impossible; however, the classical method of preparing the substance is no longer necessary, since, as mentioned previously, pure isolated products are no longer required for the recognition of structures.

The quantitative evaluation of the capillary-chromatographic analysis was carried out after storage of the chromatogram on a magnetic tape by play-back through an automatic electronic direct integrator, which has the properties of a simple minicomputer. Ten minutes after the beginning of the first capillary chromatogram, the directly coupled mass spectrometer recorded the unmistakable mass spectrum of benzene by means of a UV fast recorder. Twenty minutes after a repeated GC recording, the mass spectrum of the signal showed conclusively the presence of toluene. The other main components were identified in the third combination GC/MS run by combined evaluation, and the results were checked by quantitative determination of the hydrocarbons by complete catalytic hydrogenation of the pyrolysis distillate in the form of a structure balance analysis. It is not necessary here to go into details of the apparatus and procedure, which correspond to present-day practice [9].

An interesting historical connection should be mentioned. The production of portable gas was started by *Gordon*, who asked *Faraday* for his assistance. Compressed coal gas was later also sold in portable containers, in order to supply gas to consumers whose homes were not yet connected to gasworks. At the age of 27, the Mannheim goldsmith and jeweller *Friedrich Engelhorn* (1821–1902) founded the firm "Engelhorn und Comp." for the production and sale of portable gas. Three years later, in conjunction with two gas engineers, he founded the "Badische Gesellschaft für Gasbeleuchtung", which installed street lighting in Mannheim. In 1861, *Engelhorn* set up a new company, "Sonntag, Engelhorn und Clemm"; this was the first tar factory in Germany, which produced, not only coal-tar dyes, but also their precursors such as aniline *via* benzene from tar. This Mannheim aniline factory ultimately became the Badische Anilin- und Soda-Fabrik AG., to whose management the author is deeply indebted for their generous support of his analytical investigations.

I am grateful for the idea of this work to Dr. H. Wolter, Völklingen, who has taken a particularly profound interest in the history of Faraday's work. I am also grateful to Dr. W. Benz, who carried out the mass-spectrometric investigations and evaluations, to Dr. E. Frommer for the gas analysis, and to Fräulein L. Arnold, Herr H. Fiedler, Fräulein C. Schneider, and Herr W. Schäfer for the preparation, working-up, and chromatographic analysis of the sperm oil pyrolysis products.

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Translated by Express Translation Service, London

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The Biosynthesis of Aromatic Amino Acids and its Regulation

BY F. LINGENS [*]

Microorganisms synthesize the aromatic amino acids phenylalanine, tyrosine, and tryptophan, as well as the related compounds p-aminobenzoic acid, tetrahydrofolic acid, p-hydroxybenzoic acid, ubiquinone, vitamin K, and nicotinic acid, by a highly branched route passing through shikimic acid. The biosynthesis is not regulated in the same way in all the organisms studied. The regulation is strongly dependent on the ability of the enzymes involved to be resolved into isozymes, their ability to be inhibited, and their activation, repression, and induction.

1. Introduction

The synthesis of aromatic amino acids in nature starts with intermediates of the carbohydrate metabolism. The main pathway ("shikimic acid route") of this highly branched biosynthetic chain leads to phenylalanine, tyrosine, tryptophan, and *p*-aminobenzoic acid. In some microorganisms, in mammals, and even in humans, tryptophan is used *inter alia* as a starting material for the biosynthesis of nicotinic acid; *p*-aminobenzoic acid is used for the biosynthesis of tetrahydrofolic acid. It has very recently been discovered that vitamin K and ubiquinone are also derived from the main pathway for the biosynthesis of aromatic compounds (see Scheme 1). The single biosynthetic chain described here is subject to biochemical regulation.

The investigations described in this review were carried out mainly on the Enterobacteriaceae *Escherichia coli*, *Aerobacter aerogenes*, and *Salmonella typhimurium*, on yeasts (particularly *Saccharomyces cerevisiae*), and on

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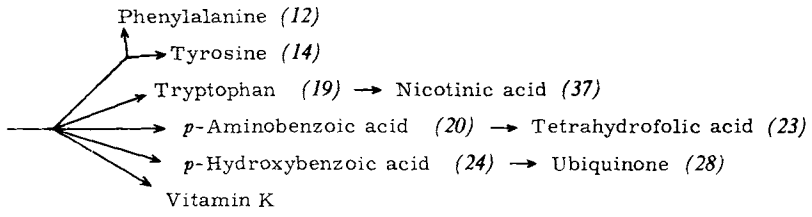


Scheme 1. General scheme of the biosynthetic pathways.

the mold *Neurospora crassa*. It must be pointed out that findings relating to a single organism, particularly in connection with the regulation of biosynthetic processes, cannot be generalized without further investigation. For example, nicotinic acid can be biosynthesized in microorganisms in several different ways; moreover, many microorganisms cannot produce either ubiquinone or vitamin K.

The regulation of biosynthetic chains is a means of ensuring that the end products are formed only as required. The end product of a chain may, for example, inhibit the first enzyme of the chain (negative feedback). The end product may also inhibit the biosynthesis of some or all of the enzymes of the chain (repression).

In a branched biosynthetic chain, it is necessary to regulate the main pathway as well as each individual chain. This is possible *e.g.* if the first step of the main pathway is catalyzed by isozymes, each of which is specifically inhibited by an end product situated beyond the branching point (see Scheme 1). However, this control may also be exerted through a single enzyme, which is inhibited only when all the end products are present at the same time (multivalent negative feedback). A third possibility for regulation in the main pathway is that biosynthesis of the enzyme is suppressed only by the simultaneous presence of end products of several chains (multivalent repression). It would be useful if the end product of one chain in a branched biosynthetic chain not only inhibited the first enzyme of its own chain, but also simultaneously activated the first enzyme of another chain. Multivalent induction, in which an enzyme of one chain is induced by end products of several chains, has also been observed.

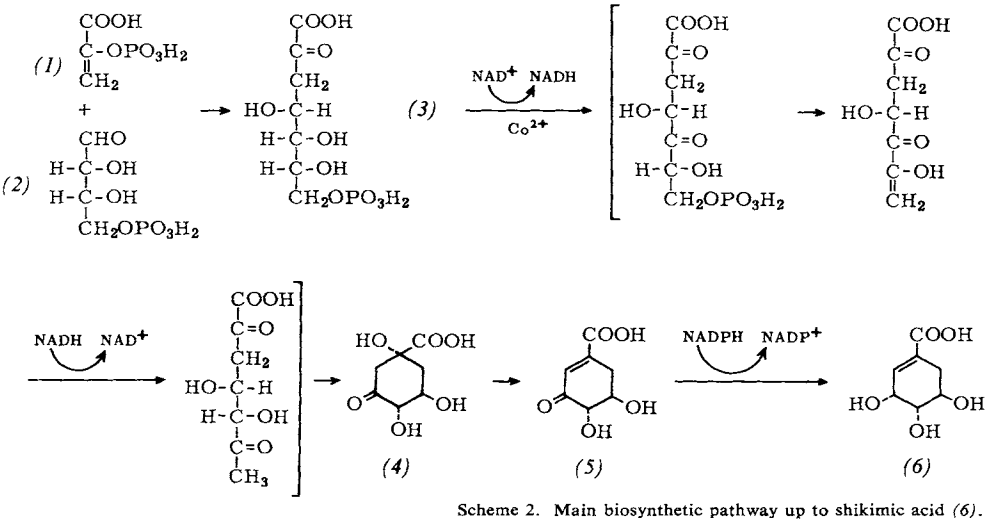
Biochemical deficiency mutants having a suitable genetic block have frequently been introduced into the synthetic chain in order to study biosynthetic processes. (For descriptions of methods, see [1].)

