The term alkaloid was coined in 1819 by the German Scientist Carl F. W. Meissner [1] and is derived from Arabic al qualja “means ashes of plants”. Alkaloids are groups of natural occurring simple or complex, low molecular weight nitrogen containing compounds which are basic in nature. They are secondary metabolites abundantly found in plants, but also to a lesser extent in microorganisms (bacteria and fungi) and animals [2]. Alkaloids perform various physiological functions in living organisms.

Alkaloid may be classified according to the structural relationship between the nitrogen-containing structure such as pyrrolidine, piperidine, quinoline, isoquinoline and indole and the alkaloid skeleton [3]. Generally, amino acids such as ornithine, lysine, phenylalanine, tyrosine, tryptophan and histidine are precursor for most of the alkaloids (figure 1).

**Decarboxylation of amino acid**

Amino acids are the most common precursors in the biosynthesis of alkaloids. Decarboxylation of amino acids [4] is first step towards alkaloid biosynthesis. It is performed by an enzyme often using the cofactor pyridoxal phosphate. The reaction is initiated with the nucleophilic attack of the amino function of amino acid to the aldehyde function of pyridoxal
phosphate. The resulting imine intermediate undergoes decarboxylation giving a carbanion in which the negative charge can be delocalized. Protonation of the carbanion followed by hydrolysis of imine gives an amine and pyridoxal phosphate which is available for further use in the next reaction (Figure 2).
Alkaloids derived from Ornithine

L-Ornithine is a natural amino acid not found in proteins. In animals, it is produced from arginine during urea cycle, a reaction catalyzed by the enzyme arginase. In plants, it is produced from L-glutamic acid. Ornithine contains two amino functions: α and δ-amino group, δ- amino group is a part of alkaloid structure along with the carbon chain excluding carboxyl group. Thus, pyrrolidine ring system (C4N) in alkaloid derived from ornithine. It is also present in tropane alkaloids (figure. 3).

Ornithine gives mainly two class of alkaloids: pyrrolidine and tropane alkaloids. Some of the common examples [4] of this series are shown below.
Biosynthesis of Polyamines

The simple polyamines such as putrescine, spermidine, and spermine play critical biological roles in eukaryotic cells and are synthesized from L-Ornithine and L-Methionine. Further, in animals, putrescine is synthesized from the ornithine through PLP dependent decarboxylation reaction. In plants and microorganisms, putrescine is also synthesized simultaneously from arginine [5]. In this route, L-ornithine is converted to L-arginine which undergoes decarboxylated via PLP to form agmatine. The hydrolysis of imine function in guanidine in agmatine yields N-carbamoyl putrescine, which on further hydrolysis gives putrescine. At this point, alkylation of putrescine gives spermidine and spermine respectively. It is noted here that aminopropyl group comes from a decarboxylated SAM (dcSAM) to putrescine. These reactions are catalyzed by enzyme spermidine synthase and spermine synthase respectively as shown in figure 4.
Biosynthesis of Cocaine

Cocaine is an example of tropane alkaloid which is generally found in plants of Solanaceae family [6]. This family also contains other alkaloids such as hyoscyamine, hygrine, cusohygrine etc. The biosynthesis of cocaine is very complex, involving many steps. First, putrescine is synthesized from amino acid glutamic acid as shown in figure 4. Next, putrescine is methylated to N-methylputrescine by enzyme, putrescine N-methyltransferase. N-methylputrescine undergoes oxidative deamination to yield the aldehyde which finally gives N-methyl-Δ1-pyrrolinium cation as a result of Schiff base formation (Figure 5).

