NATIONAL OPEN UNIVERSITY OF NIGERIA

COURSE CODE: CHM 318

COURSE TITLE: NATURAL PRODUCT CHEMISTRY I

Course Code	**CHM 318**
Course Title	**Natural Product Chemistry I**
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Introduction

Natural Product Chemistry 1 is a semester course which is part of the courses designated as part of requirements for the award of B.Sc Chemistry

What You will Learn in this Course

The course consists of units and a course guide. The course guide is primarily a simple description of what the course is made up of, the materials to be use and how you can work with these materials. In addition, it advocates some general guidelines for the time you are likely to spend on each unit of the course in order to complete it successfully.

Also, you find in it your Tutor Marked Assignment which will be made available in the assignment file. Moreover, there are regular tutorial questions and classes that will assist in the better understanding of the course. You are advised to make yourselves available during the tutorial classes.

Course Aims

The aim of the course is to provide a basic understanding of the basic nature of chemical materials and the emerging trend. In addition, it seeks to address the massive drive to understand these materials and improve their properties in order to meet material requirements.

Course Objectives

To achieve the set aims, the course has a set of objectives. Each of the unit contained in a specific module has stated objectives which are included at the beginning of the particular unit. A clearer understanding of each of the objectives is a prerequisite for the better comprehension of the contents of the unit. It is highly essential to reflect, as you work through each unit, on the objectives.

The main objectives of the course are listed below. By meeting these objectives, you should have achieved the aims for which the course has been studied. At the end of this course, you should be able to:

i. Know what natural products are
ii. Understand the different types of natural products
iii. Give various examples of natural products
iv. Describe chemical properties of natural products
v. State the applications of these natural products

Working through this Course

In order to be able to successfully complete this course, you are required to carefully study each unit along with recommended textbooks and other materials that may be provided by the National Open University. You may also need to exploit other e-reading such internet for further useful information on the course.

Each unit contains self assessment exercise and at certain points in the course you would be required to submit assignment for grading and recording purposes. You are also to participate in the final examination at the end of the course. It is recommended that you devote an abundant time for reading and comprehension. It is highly necessary that you avail yourselves the opportunity of attending the tutorial sessions where you will be able to compare your understanding of the course contents with your colleagues.

The Course Materials

The main components of this course are:

1. The Course Guide
2. Study Units
3. Self Assessment Exercise
4. Tutor Marked Assignments
5. Further Readings

Study Unit

The study units in this course are as follows:

Module 1 Terpenes

Unit 1 Nature of Terpenes
Unit 2 Biosynthesis of Terpenes

Module 2 Steroids

Unit 1 Nature of Steroids

Module 3 Alkaloids

Unit 1 Nature of Alkaloids
Unit 2 Classification of Alkaloids

The first unit addresses the nature of terpenes. It focuses on history, biosynthesis and importance of terpenes. The second unit described in details the different of terpenes and their examples. The third unit is primarily concerned with the synthesis and structures of steroids. The fourth unit addresses the properties, distribution, extraction and application of alkalods. The fifth unit deals with the diversity of alkaloids and their specific importance.

Each of the unit is made up of one or two weeks' work consisting of introduction, objectives, reading materials, self assessment exercise, conclusion, summary and Tutor marked Assignment (TMA), suggestion for further reading and source materials. The unit directs you to work on exercises related to the required reading. Together with the TMAs, they are meant to test your basic understanding and comprehension of the course materials, which is a prerequisite for the achieving the stated aims and objectives of the course.

Presentation Schedule

The course materials have important dates for the timely completion and submission of your TMAs and tutorial lessons. You are vividly reminded of the need to promptly submit answers to tutorials and assignments as at when due.

Assessment

The course assessment consists of three aspects namely the self assessment exercise, the tutor marked assignment and the written examination/end of course examination.

It is essential that you attempt all exercises and assignments and submit appropriately to the course facilitator for grading. Let your answers be concise and as accurate as possible. You are expected to consult other material course in addition to your course materials in order to be able to present accurate answers to the questions. Kindly note that the tutor marked assignment covers only 30% of the total marked for the course.

Tutor Marked Assignment (TMA)

The TMA is a continuous assessment component of your course. It accounts for 30% of the total score. You will be given five (5) TMAs to answer. Three of these must be answered before you are allowed to sit for the end of the course examination. The TMAs will be given to you by your facilitator and returned after you have done the assignment. Note that these assignments are already contained in the assignment file to be given to you. You may do yourself good by reading and researching well before you attempt to answer the questions.

You are warned to submit these assignments to the facilitator at the stipulated time as could be seen in the assignment file. However, if for any reason you are unable to meet the deadline, you are highly required to intimate the facilitator of your problem before the due date and seek for an extension which may be granted or not.

Final Examination and Grading

The end of the course examination for Natural Product Chemistry 1 will be for about 3 hours with maximum score value of 70% of the total course work. The examination will be made up of questions which normally reflect on what you have learnt in the course materials/further reading. In addition, they may be prototype of the self assessment exercises and the TMAs. The end of the course examination is intended to cover information from all parts of the course.

Avail yourself the opportunity of the time-lag between the completion of the course content and the beginning of the examination to revise as much as possible the whole course materials, the exercise and assignments.

Course Marking Scheme

Assignment	**Marks**
Assignments 1-5	Five assignments, best three marks of the five count at 10% each i.e. 30% of the course marks
End of course Examination	70% of overall course marks
Total	100% of the course materials

Facilitators/Tutors and Tutorials

There are 17 hours of tutorials provided in support of this course. You will be informed appropriately of the name, telephone number and e-mail address of your facilitator. In addition, the time, dates and location of the tutorial lessons will be communicated beforehand. You are required to mail or submit your Tutor Marked Assignment to your facilitator, at least two working days, before the schedule date. Note that all the submitted assignments will be duly marked by the facilitator with further comments that can improve on your performances. The facilitator will from time to time takes track record of your comprehension, progress and difficulty in the course.

