Birch *et al.*, 1954; Birch, 1957). The typical polyketide ring in (**1**) has "introduced" Me groups in tasmanone (**2**) and "introduced" C_5-terpene units in humulone (**3**).

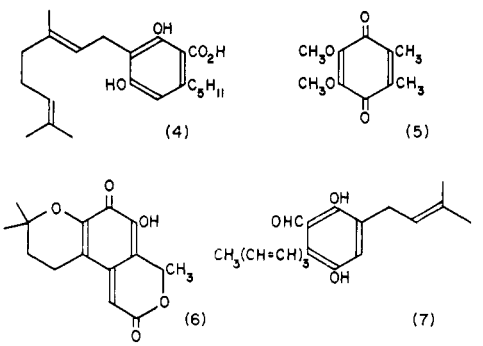


(1) (2) (3)

Based on biochemical analogy with known mechanisms of O-, N-, and S-methylation, we proposed for the first time (Birch *et al.*, 1954) and confirmed biochemically (Birch *et al.*, 1957b) the process of C-methylation from methionine. This is mechanistically related to the laboratory reactions of carbonium ions, and we were led to postulate a biochemical source of isopentenyl carbonium ions, initially thought by analogy to be "active" methionine analogs (Birch and Slaytor, 1961). However, the source turned out to be the pyrophosphates, although it is still being suggested (Baldwin *et al.*, 1968; Blackburn and Ollis, 1968) that S-isoprenoid derivatives may be important in other processes.

Many plant and mold products, from inspection of structures, contain isoprenoid units introduced into skeletons derived from other sources. However, from biochemical experiments, direct alkylation is not the only mechanism of junction of such units. A large class of alkaloids, for example, contains a terpenoid skeleton introduced by reactions with the oxidized and cyclized terpene unit loganin (Battersby *et al.*, 1970; Escher *et al.*, 1968). We deal here only with direct alkylation reactions. The cannabis resin constituents, for example, are probably based on the direct alkylation process, despite the fact that a convenient chemical synthesis of the skeleton involves the condensation of citral with an appropriate phenol. This conclusion is based on the occurrence of the minor phenol (**4**) (Mechoulain and Ben-Zvi, 1969), a typical alkylation product of a polyketide nucleus.

Examples of biologically important molecules containing introduced terpene units are the ubiquinones, plastoquinones, and vitamin K. The first examples in which this type of introduction into phenolic nuclei was clearly demonstrated were fuscin and auroglaucin, discussed below. The first model for general carbonium ion type alkylations of quinones was auroantioglocladin (**5**) where one of the Me was shown (Birch *et al.*, 1958c,d; Birch, 1961) to come from methionine.



(4) (5) (6) (7)

FUSCIN (6) AND AUROGLAUCIN (7)

These are instances of the introduction of a terpene unit into a nucleus of different biosynthetic origin (Birch *et al.*, 1958e, 1965). In both cases feeding with [^{14}C]acetate and [^{14}C]mevalonate showed the nucleus to be acetate-derived (polyketide) and the C_5 unit to be mevalonate-derived. Extents of incorporations of [^{14}C]acetate into the two portions of the molecule differed, as in the case of mycophenolic acid, discussed in more detail later. The irreversibility of mevalonate to acetate in these systems was shown by the lack

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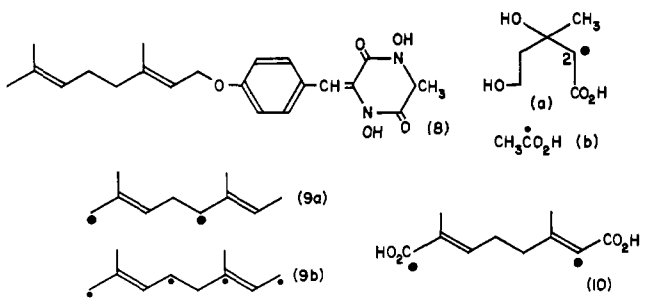
of labeling of the polyketide portion when [^{14}C]mevalonate was added. They provided models to lend credibility to other schemes involving direct introduction of terpene units into quinones, probably at the stage of the reduced phenols, or phenolic precursors.