1.1. Definitions

An organism that can grow with CO_2 as its source of carbon is said to be autotrophic; if an organic carbon source is necessary, the organism is heterotrophic. Many microorganisms in nature ("wild strains" = prototrophic forms) synthesize all the compounds that they need to live from a simple organic carbon source and inorganic salts. In a prototrophic organism, the DNA can be changed in such a way by the action of a mutagen that one enzyme disappears (genetic blockage by mutation). The resulting "auxotrophic" forms (biochemical deficiency mutants) also require the end product or one of the compounds of the pathway beyond the genetic block for their growth. A single mutation can also lead to a polyauxotrophic organism, which requires several end products for its growth, owing to mutation in the main stem of a branched biosynthetic chain. Biochemical deficiency mutants cannot grow in media that lack the end product of the broken synthetic path. However, the synthetic chain remains capable of functioning as far as the genetic block; the intermediate product formed in this way is often released into the medium (accumulation).

2. The Main Pathway of the Biosynthesis of Aromatic Amino Acids

The first step in the main pathway is the condensation of phosphoenolpyruvic acid *(1)* with erythrose 4-phosphate *(2)* to form 2-keto-3-deoxyarabinoheptonic acid 7-phosphate *(3)* [2] (see Scheme 2).



Scheme 2. Main biosynthetic pathway up to shikimic acid *(6)*.

[1] *H. Hellmann* and *F. Lingens*, Angew. Chem. *73*, 107 (1961).

[2] *P. R. Srinivasan*, *M. Katagiri*, and *D. B. Sprinson*, J. Amer. chem. Soc. *77*, 4943 (1955).

The enzyme that catalyzes this reaction (DAHP synthetase = PODH lyase: E.C. 4.1.2.15) requires neither a metal ion nor another cofactor [3]. Later investigations showed that in *E. coli* and many other microorganisms this step is catalyzed by isozymes, which all initiate the same reaction and are all characteristically inhibited by the end products of the branched biosynthetic chain.

The second step in the biosynthesis is the conversion of *(3)* into 5,5-didehydroquinic acid *(4)* [4].

This ring closure probably proceeds *via* three intermediates with seven carbon atoms in each. The oxidation at C-5 of *(3)* facilitates the elimination of phosphate in the next step. This is followed by reduction of this carbonyl group to a hydroxyl group, with restoration of the original configuration of *(3)*. The resulting 2,6-diketone cyclizes to give *(4)* [5].

In the third step, *(4)* is dehydrated to form 5,5-didehydroshikimic acid *(5)*. The enzyme involved in this dehydration is highly specific, and does not dehydrate quinic acid to shikimic acid [6]. *(5)* is then reduced to shikimic acid *(6)* (the reductase requires NADPH as the cofactor [7]).

A polyauxotrophic mutant of *E. coli* whose phenylalanine, tyrosine, tryptophan, *p*-aminobenzoic acid, and *p*-hydroxybenzoic acid requirements can be satisfied by shikimic acid alone releases *(5)* into the medium under starvation [8]; this mutant lacks the reductase for the conversion of *(5)* into *(6)*. In polyauxotrophic mutants of *E. coli* [9,10] and *S. cerevisiae* [11] that cannot utilize shikimic acid for growth, shikimic acid has been detected as an accumulated product.

Shikimic acid is phosphorylated with ATP to the 5-phosphate *(7)* [12,13] (see Scheme 3), which then reacts with phosphoenolpyruvic acid to give the 3-enolpyruvyl ether *(8)* of shikimic acid 5-phosphate [14].

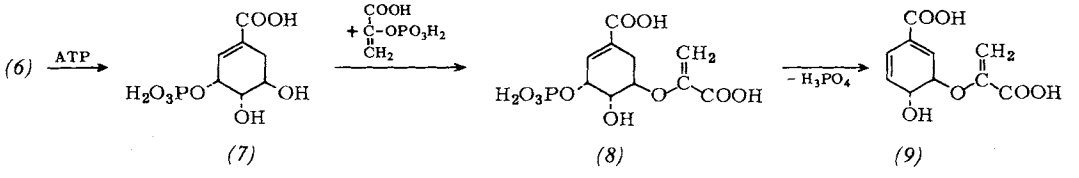
Phosphates frequently cannot be detected as accumulation products, since they are ionized compounds and so do not pass through the cell wall [15]. Moreover, phosphates are readily attacked by "nonspecific" phosphatases, and then cannot be found.

The compound *(8)* was for a long time erroneously regarded as the product at the branching point in the biosynthesis, from which the syntheses of phenylalanine, tyrosine, tryptophan, *etc.*, begin. It was noticeable, however, that *(8)* occurred as an accumulated product (in the dephosphorylated form) only in polyauxotrophic mutants. A product of the branching point, on the other hand, should occur as an accumulated product in mutants that are blocked in the first step after the branch in one of the possible biosynthetic chains. Thus different mutants should give the same accumulated product. This has in fact been found for various *S. cerevisiae* mutants, which accumulated the same branching product [16]. This secondary product of *(8)* was first detected with an *A. aerogenes* mutant, which was dependent on the simultaneous supply of phenylalanine, tyrosine, and tryptophan as a result of several mutations [17,18].

Finally, *(8)* loses phosphoric acid to give the 3-enolpyruvyl ether of *trans*-3,4-dihydroprotocatechuic acid *(9)* (chorismic acid, χωρισμος = separation) [19].

Chorismic acid closes the main stem of the biosynthesis of aromatic amino acids. The five synthetic chains that branch out from this point will now be discussed.

It should be noted that quinic acid has also been postulated as a link in the main chain. This assumption is based on the observation of the activity of this compound as a growth factor for *Aerobacter aerogenes*. This organism can synthesize 5,5-didehydroquinic acid from quinic acid [20,21]. No other microorganism examined so far has this ability. However, quinic acid is not a link in the biosynthetic chain, but serves *A. aerogenes* as an additional source of 5,5-didehydroquinic acid.



Scheme 3. Main biosynthetic pathway up to chorismic acid *(9)*.

It was particularly difficult to establish the structure of this intermediate, since it is unstable and is released in the dephosphorylated form by suitably blocked mutants.