Be kind enough to attend tutorial lessons at the fixed appointment. It is probably the only avenue to meet face to face and discuss with you facilitator. There, you will be able to ask question or seek clarification on seemingly grey area in the course material. You may as well have prepared questions and comments for your facilitator before the due date. An active participation during the tutorial lessons will be an added advantage to boost confidence level.

In case any of the situations listed below arises, do not hesitate to intimate your facilitator using his or her telephone number or via e-mail address;

. You do not understand any part of the study or the assigned readings

. You are not skill enough to attempt the self assessment exercise

. The questions in the TMAs are not clearly understood

Summary

Natural Product chemistry is a course which is intended to provide students with the nature and classes of natural products. Upon completion of this course, you will be highly equipped to answer questions below and related ones:

. What do natural products represent?

. What are the different type, chemical nature and features of natural products?

. Know different classification of natural products

. Identify the examples of terpenes, steroids and alkaloids.

. Discuss the application of terpenes, steroids and alkaloids.

Accept my best wishes in the course and I do hope that you benefit considerably from its application.

Module 1: Terpenes

Unit 1: Biosynthesis of Terpenes

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1.0Introduction

During the 19th century, chemical works on turpentine led to name "terpene" the hydrocarbons with the general formula $C_{10}H_{16}$ found in complex plant product. These terpenes are frequently found in plant essential oils which contain the "*Quinta essentia*", the plant fragrance. They are universally present in small amounts in living organisms, where they play numerous vital roles in plant physiology as well as important functions in all cellular membranes. On the other hand, they are also accumulated in many cases, and it is shown that the extraordinary variety they then display can be due to ecological factors playing an evolutionary role.

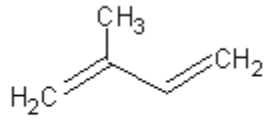
2.0 Objectives

At the end of this unit, students should be able to
i. Define terpenes and terpenoids
ii. Understand the history behind terpenes
iii. Describe the biosynthesis of terpenes
iv. State the form in terpenes occur naturally

3.0 Definition of Terpenes and Terpenoids

The name "terpene" is derived from the word "turpentine". Terpenes may be defined as a group of molecules whose structure is based on a various but definite number of isoprene units (methylbuta-1,3-diene, named hemiterpene, with 5 carbon atoms). When terpenes are modified chemically, such as by oxidation or rearrangement of the carbon skeleton, the resulting compounds are generally referred to as *terpenoids*.

Terpenoids (or isoprenoids), a subclass of the prenyllipids (terpenes, prenylquinones, and sterols), represent the oldest group of small molecular products synthesized by plants and are probably the most widespread group of natural products. Terpenoids can be described as modified terpenes, where methyl groups are moved or removed, or oxygen atoms added. Inversely, some authors use the term "terpenes" more broadly, to include the terpenoids.



Isoprene

3.1 History of Terpenes

Terpenes history spans various civilizations. As they are largely found in essential oils, they were used in the Ancient Egypt for various religious aims. Camphor was introduced in Europe from the East by the Arabs around the 11th century. The process of obtaining plant essential oils by fatty extraction was known by the early Middle Ages. In the 12th century, Arnaud de Villanosa

described distillation of oils from rosemary and sage. He made an "*oleum mirabile*" from oils of turpentine and rosemary.

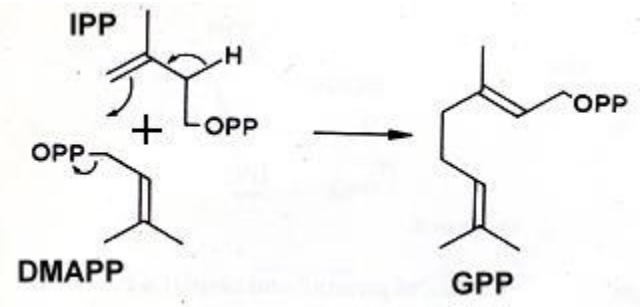
It is noticeable that some 60 oils were described in the Nuremberg edition of "*Dispensatorium valerii cordi*" written in 1592. Analyses of oils of turpentine were made in 1818 by JJ Houston de la Billardière. Dumas proposed in 1866 the name "terpene", derived from turpentine, instead of camphor for crystalline oxygenated substances extracted from essential oils. In 1887, Wallach O proposed that one isoprenic unit of 5 carbon atoms (C_5H_8) is always present in the molecule of terpenes.

The structure of camphor was established by Bredt in 1893, that of pinene by Wagner in 1894 and that of citral by Tiemann in 1895. β-Carotene was isolated in 1837 by Wackenrodder from carrots, and its correct molecular form was determined in 1907 by Willstätter. The period since 1945 has seen an extensive explosion in natural product chemistry due to the advent of chromatographic and spectroscopic techniques.

The discovery of the isoprene unit is the basis of the concept of the "isoprenic rule" edicted in 1953 by Ruzicka and completed by Lynen. Mevalonic acid was shown in 1956 to be a biosynthetic precursor of cholesterol and later, its incorporation into a number of terpenoids has been demonstrated. Actually, an increasing number of terpenoids are described in the plant kingdom and many of them were shown to have important biological activities. Thus, several sesquiterpenes and diterpenes have antibiotic properties, some sesquiterpenes and diterpenes are insect and plant hormones, respectively

3.2 Biosynthesis of Terpenes

Terpenoids are extraordinarily diverse but they all originate through the condensation of the universal phosphorylated derivative of hemiterpene, isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) giving geranyl pyrophosphate (GPP).



In higher plants, IPP is derived from the classic mevalonic acid pathway in the cytosol but from the methylerythritol phosphate pathway in plastids. It is generally accepted that the cytosolic pool of IPP serves as a precursor of sesquiterpenes, triterpenes, sterols and polyterpenes whereas the plastid pool of IPP provides the precursors of mono-, di- and tetraterpenes.