In the next step, the additional carbon atoms required for cocaine synthesis are provided by acetyl-CoA which in turn obtained from addition of two acetyl-CoA units. The first step is a Mannich-like reaction in which the enolate anion from acetyl-CoA acts as a nucleophile towards the pyrrolinium cation and give two products with S and R configuration. The second step is Claisen condensation that produces 2-substituted pyrimidine with the retention of the thioester group of the second acetyl-CoA. In the cocaine biosynthesis, tropane rings is only obtained by the cyclization of only (S)-enantiomer. This involves series of Mannich-line reaction. The oxidation of 2-substituted pyrrolidine yields the pyrrolinium cation and formation of an enolate anion in the side chain that undergoes intramolecular Mannich reaction to give tropane skelton. The tropane ring system undergoes hydrolysis, SAM-dependent methylation and reduction via NADPH to yield methylecgonine. Here, reduction of the carbonyl group of tropinone occurs from the opposite face. Thus, in ecgonine, hydroxyl group is on 3β configuration. Cocaine is a benzoyl ester of methylecgonine. At this stage, phenylalanine is converted into benzoyl-CoA via cinnamic acid that provide benzoyl group for esterification of methylecgonine to yield cocaine. The overall reactions [7] are schematically shown in figure 6.
Alkaloids derived from Lysine

Lysine is mainly involved in the biosynthesis of piperidine, pyridine and quinolizidine type of alkaloids. It is the homologoue of L-Ornithine except it has one extra methylene which provides six-membered piperidine (C5N) rings in alkaloids as shown in figure 7.

Some of the well-known examples [4] of this class include anaferine, sedamine, pelletrine, nicotine, (-)-sparteine, swainsonine etc. as shown below.
Biosynthesis of Anaferine

Anaferine is commonly found in Withania somnifera (Solanaceae) and is used as medicine since ancient times [8]. In the anaferine biosynthesis, L-lysine is converted into piperideine salt involving diamine cadaverine pathway. The nucleophilic attack of acetoacetyl-CoA anion on ∆1-piperidinium salt involving Mannich like reaction yield product which on hydrolysis and decarboxylation yields pelletierine alkaloids. Anaferine is biosynthesized [7] from pelletierine in which piperidine ring is added via an intermolecular Mannich reaction. The reactions are given in figure 8.

Biosynthesis of Nicotine

Nicotine is an example of pyridine alkaloids. It is commonly found in tobacco (Nicotiana tabacum; Solanaceae) along with another alkaloid anabasin. Nicotine consists of pyridine ring containing pyrrolidine ring at position-3. The biosynthesis of nicotine [7] is given in figure 9. Nicotinic acid is reduced into intermediate dihydronicotinic acid by an enzyme
NADPH. The reduced nicotinic acid undergoes decarboxylation to yield an electron-rich enamine 1, 2-dihydropyridine. N-methylpyrrolinium cation, synthesized from L-ornithine via putrescine undergoes aldol type reaction with the 1, 2-dihydropyridine rings. The reaction is followed by dehydrogenation of dihydropyridine ring to pyridine yields nicotine.
Alkaloid derived from Phenylalanine and Tyrosine

Tyrosine and phenylalanine are the precursor of many alkaloids [4]. The members of this group contain β-phenylethylamine, C6H5CH2CH2NH2 in their scaffolds. Some of the common examples of this category are Dopamine, epinephrine, mescaline, ephedrine, codeine, morphine, etc.

Biosynthesis of Epinephrine (adrenaline)

Tyrosine is involved in biosynthesis of many alkaloids [7]. First, tyrosine undergoes oxidation to 3,4-dihydroxytyrosine (L-DOPA) with the help of an enzyme tyrosine hydroxylase. Subsequently, it undergoes PLP-dependent decarboxylation into 3,4-dihydroxyphenyl-ethylamine (dopamine). Further, β-hydroxylation of dopamine with the help of an enzyme dopamine-b-monooxygenase yields noradrenaline, a mammalian neurotransmitter. Methylation of noradrenaline by enzyme phenylethanolamine N-methyl transferase gives adrenaline, a hormone released in animals from the adrenal gland during stress. Moreover, dopamine can undergo aromatic hydroxylation and o-methylation to gives mescaline. Mescaline alkaloid is found in the cactus Lophophora williamsii (Cactaceae) and is known for psychoactive and hallucinogenic properties [9]. The overall biochemical reactions are shown in figure 10.
Biosynthesis of norcoclaurine