3. Biosynthesis of Phenylalanine and Tyrosine

The common starting material for the biosynthesis of phenylalanine and tyrosine is prephenic acid *(10)* which is formed enzymatically from chorismic acid *(9)* [22]. The conversion of *(9)* into *(10)*, which is catalyzed by chorismate mutase, may be regarded as a Claisen rearrangement. It can also be effected in the

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[7] *H. Yaniv* and *C. Gilvarg*, J. biol. Chemistry *213*, 787 (1955).

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[12] *B. D. Davis* and *E. S. Mingioli*, J. Bacteriol. *66*, 129 (1953).

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[14] *I. G. Levin* and *D. B. Sprinson*, Biochem. biophysic. Res. Commun. *3*, 157 (1960); J. biol. Chemistry *239*, 1142 (1964).

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[17] *M. I. Gibson* and *F. Gibson*, Biochem. J. *90*, 248 (1964).

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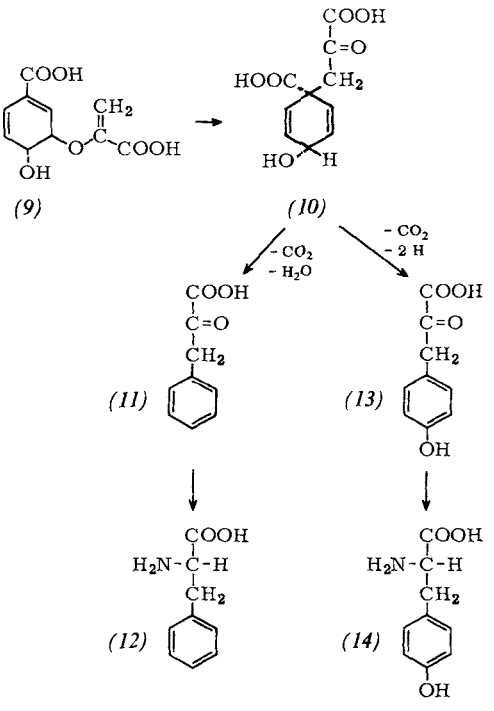
absence of enzyme by careful heating of *(9)* in buffer solutions at pH = 7.0.

Prephenic acid *(10)* is enzymatically aromatized at pH = 7 to phenylpyruvic *(11)* and *p*-hydroxyphenylpyruvic acid *(13)*. The formation of *(11)* is catalyzed by prephenate dehydratase [23].

This reaction proceeds readily in weakly acidic media in the absence of enzyme. This explains why a mutant that lacks prephenate dehydratase, and which accumulates *(10)* under deficiency conditions, can grow readily with the accumulated product after decomposition to form *(11)* if the acidification of the medium is not prevented by continuous addition of alkali [24, 25].

Reductive transamination of phenylpyruvic acid *(11)* leads to phenylalanine *(12)* (see Scheme 4).

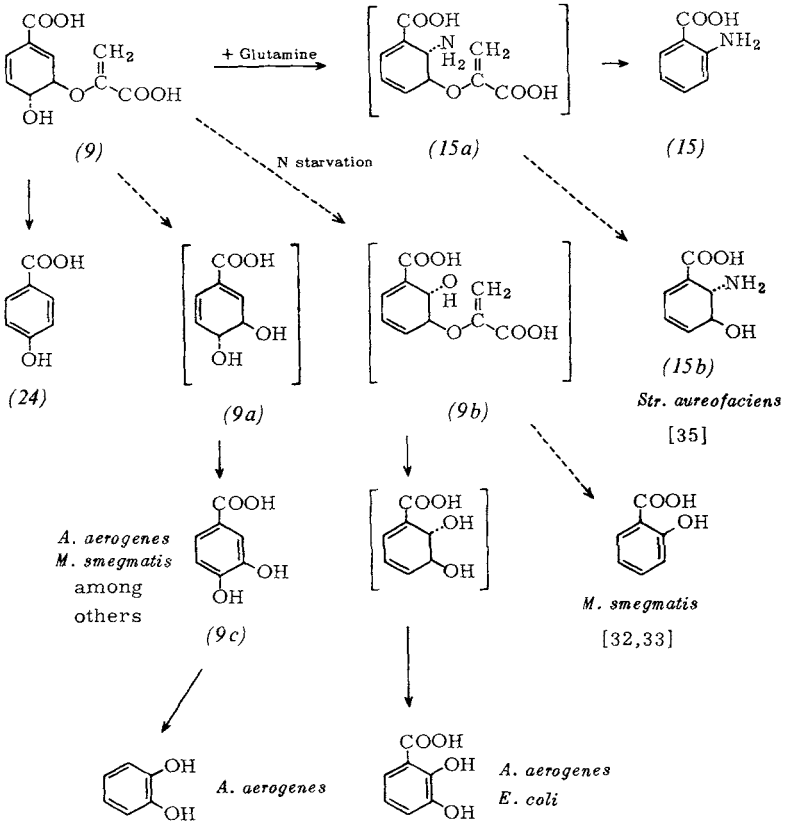
p-Hydroxyphenylpyruvic acid *(13)* is formed from prephenic acid *(10)* with catalysis by prephenate dehydrogenase. This reaction requires NAD as a cofactor [26]. The reductive transamination of *(13)* yields tyrosine *(14)*.



Scheme 4. Biosynthetic pathways to phenylalanine *(12)* and tyrosine *(14)*.

4. Biosynthesis of Tryptophan

The first link in the biosynthetic chain leading to tryptophan is anthranilic acid *(15)* (see Scheme 5). Though the transformation of chorismic acid *(9)* into anthranilic acid is a complex process, this reaction is catalyzed [27,28], at least in *N. crassa* and *S. cerevisiae*, by a single enzyme. The amide nitrogen of glutamine gives the amino group in *(15)* [29]. It might be assumed that this biosynthesis proceeds *via* the 3-enolpyruvyl ether of *trans*-2,3-dihydro-3-hydroxyanthranilic acid *(15a)*;



Scheme 5. Biosynthetic pathway to anthranilic acid *(15)* and branches.

[23] *B. D. Davis*, Federat. Proc. *14*, 691 (1955).

[24] *B. D. Davis*, Science (Washington) *118*, 251 (1953).

[25] *M. Katagiri* and *R. Sato*, Science (Washington) *118*, 250 (1953).

[26] *I. Schwinck* and *E. Adams*, Biochim. biophysica Acta *36*, 102 (1959).

[27] *J. A. DeMoss*, J. biol. Chemistry *240*, 1231 (1965).

[28] *F. Lingens, B. Sprössler*, and *W. Goebel*, Biochim. biophysica Acta *121*, 164 (1966).

[29] *P. R. Srinivasan*, J. Amer. chem. Soc. *81*, 1772 (1959).

however, this compound has not yet been detected [16, 30, 31].