There are two metabolic pathways of creating terpenoids:

3.2.1 Mevalonic acid pathway

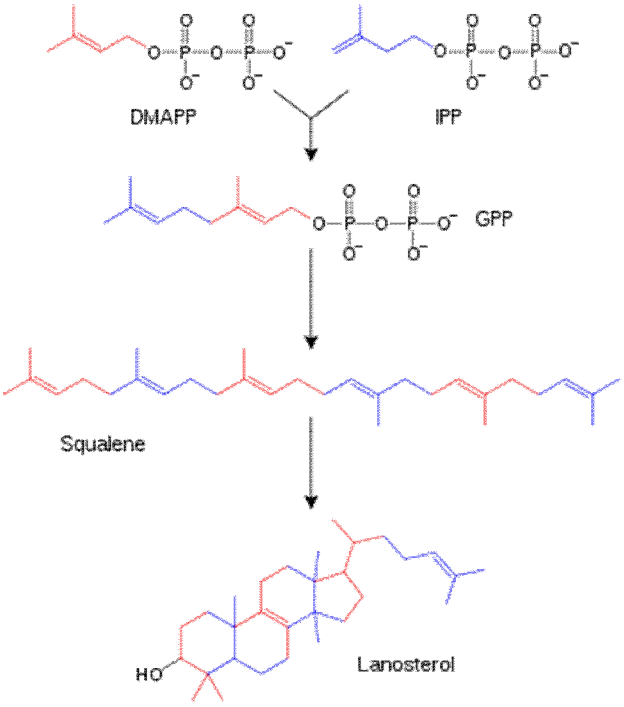
Many organisms manufacture terpenoids through the HMG-CoA reductase pathway, the pathway that also produces cholesterol. The reactions take place in the cytosol. The pathway was discovered in the 1950s.

3.2.2 MEP/DOXP pathway

The 2-*C*-methyl-D-erythritol 4-phosphate/1-deoxy-D-xylulose 5-phosphate pathway (MEP/DOXP pathway), also known as non-mevalonate pathway or mevalonic acid-independent pathway, takes place in the plastids of plants and apicomplexan protozoa, as well as in many bacteria. It was discovered in the late 1980s.

Pyruvate and glyceraldehyde 3-phosphate are converted by DOXP synthase (Dxs) to 1-deoxy-D-xylulose 5-phosphate, and by DOXP reductase (Dxr, IspC) to 2-*C*-methyl-D-erythritol 4-phosphate (MEP). The subsequent three reaction steps catalyzed by 4-diphosphocytidyl-2-*C*-methyl-D-erythritol synthase (YgbP, IspD), 4-diphosphocytidyl-2-*C*-methyl-D-erythritol kinase (YchB, IspE), and 2-*C*-methyl-D-erythritol 2,4-cyclodiphosphate synthase (YgbB, IspF) mediate the formation of 2-*C*-methyl-D-erythritol 2,4-cyclopyrophosphate (MEcPP). Finally, MEcPP is converted to (*E*)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMB-PP) by HMB-PP synthase (GcpE, IspG), and HMB-PP is converted to isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP) by HMB-PP reductase (LytB, IspH).

IPP and DMAPP are the end-products in either pathway, and are the precursors of isoprene, monoterpenoids (10-carbon), diterpenoids (20-carbon), carotenoids (40-carbon), chlorophylls, and plastoquinone-9 (45-carbon). Synthesis of all higher terpenoids proceeds via formation of geranyl pyrophosphate (GPP), farnesyl pyrophosphate (FPP), and geranylgeranyl pyrophosphate (GGPP).



Although both pathways, MVA and MEP, are mutually exclusive in most organisms, interactions between them have been reported in plants and few bacteria species.

Organism	Pathways
Bacteria	MVA or MEP
Archaea	MVA
Green Algae	MEP
Plants	MVA and MEP
Animals	MVA
Fungi	MVA

3.3 Summarized Classification of Terpenes

A rational classification of the terpenes has been established based upon the number of isoprene (or isopentane) units incorporated in the basic molecular skeleton:

	Terpenes	**Isoprene units**	**Carbon atoms**
1	Monoterpenes	2	10
2	Sesquiterpenes	3	15
3	Diterpenes	4	20
4	Sesterpenes	5	25
5	Triterpenes	6	30
6	Carotenoids	8	40
7	Rubber	> 100	> 500

Mono-, sesqui-, di-, and sesterpenes contain the isoprene units linked in a head to tail fashion. The triterpenes and carotenoids (tetraterpenes) contain two C15 and C20 units respectively linked head to head. Many terpenes are hydrocarbons, but oxygen-containing compounds such as alcohols, aldehydes or ketones are also found. These derivatives are frequently named terpenoids. Mono- and sesquiterpenes are the chief constituents of the essential oils while the other terpenes are constituents of balsams, resins, waxes, and rubber.

3.4 Importance of Terpenes

The terpenoids, sometimes called *isoprenoids*, are a large and diverse class of naturally-occurring organic chemicals similar to terpenes, derived from five-carbon isoprene units assembled and modified in thousands of ways. Most are multicyclic structures that differ from one another not only in functional groups but also in their basic carbon skeletons. These lipids can be found in all classes of living things, and are the largest group of natural products.

Oleoresin is a roughly equal mixture of turpentine (85% C10-monoterpenes and 15% C15-sesquiterpenes) and rosin (C20-diterpene) that acts in many conifer species to seal wounds and is toxic to both invading insects and their pathogenic. A number of inducible terpenoid defensive compounds (*phytoalexins*) from angiosperm species are well. These include both sesquiterpenoid and diterpenoid types.