MYCELIANAMIDE (8)

This mold product (Birch *et al.*, 1955) proved to be a particularly useful vehicle for examining some aspects of simple terpene biosynthesis, because metal–ammonia reduction gave *trans*-methylgeraniolene (**9**). [^{14}C]Acetate feeding produced the expected labeling pattern (**9b**), which was not altered by using [^{14}C]malonate. In this organism, therefore, the terpene route, unlike the polyketide route, does not involve malonate, or else malonate and acetate are very rapidly equilibrated. 2[^{14}C]Mevalonate ([^{14}C] = •) gave methylgeraniolene (**9a**) labeled as shown (Birch *et al.*, 1962). This pattern was demonstrated by feeding the hydrocarbon to rabbits and isolating the metabolite, Hildebrandt's acid (**10**), with the stereochemistry (nmr) and labeling shown. This result directly confirmed for the first time the nonrandomization of label between the terminal Me, from the 2 position of mevalonate, which had previously (Birch *et al.*, 1959; Britt and Arigoni, 1958) been indirectly deduced from cyclized terpenes.

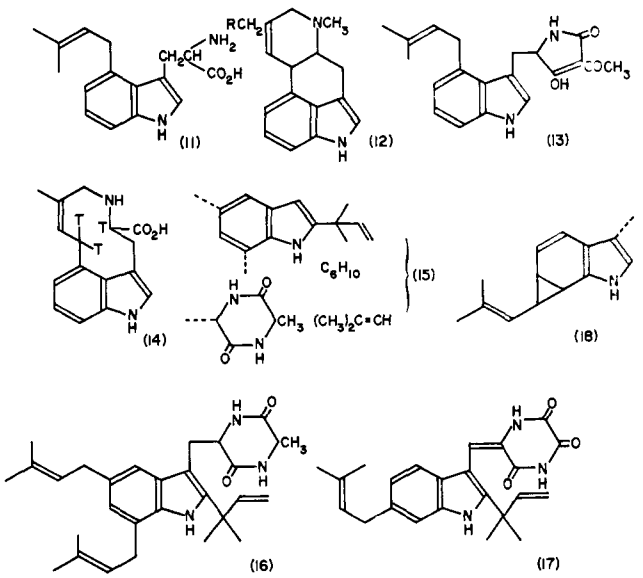


ERGOT ALKALOIDS, *e.g.* (12)

A number of hypotheses had been put forward to explain the origin of the nonindolic portion (Miller, 1961), which seemed less likely to us (Birch and Smith, 1958b; Birch, 1960a), and independently to Mothes *et al.* (1958), than an origin from a C_5-terpene unit. We specifically suggested (Birch, 1960a), without any evidence as to the detailed compound involved, the probable intermediate after tryptophan as the amino acid (**11**). This has been found to accumulate in ethionine-inhibited cultures (Agurell and Lindgren, 1968). The overall correctness of the hypothesis was initially shown by demonstrating appropriate incorporation of [^{14}C] acetate and [^{14}C]mevalonate into elymoclavine (**12**, R = OH) and agroclavine (**12**, R = H) (Birch *et al.*, 1960; Bhattacharji *et al.*, 1962). Much interesting work has since been done on the details of the oxidative ring closures involved (Naidoo *et al.*, 1970). Another structurally related mold metabolite recently isolated is (**13**) (Holzapfel *et al.*, 1970).