In the investigation of the conversion of *(9)* into *(15)*, the formation of phenolcarboxylic acids and phenols has been observed with some microorganisms [34]. The occurrence of large quantities of *p*-hydroxybenzoic acid *(24)* is understandable, since this compound is readily formed, both enzymatically and spontaneously, from *(9)*. The formation of protocatechuic acid *(9c)* could be imagined as resulting from the initial cleavage of the ether linkage in *(9)* to form *trans*-3,4-dihydroprotocatechuic acid *(9a)*, which is then dehydrogenated. Decarboxylation of *(9c)* yields pyrocatechol. If starved of nitrogen, a 3-enolpyruvyl ether of *trans*-2,3-dihydro-2,3-dihydroxybenzoic acid *(9b)* could occur as an analog of the nitrogen compound. The occurrence of this compound would readily explain the formation of salicylic acid (removal of pyruvic acid), as well as the formation of 2,3-dihydroxybenzoic acid (cleavage of the ether linkage and dehydrogenation). *trans*-2,3-Dihydro-3-hydroxyanthranilic acid *(15b)* has been isolated from a *Streptomyces aureofaciens* mutant having a reduced ability to synthesize tetracycline [35]. It may be assumed that this compound is formed by cleavage of the ether linkage in the postulated intermediate *(15a)*.

Cox and *Gibson* [36] very recently showed that 2,3-dihydroxybenzoic acid has an additional growth effect on polyauxotrophic mutants of *E. coli*, but is not a precursor of ubiquinone or vitamin K. However, this compound is evidently also formed in excess of actual requirements, since the accumulation of the serine compound of 2,3-dihydroxybenzoic acid has been observed with *E. coli* [37].

2,3-Dihydro-2,3-dihydroxybenzoic acid was recently detected as an intermediate in the biosynthesis of 2,3-dihydroxybenzoic acid [37a].

N-Pyruvoylanthranilic acid, which is reported to occur as an accumulation product of *A. aerogenes* [38], has been postulated as an intermediate in the conversion of chorismic acid *(9)* into anthranilic acid. *N*-Pyruvoylanthranilic acid has been synthesized [39], but could not be converted into anthranilic acid in enzymatic tests with *S. cerevisiae* extracts [28].

The conversion of *(9)* into *(15)* can be inhibited by glutamine-like substances. No intermediates of the transformation could be detected in inhibition experiments with 6-diazo-5-oxonorleucine. A mutant that normally accumulates anthranilic acid as a result of genetic blocking of the tryptophan biosynthesis chain gives chorismic acid *(9)* and products of the other biosynthetic branches in the presence of 6-diazo-5-oxonorleucine [40]. *(9)* is accumulated in good yield by a series of phe$^-$ and/or tyr$^-$ mutants [*] of *S. cerevisiae* and *E. coli*. The yield can be increased by the addition of diazooxonorleucine if suitably precultured and accumulated [41].

It is interesting to note that chorismic acid can be detected as an accumulation product when diazooxonorleucine is allowed to act on the wild strains of *E. coli* and *S. cerevisiae* [41].

The next step in the biosynthesis of tryptophan is the reaction of anthranilic acid *(15)* with 1-pyrophosphoryl-D-ribose 5-phosphate to give 1-*o*-carboxyphenyl-D-ribosylamine 5-phosphate *(16)* (see Scheme 6). This compound, which had for a long time been formulated as an intermediate [42], was recently also detected enzymatically [43].

The corresponding phosphate-free compound should be expected as an accumulation product with suitably blocked tryptophan-deficient mutants. However, only anthranilic acid is in fact found.

The assumption that 1-*o*-carboxyphenyl-D-ribosylamine could not be detected because of its instability was incorrect; the compound [42] could be recovered unchanged from the culture medium by microorganism in a model experiment [44]. It must therefore be assumed that the unstable primary accumulation product *(16)* breaks down into anthranilic acid and ribose 5-phosphate, which is transferred to the carbohydrate metabolism.

As the biosynthesis proceeds, 1-*N*-(*o*-carboxyphenylamino)-1-deoxy-D-ribulose 5-phosphate *(17)* is formed by an Amadori rearrangement of *(16)*.

Tryptophan-requiring mutants of *A. aerogenes* [45] and *S. cerevisiae* [46] having a genetic block in the next stage of the biosynthetic chain accumulate 1-*N*-(*o*-carboxyphenylamino)-1-deoxy-D-ribulose if starved of tryptophan. This compound and its phosphate *(17)* can also be obtained by synthesis [47].

(17) is cyclized in the next step to form an indole compound *(18)* by dehydration and decarboxylation on the C atom that carried the carboxyl group, as could be shown by the conversion of 4-methylanthranilic acid into 6-methylindole [48]. The C atoms 1 and 2 of the ribulose supply the missing C atoms of the pyrrole ring [49].

The formation of 3-(indol-3-yl)glycerine-1-phosphate *(18)* was detected with enzyme extracts [50]. Tryptophan-requiring mutants of *E. coli* and *Salmonella typhimurium* release 1-indol-3-ylglycerine into the medium [42]; correspondingly blocked mutants of *S. cerevisiae* surprisingly accumulate not

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[30] *I. G. Levin* and *D. B. Sprinson*, J. biol. Chemistry *239*, 1142 (1964).

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[35] *J. R. D. McCormick, J. Reichenthal, U. Hirsch*, and *N. O. Sjolander*, J. Amer. chem. Soc. *83*, 4101 (1961); *84*, 3711 (1962).

[36] *C. B. Cox* and *F. Gibson*, J. Bacteriol. *93*, 502 (1967).

[37] *N. Brot, J. Goodwin*, and *H. Fales*, Biochem. biophysic. Res. Commun. *25*, 454 (1966).

[37a] *I. G. Young, L. M. Jackman*, and *F. Gibson*, Biochim. biophysica Acta *148*, 313 (1967).

[38] *C. Ratledge*, Nature (London) *203*, 428 (1964).

[39] *F. Lingens* and *B. Sprössler*, Liebigs Ann. Chem. *702*, 169 (1967).

[40] *F. Lingens, W. Lück*, and *G. Müller*, Hoppe-Seylers Z. physiol. Chem. *343*, 282 (1966).

[*] See Section 1.1.

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[49] *C. Yanofsky*, J. biol. Chemistry *217*, 345 (1955).

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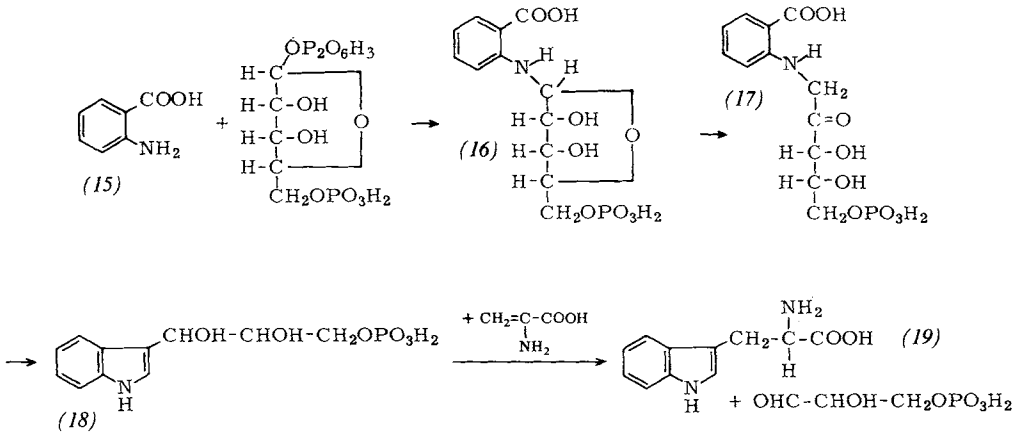


Scheme 6. Biosynthetic pathway to tryptophan *(19)*.

