

Introduction

Alkaloids are the most diverse group of secondary metabolites and over 5000 compounds are known. They are most commonly encountered in the plant kingdom, but representatives have been isolated from most other orders of organisms ranging from fungi to mammals. For years, there has been interest in their pharmacological activities, and for a long time selected plant products (containing alkaloids) have been used as poisons for hunting, murder, euthanasia, as euphoricants, psychedelics, and stimulants (e.g. morphine and cocaine) or as medicines (e.g. ephedrine). Many of our modern drugs now contain the same compound or synthetic analogues, and the pharmacological and toxicological properties of these compounds are thus of immense interest and importance.

Almost two centuries have elapsed since Sertürner isolated the first organic base clearly recognised as such, a crystalline substance that he obtained from the opium poppy, *Papaver somniferum*, and called morphine. The name alkaloid is applied to the members of a class of natural products of basic nature, and is derived from the name "vegetable alkali" first applied to these substances. They all owe their basic nature to an amino nitrogen. It is more difficult than at first might be supposed to define the term alkaloid. The work was coined in 1818 by Meissner and implies a compound similar to an alkali, referring to the basic properties of this class of substance. Meyer's *Konversations-Lexikon* of 1896 states, "Alkaloids (plant bases) occur characteristically in plants and are frequently distinguished by their remarkable physiological activity. They contain carbon, hydrogen and nitrogen and in most cases oxygen as well; in many cases they resemble the alkalis". Modern dictionary definitions only differ in minor details from those of the older nontechnical literature.

A definition due to Pelletier in 1982 includes cyclic nitrogen-containing molecules which are true secondary metabolites (i.e. of limited occurrence and produced by living organisms). Simple acyclic derivatives of ammonia and simple amines are thus excluded, and the additional requirement, that the nitrogen atom must have a negative oxidation state, excludes nitro and nitroso compounds.

As for other natural products, no uniform system of nomenclature has so far been devised for alkaloids. In most cases the name of the alkaloid has been derived from the plant name. Thus, papaverine was called after the *Papaver* species from which it was isolated. The names cocaine (from *Erythroxylum coca*) and atropine (from *Atropa belladonna*) are other examples. Frequently several alkaloids are obtained from the same plant, and the names devised for them will depend on the inspiration of the natural products chemist who isolated them.

Alkaloids as a class have interested organic chemists partly on account of their physiological action on the animal organism, and partly on account of the complex structural and synthetical puzzles that they pose. The chemistry of the alkaloids is but a branch of the wide chemistry of nitrogenous heterocyclic compounds, but the methods by which the structures of individual bases are deduced from degradative evidence and confirmed by total synthesis are typical of the methods applied for these purposes. The whole field of the chemistry of natural products is illustrative of the general fundamental principles of organic chemistry.

Structural types

Alkaloids are usually classified according to the amino acids (or their derivatives) from which they arise. Thus, the most important classes are derived from the following Amino acids:

- Ornithine and Lysine
- Aromatic amino acid phenylalanine and tyrosine
- Tryptophan and a moiety of mevalonoid origin

Also a number of compounds are also derived from:

- Anthranilic acid
- Nicotinic acid

This classification however, fails to include the alkaloids derived from a polyketide or a terpenoid, with the incorporation of a nitrogen atom, ultimately from ammonia. Examples are Conine and batrachotoxin which are often known as 'pseudoalkaloids'. Other compounds covered by Pelletier's definition also exist. Examples are the antibiotic cycloserine, mitomycin C, mushroom toxin muscimol and the purine alkaloids such as caffeine.

There is another classification of the alkaloids according to the location of the nitrogen atom in certain structural features:

1. Heterocyclic alkaloids
2. Alkaloids with exocyclic nitrogen and aliphatic amines
3. Putrescine, spermidine and spermine alkaloids
4. Peptide alkaloids
5. Terpene and steroidal alkaloids

Classifying the whole range of alkaloids according to this system result in them being dividing them up unequally as the great majority fall into the heterocyclis group and the smallest group is the putrescine, spermidine and spermine alkaloids.