ECHINULIN (16)

This mold product was the first instance in which the incorporation of labeled substrates was used directly to assist in determination of the structure. Another recent example of this in a related area is the mold metabolite clavicipitic acid (**14**), where tritium labeling experiments (Robbers and Floss, 1969) showed that the α hydrogen of tryptophan and

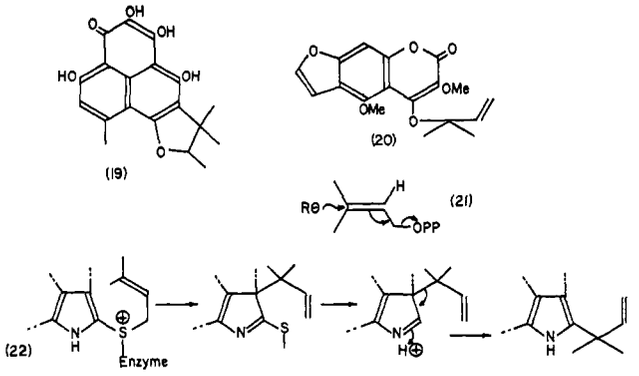


both hydrogens at C-5 of mevalonic acid are retained, proving that the ten-membered ring has not been closed between these positions as in other *Claviceps* alkaloids.

When we began work on echinulin, the formula was in the state (**15**) (Quilico and Cardani, 1958). The known portions of the aliphatic sections of the molecule suggested to us the probable presence of three isoprene units (one attached in reverse), and a tryptophan nucleus. Tracer incorporations of[^{14}C]acetate and mevalonate and degradations to acetone and formaldehyde confirmed the presence of three C_5 units. These units must be attached to tryptophan, in positions known from the previous degradation evidence. This conclusion and the presence of a diketopiperazine ring involving alanine required the revision of the empirical formula by addition of a CH_2. The probable formula then became (**16**) (Birch *et al.*, 1961). Professor Quilico (Casnati *et al.*, 1962), independently on chemical grounds, arrived at the same structure. [^{14}C]Tryptophan is incorporated (Birch and Farrar, 1963) as expected.

Recently (Barbetta *et al.*, 1969) the same mold has been found to yield neoechinulin (**17**) which has an introduced isoprene unit in a different place to either of those on the benzene ring of echinulin. Our original hypothesis was based on the mechanistically acceptable reactions of cations with a reactive enolate system; it is more difficult to see what activation is available in cases such as this. However, C-methylation was later found to occur on relatively unactivated chains (Alexander and Schwenk, 1957; Birch *et al.*, 1958g), possibly through a carbene-type mechanism. A similar explanation may be applicable here, with, for example, an unstable cyclopropane derivative such as (**18**), forming an intermediate which can rearomatize in two ways. However, the retention of two T in the 5 position of mevalonic acid in (**14**) is evidence against the hypothesis in this case at least.

Another problem is that of reverse attachment of an isoprene unit to the pyrrole ring. This occurs not infrequently on carbon, as in atrovenetin (**19**), or on oxygen, as in halfordinin (**20**). There is no mechanistic difficulty about attack at the rear of an isopentenyl pyrophosphate (**21**), but an attractive hypothesis is a normal alkylation of a heteroatom group in the molecule (O, S, N) followed by Claisen-type rearrangement. Circumstantial schemes, one involving sulfur (Bycroft and Landon, 1970) and nitrogen (Casnati and Pochini, 1970) intermediates among others, have been postulated, but no real biochemical evidence exists.



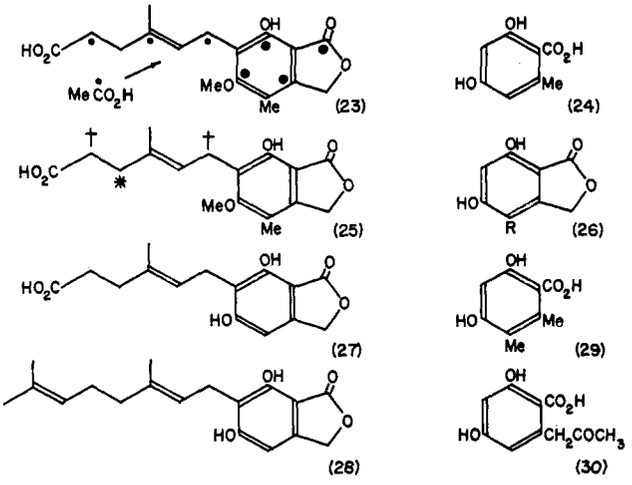
MYCOPHENOLIC ACID (23)