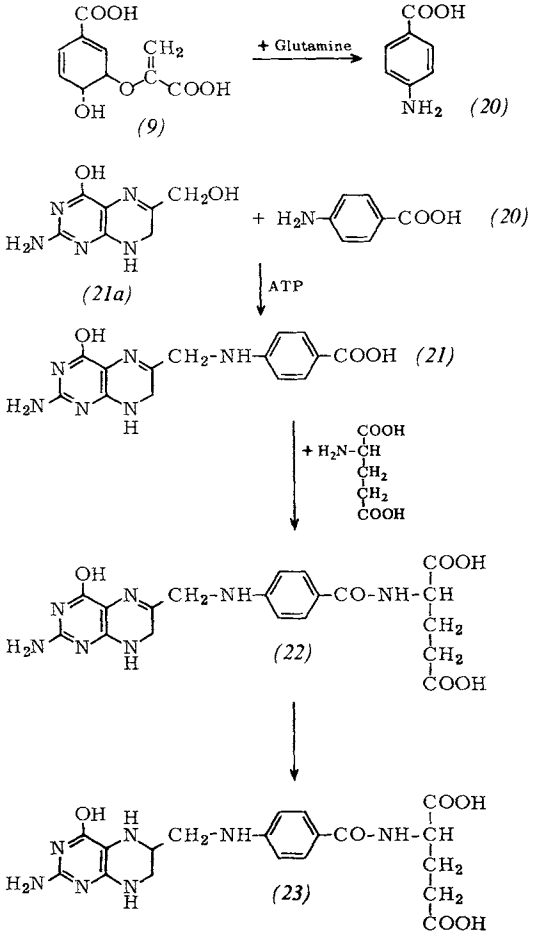
this compound, but 3,3-di(indol-3-yl)-1,2-propanediol[51]. A crude enzyme extract of *S. cerevisiae* converts *(18)* into the 1-phosphate of 3,3-di(indol-3-yl)-1,2-propanediol[51].

3-Hydroxy-3-(indol-3-yl)-2-oxopropyl phosphate was also detected[51]. One might have thought that a biosynthesis of tryptophan could take place *via* this compound with retention of the side chain, as in the biosynthesis of histidine. However, the intermediates tryptophanol phosphate, tryptophanol, and tryptophanal that would be required in this case could not replace tryptophan for a number of microorganisms[52].

The last step of the tryptophan synthesis is the condensation of *(18)* with α-aminoacrylic acid (formed from serine by intramolecular elimination of water), with elimination of glyceraldehyde phosphate to form tryptophan *(19)*. The tryptophan synthetase that catalyzes this reaction consists of two components A and B[53–55], and may be regarded as a multienzyme complex[56]. If part B is absent (owing to mutation), the second part of the reaction does not take place. Tryptophan-requiring mutants of this type accumulate indole if starved of tryptophan.

5. Biosynthesis of *p*-Aminobenzoic Acid and Folic Acid

It has been shown with enzyme extracts from yeast that *p*-aminobenzoic acid *(20)* is formed from shikimic acid 5-phosphate *(7)* with glutamine as the nitrogen donor and NAD[57] (see Scheme 7). Later investigations showed that this biosynthesis also proceeds *via* chorismic acid *(9)*[58]. No intermediates have yet been found in the conversion of *(9)* into *(20)*. Genetic studies[58a] and cross-feeding tests on mutants of *Neurospora*[58b] and of *E. coli*[58c] indicate that an intermediate is formed.



Scheme 7. Biosynthetic pathway to tetrahydrofolic acid *(23)*.

p-Aminobenzoic acid is the starting material for the biosynthesis of folic acid. According to studies by *Brown et al.*, the biosynthesis in *E. coli* proceeds as follows: *p*-Aminobenzoic acid is first condensed with 2-amino-4-hydroxy-6-hydroxymethyl-7,8-dihydropteridine *(21a)* in the presence of ATP to give dihydropteroic

[51] *F. Lingens* and *W. Goebel*, Biochim. biophysica Acta *107*, 183 (1965); *148*, 70 (1967).

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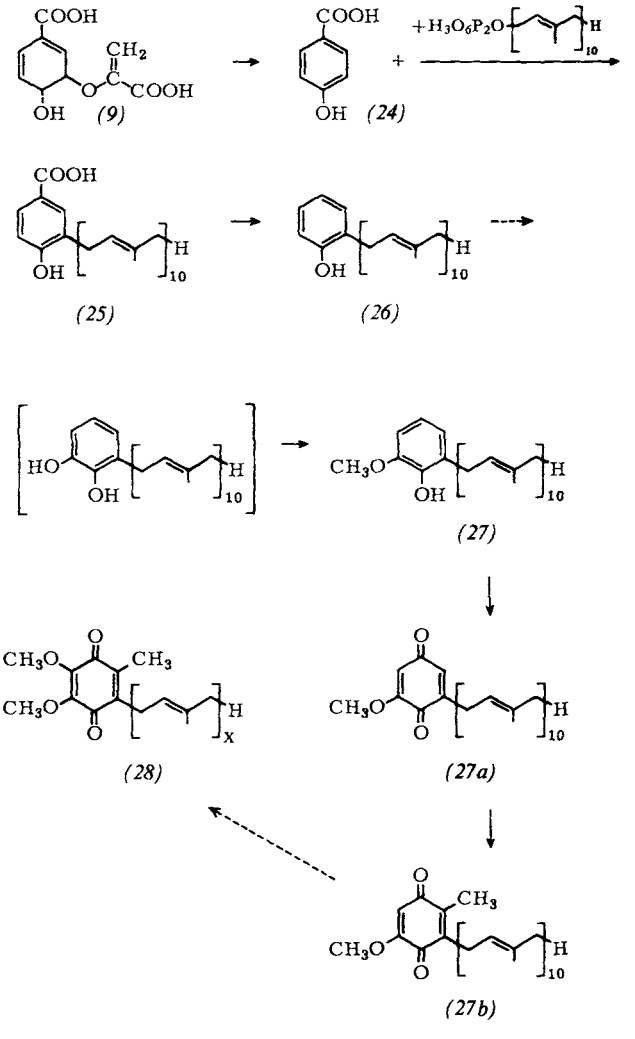
acid *(21)*; *(21)* then reacts with glutamic acid to form dihydrofolic acid *(22)*, which is finally reduced to the biologically active tetrahydrofolic acid *(23)* [59].