Occurrence

Of the more than 5000 alkaloids known, most occur in flowering plants, although the distribution is far from uniform. Thus, although 40% of all plant families have at least one species containing alkaloids, when the 10000 plant genera are considered, only about 9% of these have been shown to produce alkaloids.

Increasing numbers of alkaloids have been isolated from animals, insects, and microorganisms. Although mammalian alkaloids are rare, two examples are (-)-castoramine (a) from the Canadian beaver; and muscopyridine (b) from the musk deer.

Both compound have a role in communication as territorial marker substances.

Insects produce a variety of structural types which include the 2,6-dialkylpiperidines of the fire ant (c), the tricyclic N-oxides of the ladybird (d) and the quinazolines of the European milliped (e).

Tese compounds are used for defence.

During the last three decades Marine organisms have been investigated. Amongst the alkaloids are the exceedingly complex Saxitoxin (f) produced by a red coloured dinoflagellate. The 'red tides' contain mass aggregations of such organisms, and food poisoning when the toxic alkaloids are passed along the food chain to man. The Japanese puffer fish is highly valued as a culinary delicacy, but it is hazardous because its liver and ovaries contain the highly toxic tetrodotoxin.

Fungi also produce alkaloids, and these too, present potential hazards as food contaminants. The ergot alkaloids, for example, Chanoclavine (g) produced by the fungus *Claviceps purpurea*, were a frequent source of misery and death during the Middle Ages through the contamination of rye bread. Some of these were neurotoxic whilst others caused vasoconstriction.

During the last 40 years most of these non plant alkaloids have been isolated and their structures elucidated. The introduction of modern chromatographic and spectroscopic techniques facilitated this.

Isolation

Work on the constitution of alkaloids is often prefaced by the problem of their isolation from plant material or from residues after commercially important constituents have been removed. The isolation of each alkaloid is an individual problem there are a variety of procedures which may be entitled to generic rank. There are few plants which produce a single alkaloid so the main problem is the separation of mixtures.

Many alkaloids are basic and occur as salts of 2-hydroxybutane-1, 4-dioic acid (malic acid), or of 1,3,4,5-tetrahydroxycyclohexane (quinic acid). They can thus be extracted into acid solution using aqueous hydrochloric, tartaric, or citric acids. Neutral alkaloids such as colchicines or piperine, which are in fact amides, remain in the organic phase, whilst most other alkaloids are isolated after basification and extraction into ethyl acetate.

Steam distillation can be used also be used with low molecular weight alkaloids; but almost invariably subsequent purification of the crude alkaloid mixtures is effected by chromatography using silica or alumina, and then recrystallisation of the partially purified compounds from solvent systems like aqueous ethanol, methanol/chloroform, or methanol/acetone.

Structure elucidation

Classical era:

The classical era for structural studies on alkaloids was the 19th Century, though this could be extended to the 1930's (advent of x-ray crystallography) or even to the 1970's (advent of high resolution NMR facilities and modern methods of mass spectroscopy). Two case histories will be discussed, those of morphine and atropine.

Opium has been used by man for thousands of years, so it is not surprising that the major active ingredient, morphine, was the first alkaloid to be isolated in pure state (by Sertürner in 1805). It was not until 1923 that Sir Robert Robinson established the structure of morphine. Chemical evidence for the structure is as follows:

Standard showed that the nitrogen atom was fully substituted, and that the phenolic hydroxyl was present as it gave a positive FeCl_3 test. Two hydroxyls were present as a diacetate and dibenzoate could be formed. Both compounds contained one olefinic double bond as codeine absorbed one. It was found that a reduced phenanthrene with a two-carbon bridge containing a tertiary nitrogen atom (with methyl as on substituent) was present, and the structure of morphine and codeine were first proposed in 1923 and 1925 respectively by Robinson and Gulland. Synthesis of morphine was carried out in 1956 by Gates.

Atropine on the other hand, is not generally a natural product but arises through racemisation of (-)-hyoscyamine (see (a) below) and purification, and is thus (-)-hyoscyamine.

(-)-hyoscyamine is the most common tropane alkaloid. In 1833 atropine was isolated from *Atropa belladonna*. Hydrolysis with warm barium hydroxide solution produced racemic tropic acid and tropine.