This metabolite of *Penicillium brevicompactum* has attracted a good deal of our early attention because of its biosynthetic complexity (Birch, 1960a). Inspection of the molecule initially suggested that it contains a polyketide nucleus, *e.g.*, orsellinic acid (**24**), into which has been introduced a C–Me, an O–Me, and a terpene chain (which has been cleaved) and also suggests that oxidation has formed a lactone ring. The C-methylation was rapidly confirmed (Birch *et al.*, 1957b), it being significant that label on OMe and CMe were identical. The use of acetate-*1*-^{14}C gave some interesting results, confirming that the terpenoid chain had the expected distribution of label (**23**), but showing also that this differed quantitatively from label incorporated in the expected positions in the ring. In fact, the relative labeling was time-dependent (Birch, 1960a). In a reflooded culture of *Penicillium brevicompactum*, label from acetate-*1*-^{14}C rapidly appeared (a few minutes) in the nucleus and more slowly in the side chain. After about 1 hr the extent of label in the side chain exceeded that in the nucleus. The acetate was being incorporated into both portions of the molecule, but clearly through different intermediates. That the side chain precursor was mevalonate, at least in part, was shown by feeding 2-[^{14}C]-mevalonate to give the labeling in (**25**) († = ^{12}C, * = ^{14}C). However, since in this case the portion of the second C_5 unit containing the [^{14}C] is lost, the presence of only one C_5 unit was certain. The second was confirmed in two ways. A reflood culture with 2-[^{14}C]-mevalonate was examined for [^{14}C]acetone, which seemed to be the most likely fate of the terminal CMe_2 group. This was indeed found (Birch, 1960a), and the total label was the same as that of the side chain. There is no other obvious biosynthetic route to such labeled acetone. Further confirmation was obtained by using 5-[^{14}C]-mevalonate to give two labels in accord with the distribution (**25**) († = ^{14}C, * = ^{12}C).

Whether the initial terpene chain is C_{10} or higher does not appear from this evidence. However, the C_{10} hypothesis is the simpler one and clearly should be tested first.

Recent work (Canonica *et al.*, 1970) has shed some light on the route involved. A very good biogenetic source was found to be the methylated phthalide (**26**, R = Me) which seems clearly to be an intermediate. The unmethylated phthalide (**26**, R = H) is a much poorer source, and is probably not a normal intermediate; in fact it leads mainly to a poor yield of an analog (**27**). The geranyl derivative (**28**) gave a very poor incorporation to produce (**27**), as well as some mycophenolic acid. These results seem to be in accord with our suggestion (Birch, 1968) of the acid (**29**) as an intermediate, derived from the C-methylation of orsellinic acid. Earlier work (Ryan, 1959) had shown the incorporation of 5-[^{14}C]-orsellinic acid into mycophenolic acid, but the total incorporation was poor and there was some randomization of label; it could therefore be a facultative and not an obligatory intermediate. The mold produces some C_{10} compounds, *e.g.*, (**30**), and these could be alternative sources of the nucleus. As in a number of similar cases, it is not certain how far enzymic specificity is elastic enough to deal with unnatural possible precursors, or how far there may be more than one possible route [Bu'lock (1965) metabolic grid].

Mycophenolic acid is an interesting compound biologically with antiviral and immunosuppressive activities.