Isoprenoid units are also found within the framework of other natural molecules. Thus, indole alkaloids, several quinones (vitamin K), alcohols (vitamin E, vitamin A formed from β-carotene), phenols, isoprenoid alcohols (also known as terpenols or polyprenols) also contain terpenoid fragments. The origin of the ubiquitous isoprene unit and its conversion into various compounds has been extensively studied.

Terpenes are a large and varied class of organic compounds, produced primarily by a wide variety of plants, particularly conifers, though also by some insects such as termites or swallowtail butterflies, which emit terpenes from their osmeterium. They are the major components of resin, and of turpentine produced from resin. In addition to their roles as end-

products in many organisms, terpenes are major biosynthetic building blocks within nearly every living creature.

Terpenes and terpenoids are the primary constituents of the essential oils of many types of plants and flowers. Essential oils are used widely as natural flavor additives for food, as fragrances in perfumery, and in traditional and alternative medicines such as aromatherapy. Synthetic variations and derivatives of natural terpenes and terpenoids also greatly expand the variety of aromas used in perfumery and flavors used in food additives. Vitamin A is an example of a terpene.

The aroma and flavor of hops, highly desirable in some beers, comes from terpenes. Of the terpenes in hops myrcene, b-pinene, b-caryophyllene, and a-humulene are found in the largest quantities.

Plant terpenoids are used extensively for their aromatic qualities. They play a role in traditional herbal remedies and are under investigation for antibacterial, antineoplastic, and other pharmaceutical functions. Terpenoids contribute to the scent of eucalyptus, the flavors of cinnamon, cloves, and ginger, and the color of yellow flowers. Well-known terpenoids include citral, menthol, camphor, Salvinorin A in the plant *Salvia divinorum*, and the cannabinoids found in *Cannabis*.

The steroids and sterols in animals are biologically produced from terpenoid precursors. Sometimes terpenoids are added to proteins, e.g., to enhance their attachment to the cell membrane; this is known as isoprenylation.

Self Assessment exercise
i. Distinguish between terpenes and terpenoids
ii. Enumerate the importance of terpenes
iii. State five examples of terpenes

4.0 Conclusion

The terpenoids sometimes called *isoprenoids*, are a large and diverse class of naturally-occurring organic chemicals similar to terpenes, derived from five-carbon isoprene units assembled and modified in thousands of ways. Most are multicyclic structures that differ from one another not only in functional groups but also in their basic carbon skeletons. These lipids can be found in all classes of living things, and are the largest group of natural products.

5.0 Summary

In summary, we have learnt that
i. Terpenoids may be defined as a group of molecules whose structure is based on a various but definite number of isoprene units.

ii. The scientist that proposed the name ‘terpene’ was Dumas in 1866 by deriving it from turpentine
iii. Terpenes can be synthesized from two pathway; mevalonic acid pathway and the non-mevalonate pathway.
iv. Terpenes are a large and varied class of organic compounds, produced primarily by a wide variety of plants and some animals like insects

6.0 Tutor-marked Assignment
1. What are terpenes and terpenoids?
2. Using appropriate scheme, describe the biosynthesis of terpenes.
3. Highlight the importance of terpenes and terpenoids

7.0 Further reading
Tadhg P. Begley (2009). *Encyclopedia of Chemical Biology*. Wiley. ISBN 978-0-471-75477-0.

Paul M Dewick (2002). *Medicinal Natural Products. A Biosynthetic Approach. Second Edition*. Wiley. ISBN 0471496405.

Module 1: Terpenes

Unit 2: Classification of Terpenes

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1.0 Introduction
A rational classification of the terpenes has been established based upon the number of isoprene (or isopentane) units incorporated in the basic molecular skeleton:

	Terpenes	**Isoprene units**	**Carbon atoms**
1	Monoterpenes	2	10
2	Sesquiterpenes	3	15
3	Diterpenes	4	20
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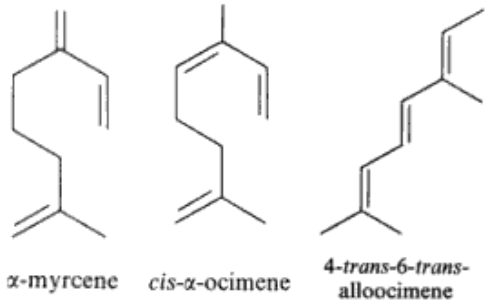
6	Carotenoids	8	40
7	Rubber	> 100	> 500

Mono-, sesqui-, di-, and sesterpenes contain the isoprene units linked in a head to tail fashion. The triterpenes and carotenoids (tetraterpenes) contain two C15 and C20 units respectively linked head to head.

2.0 Objectives
At the end of this unit, students should be able to
i. Understand the various classes of terpenes
ii. Know the distinguishing features of all classes of terpenes
iii. Give examples of each classes of terpenes

3.0 Monoterpenes
They are the terpenes that have been known for several centuries as components of the fragrant oils obtained from leaves, flowers and fruits. Monoterpenes, with sesquiterpenes, are the main constituents of essential oils. While a few, such as camphor, occur in a near pure form, most occur as complex mixtures, often of isomers difficult to separate. These essential oils have numerous actions, such as allelochemical functions between plants and between plants and predators. A role in wound healing was also observed.

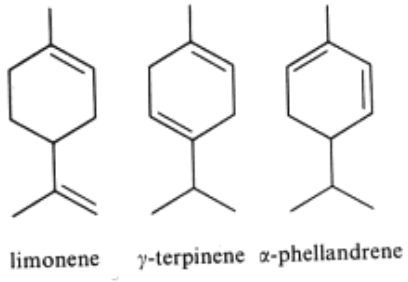
3.0.1 Acyclic Monoterpenes
Among natural molecules, the followings are well known and have several structural isomers.



Defensive role of simple terpenes have been demonstrated as for more complex compounds. Ocimene and linalool (with farnesene) were shown to be produced by *de novo* biosynthesis in plants damaged by insect herbivores. These compounds likely mediate the interaction between herbivores and their natural enemies, attracted by terpenes.