Degradative studies and then through synthesis found the structure of tropic acid:

Exhaustive degradation of tropine, carried out by Willstätter between 1885 and 1901, provided evidence for the bicyclic structure of tropine.

The most widely used process in degradative studies of alkaloids is exhaustive methylation, known as Hofmann degradation. This involves the pyrolysis of a quaternary ammonium hydroxide to form an olefin and a tertiary base:

To ensure the complete removal of the nitrogen atom when it constitutes part of a ring, two degradations must be carried out. When exhaustive methylation of cyclic compounds might be expected to give 1,4-dienes, the alkaline conditions of the reaction may result in the migration of one of the double bonds to give a 1,3-diene. For example, the exhaustive methylation of N-methylpiperidine gives 1,3-pentadiene (piperylene) and not 1,4-pentadiene.

The diene is then easily hydrogenated to form a saturated hydrocarbon. If Hofmann degradation fails to bring about ring fission of cyclic amines, Emde degradation, involving catalytic reduction of a quaternary salt by sodium amalgam or sodium in liquid ammonia, may be applied. For example, attempted Hofmann degradation of N-methyltetrahydroquinoline methoxide results in regeneration of the parent base, while Emde reduction with sodium amalgam affords the ring-opened amine.

Alkaloids containing diphenyl ether linkages, for example, bis-benzylisoquinoline, are cleaved into two fragments by reduction with sodium in liquid ammonia. For example, the structure of the alkaloid dauricine was established by reductive cleavage of O-methyl-dauricine.

Modern era:

During the last 30 years, structure elucidation has been facilitated by the use of mass spectroscopy, and ^1H and ^{13}C NMR techniques. It is now possible to determine the structure in days with a few milligrams or less of pure compound. It took 118 years to determine the structure of morphine. The mass spectrum data for morphine is highly informative and is shown below and would have helped enormously years ago.

Once the structure of an alkaloid is known, partial or total synthesis can be attempted.

Biosynthesis

It is possible to determine the amino acid from which an alkaloid is derived just by looking at the structure. Before availability of radio-isotopes ^{14}C and tritium, and more recently the stable isotopes ^{13}C and ^{15}N it was only possible to speculate about the likely biosynthetic pathways. This was sometimes successful as for example, the suggested pathway to the isoquinoline alkaloid is as follows:

It is possible to divide the biosynthesis of the alkaloids into two categories according to whether products are obtained from the amino acids ornithine and lysine, or the aromatic amino acids phenylalanine, tyrosine, tryptophan.

Alkaloids derived from ornithine and lysine:

Pyrrolidine alkaloids – hygrine, cocaine, tropinone, hyoscyamine etc

Piperidine alkaloids – piperine, (-)-lobeline etc

Quinolizidine alkaloids – sparteine, cytisine, (-)-lupinine etc

Pyridine alkaloids – nicotine, anabasine, anatabine etc

Alkaloids derived from phenylalanine and tyrosine:

Monocyclic compounds – hordenine etc

Tetrahydroisoquinoline alkaloids – morphine, codeine, thebaine, noscapine (narcotine), papaverine, heroin etc

Alkaloids derived from tryptophan:

Simple indole derivatives: psilocybin, dimethyltryptamine, physostigmine etc

Complex indole derivatives : harmaline, echinulin, ergonovine etc

No class of naturally occurring organic substances shows such an enormous range of structures as the alkaloids with over 5000 known. It would be impossible to discuss each one of these within the time limit. Therefore, this project is concerned with the following alkaloids:

Morphine (including codeine and heroin), Cocaine, Nicotine and Caffeine (including theophylline).

These alkaloids are present in enormous quantities in the world and seem appropriate to be discussed due to the current interest in their effects particularly when used illegally. They are some of the most well known alkaloids.

Morphine (Codeine and Heroin)

When the unripe seed capsules of the opium poppy, *Papaver somniferum*, is cut or pricked, a viscous liquid is exuded. After the exudates dries and darkens with exposure to air, a hard but still partly sticky mass is obtained. This is opium, which has been used for many centuries by some for medicinal purposes. Opium is important as a painkilling drug in its own right, but is also the source of other analgesic drugs such as morphine and heroin. Mankind had discovered the use of opium by the time of the earliest written records. In fact, the first recorded use of opium as a painkiller was around 6000 years ago by the Sumerians, and the Babylonian and Egyptian writings contain many references to the value of opium preparations for the relief of pain. Thomas Sydenham, the 17th Century pioneer of English medicine wrote, "Among the remedies which it has pleased Almighty God to give to man to relieve its sufferings, none is so universal and so efficacious as opium". Nowadays, although opium is no longer regarded as a universal analgesic, it is still a very important source of morphine.