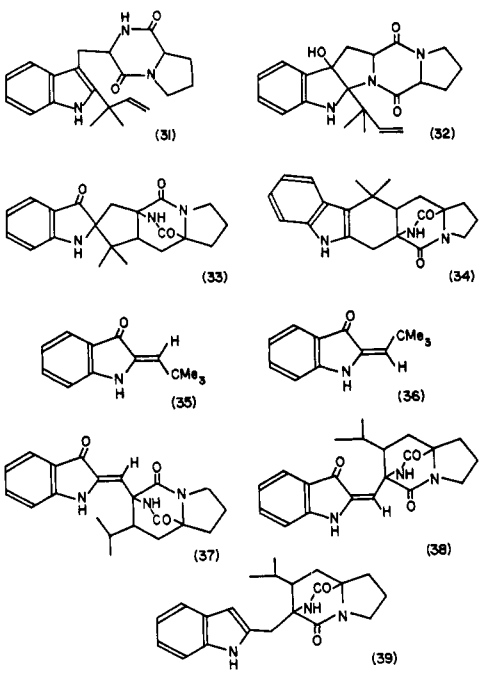


THE BREVIANAMIDES

A number of common molds produce neutral substances which show liver toxicity (Holzapfel, 1970), among them *Penicillium brevicompactum*. This fraction of the mold metabolite contains at least five indoloid compounds, brevianamides A–E (Birch and Wright, 1970), although whether any of these is responsible for the toxicity remains to be seen. Our interest was in determining the structures, initially with very small amounts of substance, although later it was possible to develop strains and conditions which gave considerably higher yields. The structures were determined by a combination of physical methods (ir, uv, nmr, and mass spectra) with biogenetic hypotheses supported by [^{14}C] precursor incorporation. We believe the common biogenetic precursor to be (**31**) and it is clearly related to brevianamide-E (**32**), from which it can be obtained by zinc reduction.

The first structure in the series investigated was that of the major component, brevianamide-A (**33**). This compound was readily shown to be a ψ-indoxyl, and by careful investigation of mass spectra nmr spectra combined with biogenetic considerations (**33**) seemed a possible molecule (Birch and Wright, 1970). Incorporation of [^{14}C]tryptophan, proline, mevalonate, and acetate to about the same extents supported this idea, despite the impossibility of locating individual labels. Several crucial physical data can be noted. The interpretable differences in chemical shifts of the Me groups in (**33**) and their virtual identity in the indole (**34**) obtained by reduction and rearrangement confirms their relationship to the ring system (*i.e.*, the reversed nature of the isoprene unit), and the absence of resonances due to the diketopiperazine protons in –NCHCO– [found in (**32**) and in models] indicates the position of the carbon bridge. Later work on (**32**) confirmed the proline unit, which could be isolated after hydrolysis, and also confirmed the presence of the reversed isoprene unit (nmr).

Brevianamide-B is very similar to brevianamide-A and was suspected of being a stereoisomer. This was confirmed by showing that reoxidation ($Pt–O_2$) of the indole (**34**) gave brevianamide-B in an apparently stereospecific rearrangement (Birch and Russell, 1971). The series of reactions has therefore reversed the stereochemistry at the spiro center.



Brevianamides-C and -D (Birch and Russell, 1971), from their ultraviolet spectra and behavior, seemed also to be ψ-indoxyls with extended conjugation, probably of the type in (**35**). They contain a carbon–carbon double bond carrying one proton. Synthesis of the model 2-indoxylidenalkanes (**35**) and (**36**), the latter being obtained from the former by irradiation, showed a very close correspondence in uv absorption curves to brevianamides-C and -D, respectively. Similar differences of the olefinic proton resonances are also observable, as is the presence of $CHMe_2$ (nmr spectrum). We conclude therefore that brevianamides-C and -D have the formulas (**37**) and (**38**), respectively. The difference being due to double bond configuration is supported by borohydride reduction to the same indole, presumably (**39**), from both. The bridged nature of the ring is also supported by the nmr spectrum.