6. Biosynthesis of *p*-Hydroxybenzoic Acid and of Ubiquinone

p-Hydroxybenzoic acid *(24)* is formed both enzymatically and spontaneously from chorismic acid *(9)* (see Scheme 8).



Scheme 8. Biosynthetic pathway to ubiquinone *(28)*. In yeast ubiquinone x = 6.

It has been shown in enzyme experiments that for *E. coli*, ^{14}C-shikimic acid is incorporated into ubiquinone. The degree of incorporation is decreased by the addition of *(24)* [60]. This shows that the biosynthesis of ubiquinone can proceed *via* *p*-hydroxybenzoic acid. It has been found with enzyme extracts from *Rhodospirillum rubrum* that *(24)* reacts first with decaprenyl pyrophosphate to form 3-decaprenyl-4-hydroxybenzoic acid *(25)*, which is then decarboxylated to give 2-decaprenylphenol *(26)* [61].

2-Decaprenyl-6-methoxyphenol *(27)* has been isolated as another intermediate in the synthesis of ubiquinone in *Rhodospirillum rubrum* [62,63]. The 3-decaprenylpyrocatechol postulated as an intermediate in the transition from *(26)* to *(27)* has not yet been detected. Other intermediates [*(27a)* and *(27b)*] of the biosynthesis of ubiquinone have recently been detected [63a].

In the discussion of the formation of ubiquinone, it must be borne in mind that *p*-hydroxybenzoic acid *(24)* can be formed, not only from chorismic acid *(9)*, but also from tyrosine. It has been assumed that *(24)* is converted into *p*-hydroxybenzaldehyde, which can also be formed from *p*-hydroxyphenylpyruvic acid by a nonenzymatic reaction. *p*-Hydroxybenzaldehyde is thought to be the starting material both for the quinone ring of ubiquinone and for *p*-hydroxybenzyl alcohol. It should be mentioned that mammals can also synthesize tetrahydrofolic acid *(23)*. The necessary *p*-hydroxybenzoic acid is presumably produced *e.g.* by rats from tyrosine, since there is no chorismic acid available [64]. It is interesting to observe that the protozoon *Tetrahymena pyriformis* can form the benzoquinone ring of ubiquinone from shikimic acid, whereas this organism lacks the enzymes for the synthesis of tryptophan and phenylalanine [65].

7. Biosynthesis of Vitamin K [*]

Davis observed that polyauxotrophic mutants of *E. coli* that depend on the simultaneous supply of phenylalanine, tyrosine, tryptophan, *p*-aminobenzoic acid, and *p*-hydroxybenzoic acid grow better when an unknown sixth factor, which is present in the usual whole medium for bacteria, is also added [66]. This factor is probably a compound that can be converted into vitamin K. It is known from investigations by *Cox* and *Gibson* that vitamin K is formed by the sixth biosynthetic pathway. ^{14}C-Shikimic acid is converted into ^{14}C-vitamin K; the radioactivity in vitamin K could not be reduced by the addition of *p*-hydroxybenzoic acid. In experiments with other substances, 3,4-dihydroxybenzaldehyde and adrenaline were found to be effective [67]. However, it cannot be concluded from this that the two compounds are true intermediates of the biosynthetic chain. *Leistner*, *Schmitt*, and *Zenk* [67a] detected α-naphthol *(29)* as a precursor of vitamin

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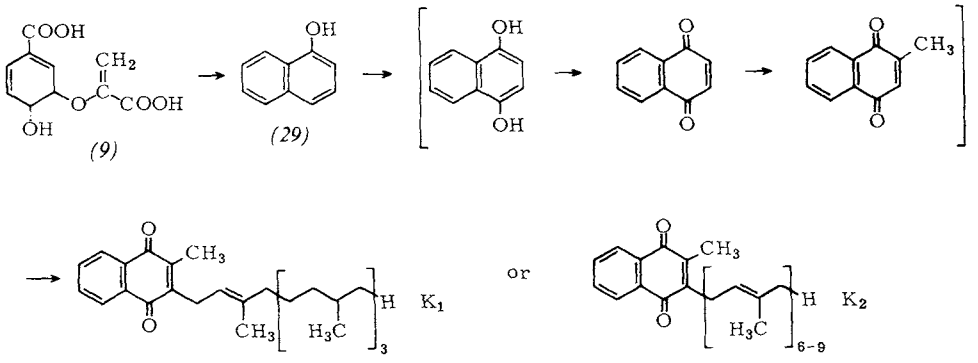


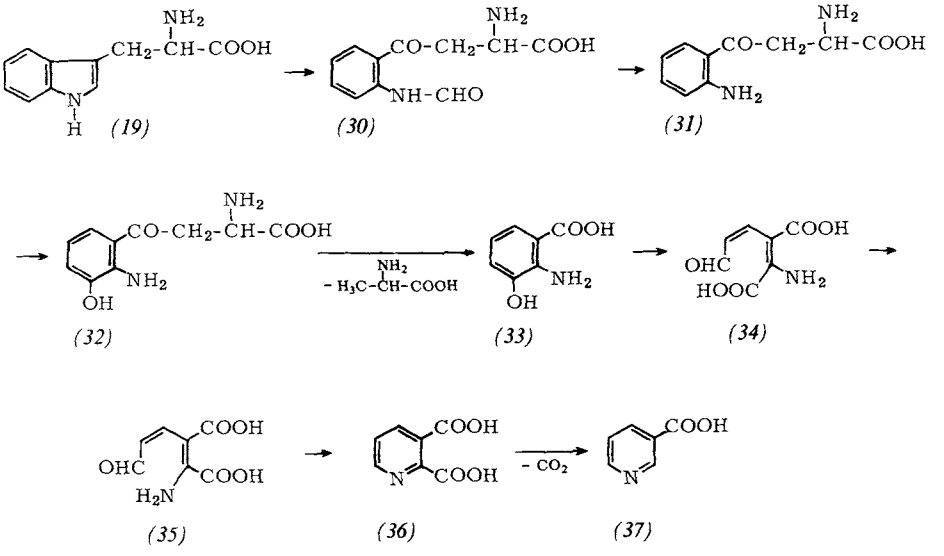
Scheme 9. Biosynthetic pathway to vitamin K.

K_2; these authors postulated other intermediates of the biosynthetic pathway (see Scheme 9).

Davis showed earlier that the sixth factor of the medium could be replaced by pyrocatechol derivatives [68]. *Martius* and *Leuzinger* found that the vitamin K-heterotrophic anaerobic bacterium *Fusiformis nigrescens* converts 1,4-naphthoquinone into 2-methylnaphthoquinone and thence into vitamin $K_{2(45)}$, *i.e.* a vitamin K_2 with 45 C atoms in the side chain. Methionine acts as a methyl donor, but active formate and the β-carbon atom of serine do not [69].