The pharmacologically active constituents of opium have been employed in medicine for many thousand of years. During the 19th century these constituents were isolated as pure chemical entities.

Morphine is a naturally occurring substance and is the major constituent of opium, constituting about 10% (sometimes up to 20%) of its weight.

Morphine was first isolated in 1805 by Friedrich Sertürner. However, its basic structure was not correctly determined until 120 years later. Morphine provides symptomatic relief of moderately severe to severe pain. Morphine acts as an anesthetic without decreasing consciousness, and it is one of the most powerful analgesics known. However, it also suppresses the respiratory system, and high doses can cause death by respiratory failure. Its analgesic properties are related to the ability of the molecule to fit into and block a specific site on a nerve cell. This eliminates the action of the pain receptor

Cocaine

Cocaine is obtained from coca leaves (*Erythroxylum coca*) and has the formula $C_{17}H_{23}O_4N$ and a molecular weight of 303.39. The anaesthetic properties of cocaine were first recognised by Köller in 1882, but it has now been largely replaced in the clinic by synthetic analogues due to its widespread abuse as a narcotic. It is, however, still much used as a stimulant by Andean Indians. After chewing the leaves, they are easily fatigued and can go on for long periods without food.

Cocaine is shipped and sold in the form of the water-soluble hydrochloride salt, which may be ingested through the nasal passages by 'snorting' orally and intravenously. There are severe physical and psychological side effects of the drug, such as brain seizures, respiratory collapse, heart attack, paranoia, and depression.

Cocaine may be hydrolysed by acids or alkalis to methyl alcohol, benzoic acid, and (-)-ecgonine, $C_9H_{15}O_3N$; only partial hydrolysis, to benzoyl- (-)-ecgonine, $C_{16}H_{19}O_4N$, and methyl alcohol when the alkaloid is boiled with water.

Cocaine can be regarded as being derived from ornithine. Willstätter worked on a tortuous synthesis (of about 20 steps) of tropinone between 1900 and 1903, but in 1917 Robinson reported his 'one-pot' synthesis and also provided what was probably the first example of a formal retrosynthetic analysis. He stated: 'By imaginary hydrolysis at the points indicated by the dotted lines, the substance may be resolved into succinaldehyde, methylamine and acetone'.

The yield of this reaction was poor but Schöpf and Lehmann reported optimised conditions (buffered solution at pH5 and 25°C) which allowed 85% yield. A variety of mechanisms are possible and the one shown below envisages a reaction between the enol form of acetone dicarboxylate and the condensation product from succinaldehyde and methylamine.

Willstätter made his own contributions based on this type of chemistry, and completed simple synthesis of tropinone in 1921 and a synthesis of cocaine in 1923. The synthesis of cocaine is as follows:

A Robinson- type reaction yielded the expected azabicyclo structure but with a fortuitous axial stereochemistry for the carbomethoxyl group. Racemic cocaine was formed after separation of the diastereoisomeric products on the reduction of the ketone and benzylation of the mixture of alcohols.

An important aspect of Robinson's route is that it represented the first biomimetic synthesis of an alkaloid. He provided inspiration for others to consider possible biosynthetic pathways, before planning their synthetic routes to alkaloids.

Nicotine

Nicotine, present in dried tobacco leaves of the plant *nicotiana tabacum* in 2-8% concentration, is the active ingredient in cigarettes and other tobacco products. The reason tobacco is used by so many people is because it contains this powerful drug nicotine. When tobacco is smoked, nicotine is absorbed by the lungs and quickly moves into the bloodstream, where it is circulated throughout the brain. All of this happens very rapidly. In fact, nicotine reaches the brain within 8 seconds after someone inhales tobacco smoke. Nicotine can also enter the blood stream through the mucous membranes that line the mouth or nose, or even through the skin. Smoking and chewing tobacco have been connected to heart and lung disease and cancer, mainly a result of the presence of carcinogens, carbon monoxide and other toxins.