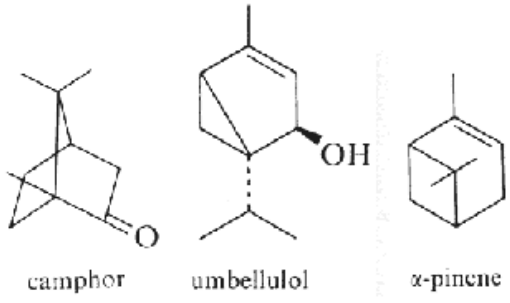
3.0.2 Monocyclic Monoterpenes

They are derived from cyclohexane with an isopropyl substituent. The most typical are:



Limonene is an important volatile emitted by the holm oak (*Quercus ilex*), and acts as allelochemical in inhibiting seed germination of other plant species.

3.0.3 Bicyclic Monoterpenes



Pinene is, as limonene, an allelochemichal emitted by the roots of *Quercus ilex*. Camphor and pinene are also allelochemicals emitted by *Salvia leucophylla*.

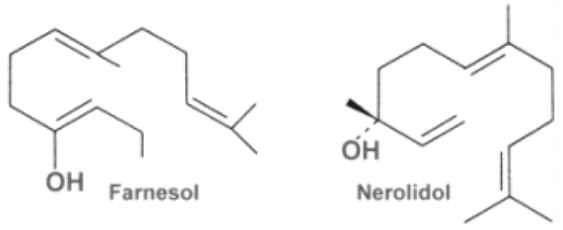
Many monoterpenes possess antitumor activity in animal and cell models. They have also antioxidant properties, □-terpene and hydroxytyrosol being among the most effective.

3.1 Sesquiterpenes

Sesquiterpenoids are defined as the group of 15 carbon compounds derived by the assembly of 3 isoprenoid units and they are found mainly in higher plants but also in invertebrates. Sesquiterpenes, with monoterpenes, are an important constituent of essential oils in plants. They are the most diverse group of isoprenoids. In plants, they function as pheromones and juvenile hormones. Sesquiterpene structures present several acyclic, mono-, bi-, tri-, and tetracyclic systems.

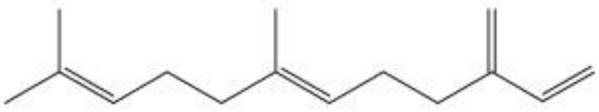
3.1.1 Acyclic sesquiterpenes

The acyclic representative are also called farnesans, term derived from the basic structure, farnesol. Farnesol and nerolidol are very common and are isolated from essential oils of various sources.



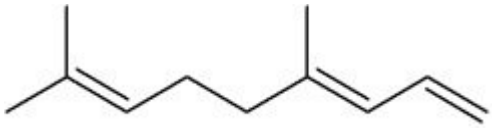
Farnesol is widely distributed in many essential oils such as citronella, neroli, cyclamen, lemon grass, tuberose, rose, musk, and balsam. It is used in perfumery to emphasize the odors of perfumes. Moreover, it is a natural pesticide for mites and is also a pheromone for several insects and mammals, including elephants (teritorial marking, individual recognition, mate attraction).

Farnesene, an analogue of farnesol, is known to act as an alarm pheromone in aphids. Released during predator attack, it causes aphids to stop feeding, disperse, and give birth to winged (rather than wingless) forms, which leave their host plants.



Farnesene

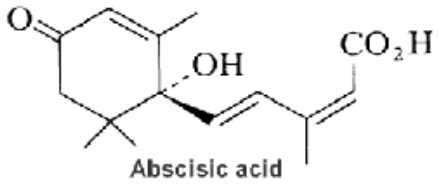
Nerolidol is present in neroli, ginger, jasmine, lavender, tea tree and lemon grass. The aroma of nerolidol is woody and reminiscent of fresh bark. It is used as a flavoring agent and in perfumery. It was also shown to be produced by the leaves of a large number of plant species in response to herbivory insects and then to be transformed into a C11-homoterpene (4,8-dimethyl-1,3,7-nonatriene) which attracts predatory insects.



4,8-Dimethyl-1,3,7-nonatriene

3.1.2 Cyclic sesquiterpenes

Abscisic acid plays a key role in plants in the regulation of stomatal closure by regulating ion channel activities and water exchanges across the plasma membrane of guard cells.

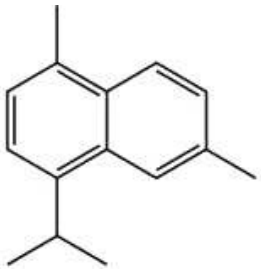


Abscisic acid

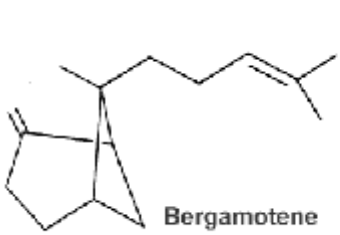
Cyclic ADP-ribose (cADPR) has been shown to mediate signaling of abscisic acid in the drought-stress response leading to activation of gene transcription and to stomatal closure. Abscisic acid has also a variety of roles in plant development, bud and seed dormancy, germination, cell division and movement. It induces storage protein synthesis in seeds and may be involved in defense against insect attack.

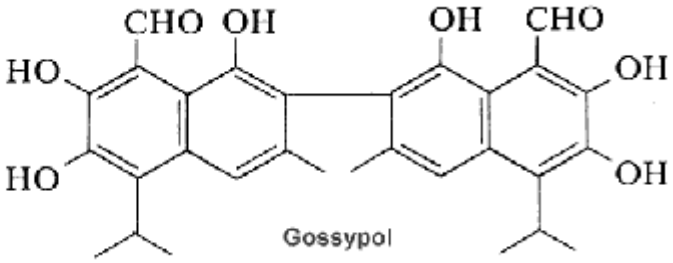
Cadalene has the cadinane skeleton and is present in essential oils and in many plants. It is used as a biomarker in paleobotanic studies. In connection with retene (1-methyl-7-isopropyl phenanthrene), it enables the estimation in sediments of the importance of Pinaceae in ancient forests.