The biogenesis of the precursor (**31**) is related to that of the tryptophan derivatives discussed above, and contains a diketopiperazine nucleus also well known in mold products. We are at present examining the possible role of (**31**) and of the isopentenylated tryptophan as precursors in order to determine the stage at which the terpene unit is introduced.

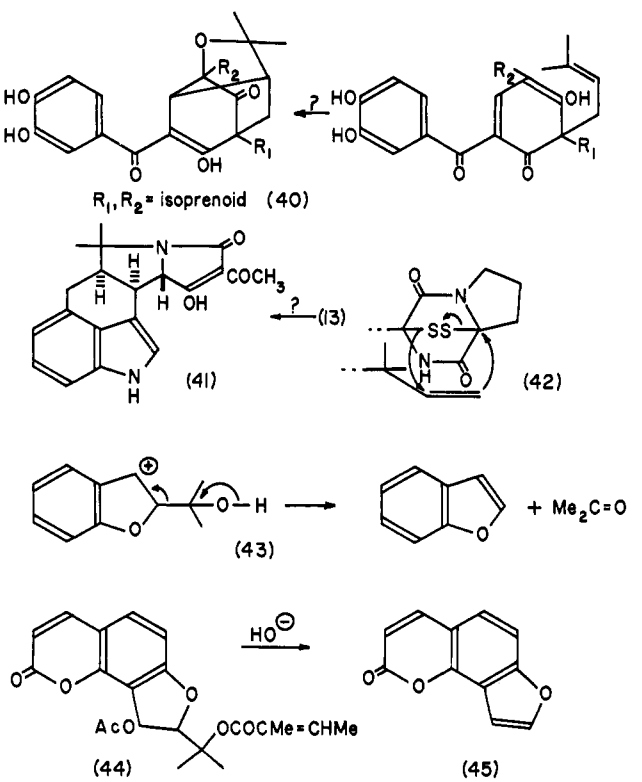
The most interesting features of the biosynthesis are the possible mechanisms of the ring closures which generate A and B, and the ring fission which generates C and D.

Closures of terpene units to form a new carbon ring which may be mechanistically related are found in compounds like gambogic acid and the slightly simpler compound bronianone (**40**) (Ollis *et al.*, 1969). Another example is the mold product (**41**) (Holzapfel *et al.*, 1970). In these the isopentenyl double bond has linked with two other atoms, one carbon and the other O or N. The process is clearly an oxidative one, although the intimate details can only be speculative; possibly radical processes are involved. A number of oxidized diketopiperazines are known as natural products, *e.g.*, (**8**) and compounds with a polysulfide bridge across such rings are also known, *e.g.*, gliotoxin. A tentative suggestion for ring closure, which is only one of a number of possible routes, is shown in (**42**). No sulfur compounds could be detected in the mold products. An alternative suggestion (Porter and Sammes, 1970) is the occurrence of a Diels–Alder type reaction on a pyrazine, which is perhaps unlikely in view of the unactivated nature of the double bond.

The production of brevianamides-C and -D from -A has been shown to occur on illumination (Birch and Russell, 1971). They may, in a sense, be artifacts, therefore, although they appear to occur in the fungus itself. The role of illumination is being further investigated.