8. Biosynthesis of Nicotinic Acid

The biosynthesis of nicotinic acid is related to the biosynthesis of aromatic amino acids, since the starting material for this synthesis in many organisms is tryptophan [70]. There is also at least one other route, which does not start with aromatic compounds. Some mammals, including man, can synthesize nicotinic acid from tryptophan, so that the definition of a vitamin is not strictly satisfied in this case. The same biosynthetic pathway is followed by fungi, yeasts, and certain phycomycetes [71–73]. In the first step, tryptophan *(19)* is converted into formylkynurenine *(30)*, from which kynurenine *(31)* is formed by cleavage with a formylkynurenine amidase [74]; *(31)* is finally hydroxylated to give 3-hydroxykynurenine *(32)* (see Scheme 10). This is cleaved by kynureninase into 3-hydroxyanthranilic acid *(33)* and alanine [75]. Ring cleavage in 3-hydroxyanthranilic acid *(33)* by a 3-hydroxyanthranilate oxygenase gives 2-amino-3-formylvinylfumaric acid



Scheme 10. Biosynthetic pathway to nicotinic acid *(37)*.

(34) [76, 77]. This compound must be isomerized into 2-amino-3-formylvinylmaleic acid *(35)* before ring closure can take place to give the pyridine system. Quinolinic acid *(36)* is formed, and decarboxylation of *(36)* yields nicotinic acid *(37)*.

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The 3-hydroxyanthranilate oxygenase was first detected in the liver [78,79]. This enzyme has recently also been detected in *Saccharomyces cerevisiae* [80].

Some authors think it possible that the ring closure is preceded by the decarboxylation, so that the synthesis does not proceed *via* quinolinic acid. However, quinolinic acid exhibits good growth activity for nicotinic acid-deficient mutants of *S. cerevisiae* [71].

Another route for the biosynthesis of nicotinic acid requires aspartic acid and a C_3 compound such as glycerol or glyceraldehyde phosphate as starting materials [81–83]. This route is used with few exceptions by bacteria, as well as by cyanophyceae, green algae, some phycomycetes, and higher plants. It is interesting in this connection to note that the biosynthesis of lysine can also proceed by two routes, *i.e. via* α-aminoadipic acid or *via* α,ε-diaminopimelic acid. A comparison of the results showed that microorganisms that form lysine *via* α-aminoadipic acid synthesize nicotinic acid from tryptophan. When the biosynthesis of lysine proceeds by the α,ε-diaminopimelic acid route, nicotinic acid is generally not formed from tryptophan [73].

9. Regulation of the Biosynthesis of Aromatic Amino Acids

The aromatic amino acids regulate their own biosynthetic pathways by allosteric inhibition, and sometimes also activation, of the following enzymes: 2-keto-3-deoxyarabinoheptonic acid 7-phosphate (DAHP synthetase) [*(1)* + *(2)* → *(3)*], chorismate mutase [*(9)* → *(10)*], prephenate dehydrogenase [*(10)* → *(13)*], prephenate dehydratase [*(10)* → *(11)*], anthranilate synthetase [*(9)* → *(15)*], and *p*-aminobenzoate synthetase [*(9)* → *(20)*] (See Scheme 11).

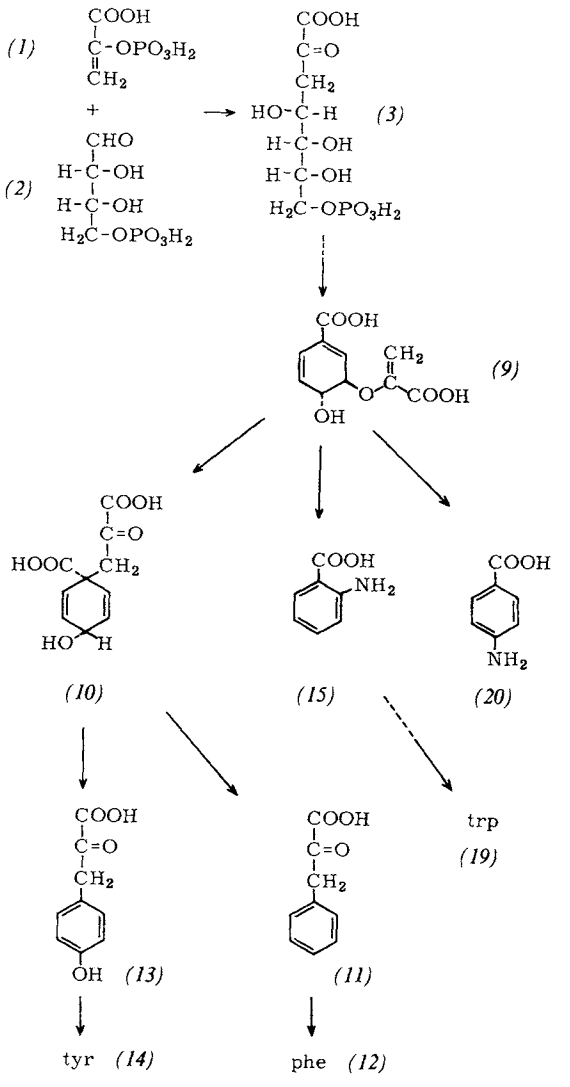
It has not yet been established how the biosynthesis of the vitamins derived from this branched synthetic chain is regulated.

Enzymes whose activities are subject to regulation are allosteric proteins. According to *Monod, Wyman*, and *Changeux* [84], these are oligomers of identical subunits, which are linked by noncovalent bonds. Each subunit has stereospecific sites for the substrate and other ligands (effectors). The oligomer (allosteric protein) occurs in the energetically different states R and T, which are in equilibrium with each other and which differ in the quaternary structure of the protein. The ligands have different affinities for the R and T states, the equilibrium between the two states depending on the concentration of the ligands. This model occurs in two forms:

1. The K system: The effectors and the substrate have different affinities for the R and T states. The effector thus influences the affinity of the enzyme protein for the substrate, and the substrate influences the affinity of the protein for the effector.

2. The V system: In this case the substrate has the same affinity for both states. Consequently the addition of the substrate is not influenced by the effector and *vice versa*. However, the two states differ in their catalytic activity, so that an effector that displaces the equilibrium in favor of the state with the lower catalytic activity inhibits the enzyme.

The investigation of the enzymes for the biosynthesis of aromatic amino acids in microorganisms has not yet progressed to the point where an assignment to these systems can be made in every case. In addition to the allosteric control of the enzymes present, regulation can also be achieved by repression and induction of the biosynthesis of all the enzymes.



Scheme 11. Regulation of the biosynthesis of aromatic amino acids.

Table 1. Inhibiting action of L-phenylalanine and L-tyrosine on enzymes from *A. aerogenes*.

Amino acid added	Inhibition of			
	Chorismate mutase		Prephenate dehydratase	Prephenate dehydrogenase
	P (%)	T (%)	(%)	(%)
L-phe (5×10^{-3} M)	65	4		
(1×10^{-3} M)			100	14
L-tyr (5×10^{-3} M)	16	2	44	
(1×10^{-3} M)				91

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In *Escherichia coli*, the first enzyme in the main chain, DAHP synthetase, consists of three isozymes, one of which is allosterically inhibited and repressed by L-phenylalanine and the other by L-tyrosine. The third enzyme is not subject to allosteric inhibition, but is repressed by L-tryptophan [85–91].