Some important sesquiterpenes



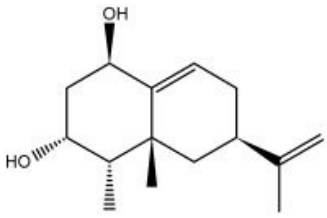
Cadalene





Gossypol is a sesquiterpene dimer found in cotton that is formed from two cadinane units. All cotton plant contains gossypol. That terpene occurs as a mixture of two enantiomers but each has different biological activities. For non-ruminant animals (rodents, chickens, humans), (–)-gossypol is significantly more toxic than the (+) enantiomer. It has anti-cancer properties and inhibits male fertility in humans. In contrast, cotton plants containing high levels of (+)-gossypol are resistant to insect damage. These terpenes must be removed from the plant parts and oil before use as animal foods.

Capsidiol is a sesquiterpenoid compound that accumulates in tobacco *Nicotiana tabacum* and chili pepper *Capsicum annuum* in response to fungal infection. It is considered as a phytoalexin.



Capsidiol

Self Assessment Exercise

1. Distinguish between acyclic and cyclic sesquiterpenes
2. Name one example each of acyclic and cyclic sesquiterpenes and describe them

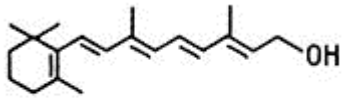
3.2 Diterpenes

They have 20 carbon atoms and are derived from geranylgeraniol pyrophosphate. They are of fungal or plant origin and are found in resins, gummy exudates, and in the resinous high-boiling fractions remaining after distillation of essential oils.

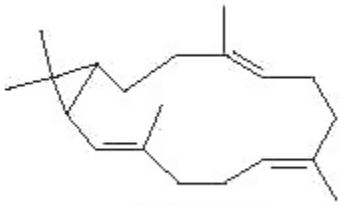
Diterpenoid groups that are physiologically active include: vitamin A activity (retinol), phytohormones that regulate plant growth and germination, e.g. gibberellins, fungal hormones that stimulate the switch from asexual to sexual reproduction, e.g. trisporic acid; disease resistance agents (phytoalexins), e.g. casbene and podocarpic acid, the anticancer drug, taxol, from the bark of the yew tree, the cancer promoter, phorbol, and natural cannabinoids.

The diterpenes have exceptionally open chain, as found in geranylgeraniol or phytol which forms a part of chlorophyll and the side chain of vitamin E and K, and crocetin which is a diacid diterpenoid and the lipid part of the crocins, glycosylated derivatives present in saffron.

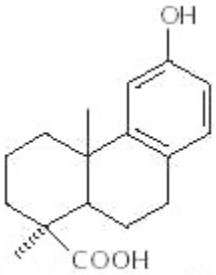
Examples of diterpene substances are given below:



all-trans retinol

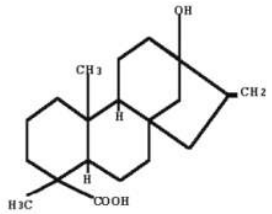


Casbene



Podocarpic acid

Steviol is the aglycone of *stevia*'s sweet glycosides, one of them being formed by replacing one hydrogen atom (bottom) with glucose via an ester link, and another hydrogen atom (top) with a disaccharide (glucose and rhamnose). The steviol glycosides are responsible for the sweet taste of the leaves of the *stevia* plant (*Stevia rebaudiana,* Asteraceae). These compounds are 40 to 300 times sweeter than sucrose. They are developed to be used in sweet drinks.

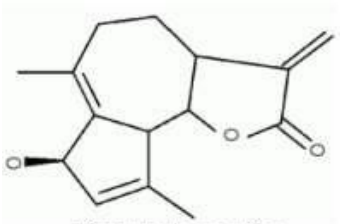


Steviol

Retene is present in tars obtained by distillation of resinous wood, it is an important pollutant eliminated by the paper factories. This diterpene is present in geological sediment where it is formed by diagenesis from abietic acid, several intermediates having been recognized.

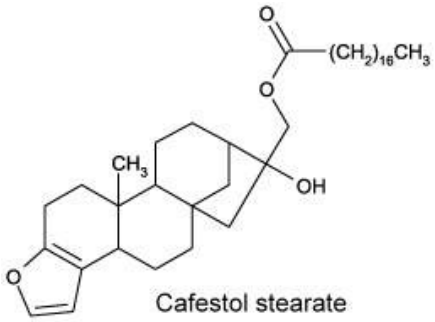
Retene

Dehydroleucodine was isolated from *Artemisia douglasiana*, a popular medicine in Argentina and was shown to have several physiological and therapeutic properties: anti-proliferative activity in G2 phase, cytoprotective agent for gastric ulcers and a general antioxidant.



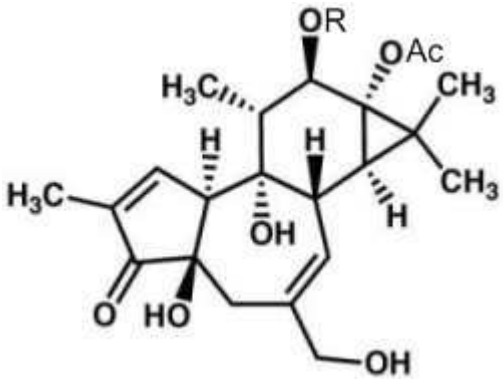
Dehydroleucodine

Cafestol and kahweol are present in high concentrations (up to 18% diterpene esters) in the oil derived from coffee beans. The only difference between cafestol and kahweol is an extra double bond present in the second cycle of kahweol. These diterpenes are esterified with one fatty acid (C14 to C24), palmitic and linoleic acids being the major esterified fatty acids.