ORIGIN OF THE FURAN RING IN BENZO- AND PYRIDOFURANS

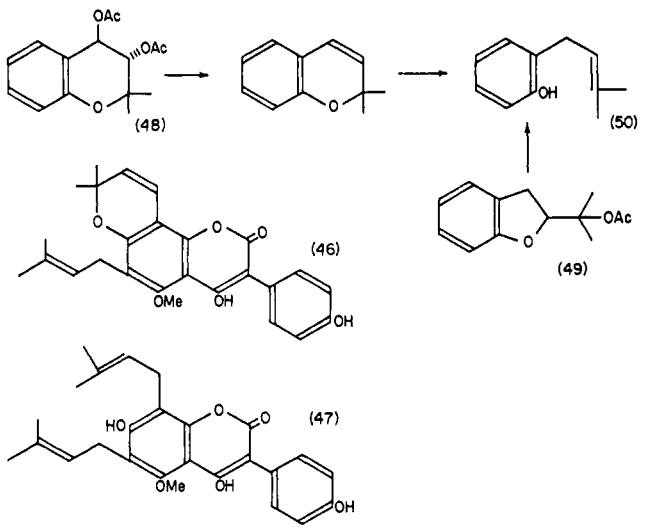
Because of the alternative occurrences of introduced C_5 units, dimethylchromenes, isopropyldihydrofurans, and unsubstituted furans in similar positions in many natural plant coumarins, chromones, and quinoline alkaloids, we suggested (Birch and Smith, 1958a) that the unsubstituted furan ring is derived from a terpene unit by loss of three carbon atoms. Seshadri (Aneja *et al.*, 1958) independently put forward a similar idea. The correctness of the hypothesis has been demonstrated for a furanocoumarin (Floss and Mothes, 1966) and some quinoline alkaloids (Chamberlain *et al.*, 1969). Our suggestion was linked to a specific mechanism, shown in generalized form in (**43**). This has received support from chemical reactions, such as the base-catalyzed conversion of libonatin (**44**) into angelicin (**45**). An alternative suggestion (Aneja *et al.*, 1958) of cleavage before ring closure seems less likely because butyrolactones might occasionally be expected to result and have never been observed.



REDUCTIVE REVERSAL OF OXIDATIVE RING CLOSURES

It is clear from the foregoing that the initial C_5 hydrocarbon chain must undergo various types of oxidation in order to

ring close on to phenols to give chromenes, isopropyldihydrofurans, and similar compounds. In order to regenerate chemically the postulated biosynthetic precursors, a reduction process is necessary, and in a surprising number of structures metal–ammonia reduction is appropriate (Birch *et al.*, 1969). Our example is the reduction of scandenin (**46**) and its angular isomer lonchocarpic acid to (**47**). Other models are the reduction of (**48**) and (**49**) to (**50**). The process could be useful both in structure determinations and in investigations requiring biosynthetic intermediates otherwise not readily accessible.



BIOSYNTHETIC PATHWAYS IN PHYLOGENY

Secondary metabolites can be used to assist in the determination of phylogeny (or its artificial cousin taxonomy) but we have emphasized (Birch, 1963) the importance of considering the position of a compound on a biosynthetic pathway rather than its structure *per se*. If the hydrocarbon terpene unit is the primitive one, extra stages represent extra biosynthetic processes developed by a plant. For example, the number of processes increases in the order: introduction of C_5 unit, oxidation (*e.g.*, to an epoxide), cyclization on to a phenol (*e.g.*, to give an hydroxyisopropyldihydrofuran), and further oxidation with elimination of C_3 to give an unsubstituted furan. The simplest chemical structure is in this case the furthest along the biosynthetic route.

To set against this, biosynthetic stages can be lost usually more readily than they are gained, as we can see from the normal plant pigment mutations (Birch, 1960b) delphinidin (3 OH) → cyanidin (2 OH) → pelargonidin (OH). The evidence, therefore, has to be cautiously interpreted.

It may assist interpretation to distinguish trivial from major synthetic developments. Trivial processes presumably can readily evolve repeatedly and independently. In the present context terpenoid ether formation is probably more trivial than reaction on carbon, and introduction of a terpene unit into a very nucleophilic environment (such as a phenol) is likely to be more trivial than into a nonphenolic benzene ring. Chemical judgment and intuition as to the probability of a given process would therefore be important.

Compounds of mixed terpenoid origins are quite widespread in some plant families, *e.g.*, *Rutaceae*, and the principles noted should make their structural examination more fruitful in considering phylogenetic relations.

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Received for review April 8, 1971. Accepted August 17, 1971. Presented at the Division of Organic Chemistry, 161st Meeting, ACS, Los Angeles, Calif., March–April 1971.