This is an example of a tyrosine alkaloid, and its biosynthesis is an example of how 1, 2, 3, 4-tetrahydrosoquinoline rings can be formed. Tyrosine undergo oxidation to form 3,4-dihydroxytyrosine which on decarboxylation yields amine.
Simultaneously, tyrosine also undergoes transamination into keto acid which on decarboxylation yields aldehyde. Aldehyde and amine are substrate for Pictet-Spengler reaction that give tetrahydroisoquinoline ring in norcoclaurine. Norcoclaurine contains phenol which on oxidation gives phenoxy radicals. These phenoxy radicals dimerize into more complex alkaloids like thebaine and (R)-reticuline. The schematic biochemical reactions [7] are shown in figure 11.

Biosynthesis of Morphine

The word morphine is derived from Morpheus, the Greek God of Dreams [10]. Morphine is a highly potent analgesic drug. It is a principal active agent in opium, along with codeine and thebaine. (R)-Reticuline is the precursor of morphine alkaloid. The biosynthesis of morphine [7] is very complex and involves many steps as shown in figure 12. Briefly, (R) reticuline forms diradical as a result of one-electron oxidation of hydroxyl functional present in each benzene ring. The diradical coupling between two rings yields dienone salutaridinone, which is found as a minor constituent alkaloid in opium poppy Papaver Somniferum (Papaveraceae) [11]. Here the coupling enzyme salutaridinone synthase is a cytochrome P-450-dependent monooxygenase. Stereospecific reduction of the carbonyl group of Salutaridinone by NADPH gives salutaridinol. Acetylation of hydroxyl group in salutaridinol with acetyl-CoA followed by nucleophilic attack of the phenol group gives thebaine. Removal of one of the two O-methyl groups, present as an enol, generates neopinone, which gives codeinone followed by codeine through a process that involves a non-enzymatic keto-enol tautomerism and NADPH-dependent reduction respectively. Finally, demethylation of codeine by means of oxygen results in morphine.
Alkaloid derived from Trptophan

L-Tryptophan is an aromatic amino acid that contains indole ring and it is precursor for biosynthesis of wide range of indole alkaloids. The well-known simple alkaloids include tryptamine and its derivatives viz. melatonin, sumatriptan, eletriptan, harmine, as well as complex alkaloids such as vinblastine, ajmalicine, serpentine, etc.
Biosynthesis of Harmane

The biosynthesis of harman is simple and straightforward [7]. The first step is decarboxylation of tryptophan to give tryptamine. The next step is condensation of tryptamine with the acetaldehyde to form an imine. The protonated imine is electron deficient and acts as a nucleophile in an intramolecular substitution reaction. This is the very well-known Pictet-Spengler reaction in organic chemistry. Subsequently, removal of a proton at the carbon-2 restores aromaticity and yields
a tetrahydro harman derivative which on oxidation gives harman. The overall reactions are shown in figure 13.

**Biosynthesis of Ajmalcine and Serpentine**

Ajmalicine is complex indole alkaloid that affects smooth muscle function and is useful in preventing strokes [12]. It is produced by a multistep biosynthesis process. The first step is decarboxylation of tryptophan to tryptamine, a reaction that is common in all examples of indole alkaloid biosynthesis. The next step is condensation of tryptamine with secologanin; a natural terpenoid in a Pictet-Spengler reaction, which generates the tetrahydro-β-carboline system and produces strictosidine.

Hydrolysis of the glycoside functional group leads to the opening of the hemiacetal and exposure of an aldehyde group which can now react with the secondary amine to give a quaternary iminium cation. Allylic isomerization moves the vinyl double bond in conjugation with the iminium, generating dehydrogeissoschizine, which is followed by cyclization to form
cathenamine. Cathenamine is reduced to ajmalicine in the presence of NADPH by another dehydrogenize. Oxidation of ajmalicine to serpentine is catalysed by a peroxidase as shown in figure 14.
References


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