Nicotine affects the entire body. Nicotine acts directly on the heart to change heart rate and blood pressure. It also acts on the nerves that control respiration to change breathing patterns. In high concentration, nicotine is deadly. In fact, one drop of purified nicotine on the tongue will kill a person. It's so lethal that it has been used as a pesticide for centuries.

So why do people smoke? The mode of action of nicotine is complex. Ingestion of the molecule may stimulate or calm the user and it may affect his or her mood, appetite, and cognition.

There appears to be little doubt that nicotine is an addictive drug, and the debate about how to regulate its availability is ongoing.

Nicotine is part of the pyridine alkaloids and is the chief alkaloid of tobacco. It can therefore be classed as a tobacco alkaloid. Nicotine has the empirical formula $C_{10}H_{14}N_2$, a molecular weight of 162.26 and was first observed by Vanquelin in 1809 and isolated 19 years later by Posselt and Reimann. Its structure is as follows:

It is a colourless liquid with a boiling point of 246.1-246.2°C and is miscible in all proportions with water below 60° and above 210°. It is less soluble between these temperatures.

When oxidised with chromic acid it yields an amino acid, $C_6H_5O_2N$, which may be decarboxylated to pyridine-β-carboxylic acid. Nicotine is therefore a 3-substituted pyridine and that the substituent is a saturated group containing five carbon atoms and one nitrogen atom. The alkaloid forms a crystalline addition compound with zinc chloride, and when this is heated with lime pyridine, pyrrole and methylamine are obtained, suggesting that the structure be as above (1). This was supported by the degradation of the alkaloid to N-methylproline (1) to (5) (below), the oxidation of dibromocotinine (6) to nicotinic acid, malonic acid and methylamine (6) to (7). Also, by the reductive hydrolysis of bromocotinine to methylamine and the dihydroxy-acid (8).

The structure of nicotine was finally confirmed by synthesis. Three syntheses of nicotine have been recorded.

The first was based on the discovery that N-acetylpyrrole is transformed by heat to C-acetylpyrrole shown to be α -acetylpyrrole.

Pictet and Cr  pieux applied this reaction to N- β pyridylpyrrole (3) (below) obtained by the reaction of β -aminopyridine1 with mucic acid (2).

The compound 3¹-pyridyl-2-pyrrole (4) was formed. An attempt to methylate the pyrrole nitrogen by heating the potassium derivative with yielded (5) (methiodide of 3¹-pyridyl-N-methyl-2-pyrrole). Distillation of this with calcium oxide gave nicotyrine (6). Selective hydrogenation of the pyrrole nucleus with a palladium-carbon catalyst converted nicotyrine (6) to nicotine with about a 25% yield.

P ICTET'S SYNTHESIS:

Pictet's classical synthesis involves two steps at high temperatures, one of which is a rearrangement. It cannot therefore be regarded as unambiguous.

However, a second synthesis by Späth and Bretschneider involves no rearrangement at high temperature and are thus structurally specific.

SPATH'S SYNTHESIS:

(1) (Above) was converted into (2) via electrolytic reduction, which on treatment with potassium and methyl sulphate gave (3) (N-methylpyrrolidone). Ethyl nicotinate was then condensed with (3) in the presence of sodium ethanoate and the resulting β -pyridyl- β^1 -(N¹-methyl- α^1 -pyrrolidonyl) – ketone (4) was hydrolysed with fuming hydrochloric acid at 130°. The derived amino ketone (5) was reduced with zinc and sodium hydroxide to the corresponding alcohol (6), which was converted to nicotine on treatment with hydrogen iodide and potassium hydroxide.

A third synthesis of nicotine by Craig was also carried out:

CRAIG'S SYNTHESIS:

Nicotinonitrile (1) (above) was reacted with γ -ethoxypropylmagnesium bromide. The product of the reaction (2) (3-pyridyl- γ -ethoxypropylketone) formed an oxime (3), which was reduced to an amino derivative (4). On heating to 150-155° with 48% hydrobromic acid this was converted to nornicotine (5), which in turn was methylated to nicotine.