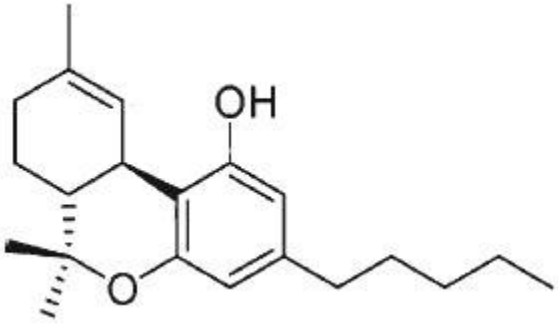
Cafestol stearate

Phorbol is a diterpene isolated in 1934 from croton oil (seeds of *Croton tiglium*). Various fatty acid esters of phorbol have important biological properties, the most notable of which is the capacity to act as tumor promoters through activation of protein kinase C as they mimic diacylglycerols. The most common phorbol ester is phorbol-12-myristate-13-acetate (PMA), which is used as a research tool in models of carcinogenesis.



Phorbol
R : myristic acid (C14:0), Ac : acetate group

Cannabinoids are a group of diterpenes present in Cannabis (*Cannabis sativa L*). All these substances are structurally related to tetrahydrocannabinol (THC) and are able to bind to specific cannabinoid receptors.

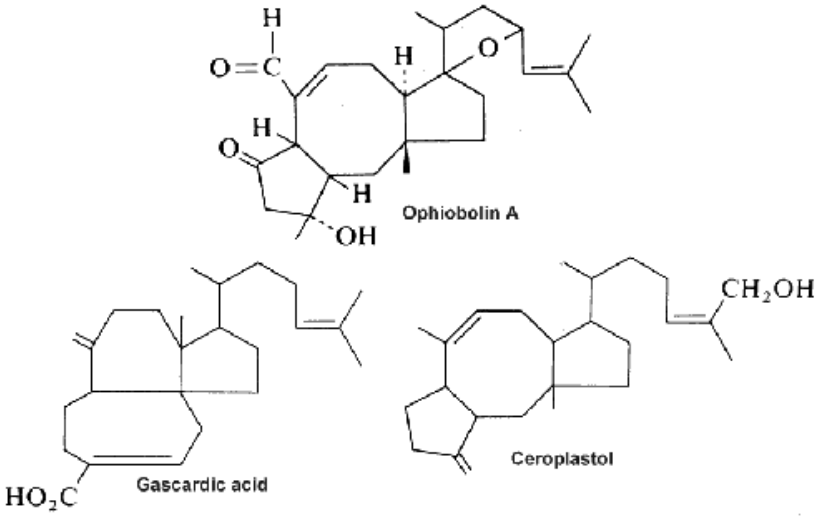


Δ^9-Tetrahydrocannabinol (THC)

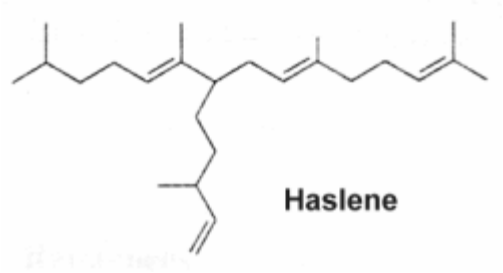
3.3 Sesterpenes

They are derived from geranylfarnesol pyrophosphate and have 25 carbon atoms. They were isolated from insect protective waxes and from fungal sources.

Three examples of sesterpenes are shown below.

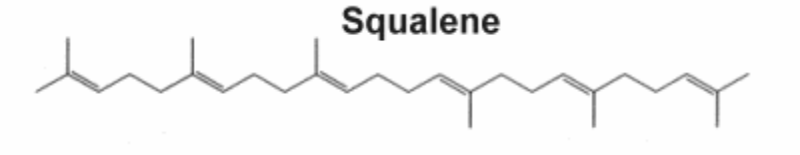


Variously unsaturated and branched sesterpenes, known as Haslenes, were found in species of diatomaceous algae.They are widely distributed and abundant in marine sediments. Several haslenes were found to be produced by a iatom iatom *Haslea ostrearia* according to the culture temperature and were shown to have cytostatic. One of them is shown below.



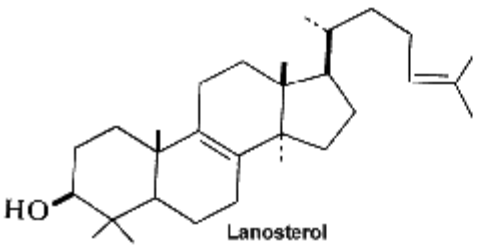
3.4 Triterpenoids

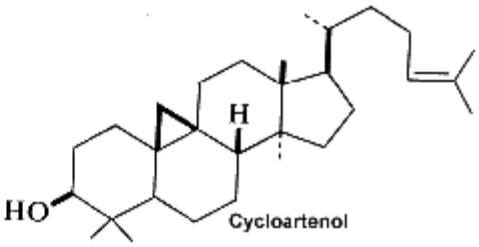
They form a large group of natural substances which includes steroids and consequently sterols. Squalene is the immediate biological precursor of all triterpenoids.