The conversion of chorismic acid *(9)* into prephenic acid *(10)* in *E. coli* and *Aerobacter aerogenes* is catalyzed by two isozymes. Each of these chorismate mutases is combined in a complex with the enzymes prephenate dehydrogenase and prephenate dehydratase, both of which are also inhibited by the end products [92]. Table 1 shows the values of the allosteric inhibition in *A. aerogenes*. The chorismate mutase P and the prephenate dehydratase are incompletely repressed by L-phenylalanine. L-Tyrosine represses one of the two isozymes and the prephenate dehydrogenase.

The enzymes of the tryptophan biosynthesis in *E. coli* and *A. aerogenes* are coordinately repressed by L-tryptophan, and the anthranilate synthetase is completely inhibited [93–95].

Jensen and *Nester* [96–99] have found that in *Bacillus subtilis*, the first step in the main branch is allosterically inhibited by prephenic acid and by chorismic acid, but not by the final amino acids. There is only one DAHP synthetase. The chorismate mutase is not inhibited either by L-tyrosine or by L-phenylalanine; however, these amino acids inhibit the prephenate dehydrogenase and dehydratase. The prephenic acid that accumulates as a result of this inhibition can inhibit the DAHP synthetase. L-Tryptophan acts as a negative effector on the anthranilate synthetase; this can lead to an accumulation of chorismic acid, which also inhibits the DAHP synthetase, though to a smaller extent. L-Phenylalanine, L-tyrosine, and L-tryptophan cause repression of the DAHP synthetase.

A peculiarity is found in the regulation of the biosynthesis of tryptophan in *Pseudomonas putida* [100]. The last enzyme in the chain, the tryptophan synthetase, is induced by its substrate 3-(indol-3-yl)-glycerol-1-phosphate. This enzyme is not affected by L-tryptophan, whereas the other enzymes of the pathway are repressed by this amino acid.

Investigations on *Saccharomyces cerevisiae* have shown [101, 102] that L-tyrosine causes allosteric inhibition of the tyrosine-sensitive isozyme of the DAHP synthetase, the chorismate mutase, and the prephenate dehydrogenase. An excess of L-tyrosine in *S. cerevisiae* can be eliminated by induction of degradation to tyrosol. L-Phenylalanine at high concentrations causes inhibition of the phenylalanine-sensitive isozyme of the DAHP synthetase and of the prephenate dehydratase. The biosynthesis of the prephenate dehydratase is also repressed by L-phenylalanine. It is reasonable that an excess of L-phenylalanine should at the same time cause both induction and activation of the prephenate dehydrogenase. The degradation of L-phenylalanine in *S. cerevisiae*, which can serve to eliminate an excess of this amino acid, leads to β-phenylethanol.

It can be shown that L-tryptophan inhibits the first enzyme in its biosynthetic chain, *i.e.* the anthranilate synthetase; the synthesis of this enzyme is repressed by L-tryptophan, which, at the same time causes an increase in the rate of synthesis in another branch of the biosynthetic chain by induction and activation of chorismate mutase. L-Tryptophan is also degraded in *S. cerevisiae*, the product being tryptophol. Simultaneous addition of excesses of L-tryptosine, L-phenylalanine, and L-tryptophan leads not only to the phenomena described, but also to multivalent induction of the *p*-aminobenzoate synthetase, with a consequent release of *p*-aminobenzoic acid into the medium.

Further investigation of the enzymes affected by regulation show that these are allosteric proteins. The two DAHP synthetases, which are inhibited by L-tyrosine and by L-phenylalanine respectively, belong to the V system, while chorismate mutase and prephenate dehydrogenase belong to the K system [102].

The chorismate mutase of *Neurospora crassa* also belongs to the K system of allosteric enzymes, and is activated by L-tryptophan and inhibited by L-tyrosine and by L-phenylalanine. The anthranilate synthetase of *Neurospora* can also be inhibited by L-tryptophan [103]. In a study of the regulation of the biosynthesis of aromatic compounds in *Claviceps paspali*, it was found that an alkaloid-producing strain has an anthranilate synthetase that is not allosterically inhibited by L-tryptophan [104, 105]. This evidently ensures that L-tryptophan is produced in sufficient quantities for the syn-

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thesis of the alkaloid. *Claviceps paspali* contains three DAHP synthetases, which are inhibited by L-phenylalanine, L-tyrosine, and L-tryptophan respectively. (The tryptophan-sensitive isozyme accounts for most (60 %) of the total activity.) The chorismate mutase, which again belongs to the K system, is inhibited both by L-tyrosine and by L-phenylalanine. This inhibition is eliminated by L-tryptophan, which thus acts as a positive effector. Some tryptophan-like compounds can also activate the chorismate mutase; the latter can be resolved into two isozymes, but only after substantial concentration [106]. The prephenate dehydratase is allosterically inhibited by L-phenylalanine and the prephenate dehydrogenase by L-tyrosine.

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Ternary Nitrides, Phosphides, and Arsenides of Lithium

BY R. JUZA, K. LANGER, AND K. VON BENDA[*]

Ternary phases have been prepared from lithium, another metal, and nitrogen, phosphorus, or arsenic. The ternary compounds, in particular the nitrides, are thermally more stable than the binary compounds. The lithium gives rise to a relatively high polar bonding component. At high temperatures, lithium and the second metal are often randomly distributed among the interstices of the metalloid lattice. The ordering processes that take place with decreasing temperature are investigated by X-ray and magnetic methods and by differential thermal analysis. The phases are classified on a structural basis into seven groups.

1. Introduction

Ternary compounds of lithium with a metal (M) (usually of the first long period) and with nitrogen, phosphorus, or arsenic (X) in various combinations have been prepared and studied. Though work in this field is by no means closed, it has already been found that these compounds can be classified on a crystallochemical basis into a few groups of widely differing natures.

The choice of lithium as the invariable component was decided at the beginning of the experiments by the following considerations:

The strongly electropositive lithium has a low ionization potential, and its compounds are relatively strongly polar. The polar bonding component in Li_3N or Li_3P is greater than in *e.g.* AlN or AlP, or in fact than in any transition metal nitride or phosphide. Thus as we pass from a binary compound of a metal with an element of the nitrogen group to a ternary compound of the same metal containing lithium, the polar bonding component should increase.

The incorporation of lithium was also expected to have special structural consequences. It was known from investigations on $LiFeO_2$ [1] and Li_2TiO_3 [2] that even relatively highly charged ions can be randomly distributed together with lithium ions over the same special position – in this case of the NaCl lattice. This interchangeability despite the large difference in charge is due to the fact that the sizes of the Li ion and of the M^{n+} ions are approximately the same. However, the random distribution of the metals is stable only at high temperatures, and is retained in a metastable state on quenching of the ternary oxides; in the structures that are stable at low temperatures, Li^+ and Fe^{3+} or Ti^{4+} are distributed in a regular manner [3–5].

The single reported observation of a ternary nitride containing lithium – Li_3FeN_2 [6] – was important for

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