The pyridine ring in nicotine is derived from nicotine acid, which itself is derived from aspartic acid and glyceraldehyde-3-phosphate:

The remaining steps en route to nicotine are shown below:

Caffeine

The purine system occurs widely in nature. Two purines, adenine and guanine, are constituents of the nucleic acids; adenine is a component of coenzymes I and II, of flavin adenine dinucleotide and of adenosine with 3 distinguished compounds: caffeine, theophylline and theobromine. They are physiologically active constituents of coffee, cocoa, and tea. The compounds have different biochemical effects, and are present in different ratios in different plant sources. These compounds are very similar and differ only by the presence of methyl groups in two positions of chemical structure as shown below:

They are easily oxidised to uric acid and other methyluric acids, which are also similar in chemical structure.

CAFFEINE – 1,3,7- trimethylxanthine

SOURCES – Coffee, tea, cola nuts, mate, guarana

EFFECTS – Stimulant of the central nervous system, cardiac muscle and respiratory system, diuretic, delays fatigue.

THEOPHYLLINE – 1,3 – dimethylxanthine

SOURCES – Tea

EFFECTS – Cardiac stimulant, smooth muscle relaxant, diuretic, vasodilator.

THEOBROMINE – 3,7- dimethylxanthine

SOURCES – Principle alkaloid of the cocoa bean (1.5-3%), cola nuts and tea.

EFFECTS – Diuretic, smooth muscle relaxant, cardiac stimulant, vasodilator.

Theophylline has a stronger effect on heart and breathing than caffeine. For this reason it is the drug of choice in home remedies for treating asthma, bronchitis and emphysema. Theophylline found in medicine is made from extracts from coffee or tea. Theobromine is weaker than caffeine and theophylline – has one tenth of the stimulating effect.

When isolated in pure form, caffeine is a white crystalline powder that tastes very bitter. Recreationally, it is used to provide a 'boost in energy' or a feeling of heightened alertness. It's often used to stay awake longer. Caffeine inhibits the action of an enzyme, phosphodiesterase, whose job it is to inactivate a molecule called cyclic adenosine monophosphate (AMP). Cyclic AMP is involved in the formation of glucose in the bloodstream. Deactivation of phosphodiesterase by caffeine frees cyclic AMP to do its job, more glucose appears, and we feel more energetic.

Caffeine is an addictive drug. Among its many actions it operates using the same mechanisms that amphetamines, cocaine and heroin use to stimulate the brain.

Caffeine's effects are milder but it is manipulating the same channels and that it is one of the things that give caffeine its addictive qualities. It is one of the most widely used drugs. More than 90% of the population Britain consume it everyday and its long-term effects are of current interest.

Purines are usually synthesised by Traube's method in which a 4, 5 – diaminopyrimidine is treated with formic acid or, better, sodium dithioformate. 4, 5 – diaminopyrimidines are themselves obtained from 4- aminopyrimidines by nitrosation followed by reduction or via diazonium coupling of activated methylene compounds followed by cyclisation and reduction. Two examples are as follows:

Uric acid (an 8-Hydroxypurine) are made using ethyl chloroformate in place of formic acid:

Uric acid is then the starting material for other purines:

Summary

The term alkaloid refers to any Nitrogen containing compound extracted from plants, although the word is used loosely and some compounds of non-plant origin are also commonly known as alkaloids. The name is derived from their characteristic basic properties (alkali-like), which are induced by the lone-pair of electrons on nitrogen. The basic nature of the alkaloids, in conjunction with their particular three-dimensional architecture, gives rise to often-potent physiological activities, e.g. the narcotics morphine and heroin.

The laboratory synthesis of an alkaloid can be a challenging problem. The goal nowadays is not only to synthesise the natural product, but also to do so from simple molecules by a short elegant pathway. Such syntheses have practical importance because many alkaloids are desirable drugs. Large amounts of these alkaloids are often difficult to obtain from natural sources. A simple synthesis can provide an alternative supply of such a drug.

The 19th century was the heyday for structural studies on the alkaloids and the 20th century was notable for the large number of elegant syntheses that have been accomplished. Virtually all of the major alkaloids have now been synthesised.