In spite of the large numbers and great diversity of alkaloid structures, it seems possible now to discern a few general principles that apply to the biosynthesis of many different alkaloids. Some broad theories of alkaloid formation have borne the test of many experimental investigations, some have received no support, some have been refuted, and some newcomers have not yet been tested adequately.

In the present chapter, brief mention will be made of experimental findings that have general significance. More information on biosynthetic pathways can be found by consulting the appropriate specific chapters or by referring to the Index for names of compounds.

Various earlier proposals for the derivation of alkaloid structures from common amino acids were considered and incorporated into the far-reaching proposals presented in 1917 by Sir Robert Robinson [23] and later expanded [24]. These comprehensive proposals were based on analogy with reactions of organic chemistry and on comparisons of structure rather than on biochemical evidence. Nevertheless, biochemical experiments have confirmed the predicted pathways to a great extent. The assumptions of Robinson’s scheme of biosynthesis may be summarized as follows:

1. The fundamental skeletons of alkaloids are derived from common amino acids and other small, biological molecules.

2. A few simple types of reaction suffice to form complex structures from these starting materials. For example, the aldol condensation:
General Theories of Alkaloid Biosynthesis

the carbinolamine condensation:

\[
\text{N-C-OH} + \text{H-C-X} \rightarrow \text{N-C-C-X}
\]

the aldehyde-amine condensation:

\[
\text{H} \quad \text{OH} \\
\text{N-H + O=C-} \rightarrow \text{N-C-} \quad \text{H}
\]

as well as simple dehydrations, oxidations, and decarboxylations. (X represents an "activating" group, such as carbonyl.)

It is important to understand that the Robinson proposals were never intended to apply to specific compounds but only to general groups of structurally related compounds. Thus a possible formation of the tropane skeleton from succindialdehyde, methylamine, and acetonedicarboxylic acid could be represented as:

\[\text{CH}_2-\text{CH} \quad \text{CH}_2-\text{COOH} \quad \text{CH}_2-\text{CH} \quad \text{CH}_2\]

\[\text{O} \quad \text{O} \quad + \text{H}_2\text{NCH}_3 + \text{C}=\text{O} \rightarrow \text{NCH}_3 \quad \text{C}=\text{O + 2CO}_2 + 2\text{H}_2\text{O}\]

However, the actual reactants in vivo might resemble more closely ornithine, glycine, and citric acid, which by relatively simple reactions could be transformed into the three represented precursors. Summarizing this categorical approach, Fig. 2-1 shows some common structural elements of alkaloids and the types of precursors from which they might be derived. A great number of experiments have been done to show that with low concentrations and under very mild conditions of temperature and pH it is possible to bring about reactions of the hypothetical precursors to form complex structures resembling alkaloids. Biochemical experiments first carried out about 1955 have continued to lend support to the overall ideas of Sir Robert Robinson, although certain discrepancies and variations have been found. The biochemical experiments will be considered in the separate chapters on the different groups of alkaloids.

Another useful generalization in considering pathways of alkaloid biosynthesis is the probable importance of amine oxidases in the production of alkaloid structures. Mann and Smithies [19] and Hasse and Maisack [8] showed that cyclic compounds were formed as the result of the action of plant diamine oxidase on 1,4-diaminobutane (putrescine) or 1,5-diaminopentane (cadaverine). Initial formation of an imine and ring closure with loss of ammonia or formation of an aldehyde and ring closure with loss of water were two possible mechanisms suggested.