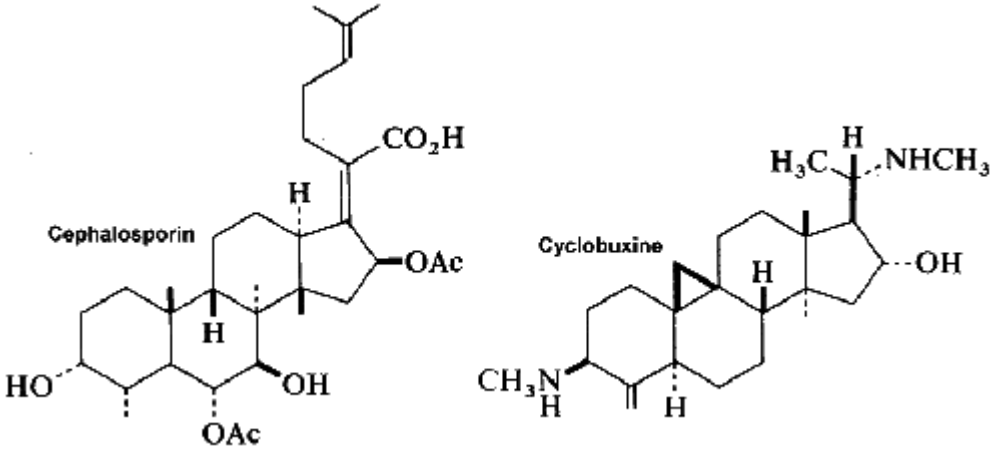


Squalene epoxide (2,3-oxidosqualene) is produced by the enzyme squalene epoxidase which use NADPH and oxygen to oxidize squalene. This metabolic step is the first in sterol biosynthesis leading to the formation of lanosterol or cycloartenol.

Squalane is a completely saturated derivative of squalene. Present in sebum, it is largely used as a component in many cosmetic products. It is obtained by hydrogenation of squalene extracted from olive oil. The large groups of *steroids*, including sterols, are present in very small amounts in bacteria but at larger amounts in plants and animals while the hopanoids are very abundant in prokaryotes where they replace cholesterol.
Among the large number of triterpenoid structures, some of them are shown below.







4.0 Conclusion

Terpenes are hydrocarbons resulting from the combination of several isoprene units. Terpenoids can be thought of as modified terpenes, wherein methyl groups have been moved or removed, or oxygen atoms added. Just like terpenes, the terpenoids can be classified according to the number of isoprene units used. The classes of terpenes include monoterpenes, diterpenes, triterpenes, sesterpenes and sesquiterpenes.

5.0 Summary

In summary, we have learnt that

i. Terpenes and terpenoids are so numerous and widespread in nature.

ii. Terpenes are classified based on the number of their isoprene units.

iii. The classes of terpenes include monoterpenes, diterpenes, triterpenes, sesterpenes and sesquiterpenes.

6.0 Tutor marked Assignment

1. Highlight the five major classes of terpenes and give examples.
2. Describe sesquiterpenes and their biological importance.

7.0 Further reading

Plemenkov VV (2001). *Introduction to the Chemistry of Natural Compounds*. Kazan.

Paul M Dewick (2002). *Medicinal Natural Products. A Biosynthetic Approach. Second Edition*. Wiley. ISBN 0471496405.

Module 2: Steroids

Unit 1: Nature of Steroids

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1.0 Introduction

The core of steroids is composed of twenty carbon atoms bonded together that take the form of four fused rings: three cyclohexane rings (designated as rings A, B, and C in the figure to the right) and one cyclopentane ring (the D ring). The steroids vary by the functional groups attached to this four ring core and by the oxidation state of the rings. Sterols are special forms of steroids, with a hydroxyl group at position-3 and a skeleton derived from cholestane.

2.0 Objectives

At the end of this unit, students should be able to
i. Describe the structure of a steroid
ii. Give various categories of steroids
iii. Discuss the biosynthesis of steroids

3.0 Definition of Steroid

A steroid is a type of organic compound that contains a specific arrangement of four cycloalkane rings that are joined to each other. Examples of steroids include the dietary fat cholesterol, the sex hormones estradiol and testosterone, and the anti-inflammatory drug dexamethasone.

Hundreds of distinct steroids are found in plants, animals, and fungi. All steroids are made in cells either from the sterols lanosterol (animals and fungi) or from cycloartenol (plants). Both lanosterol and cycloartenol are derived from the cyclization of the triterpene squalene.

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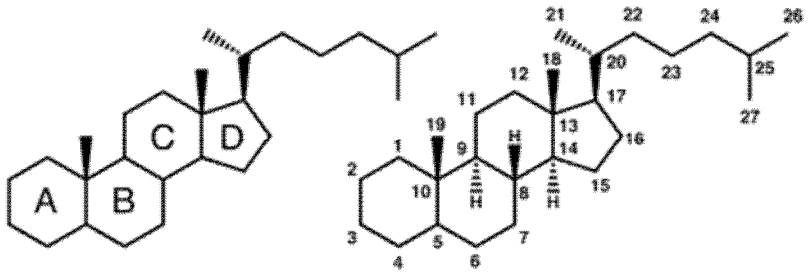
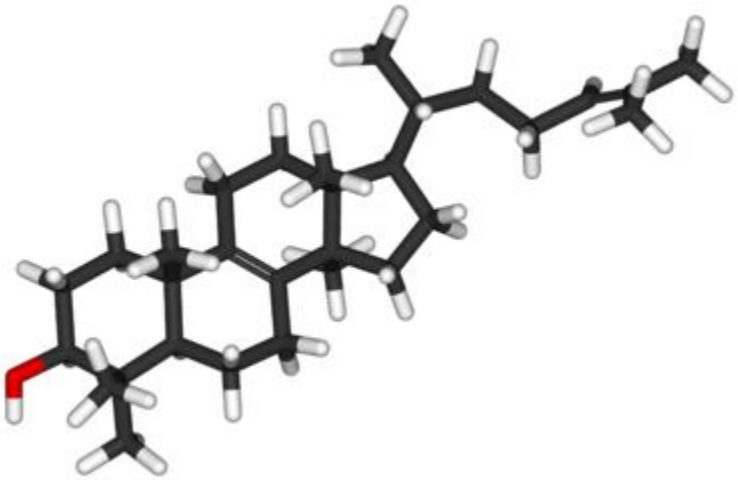


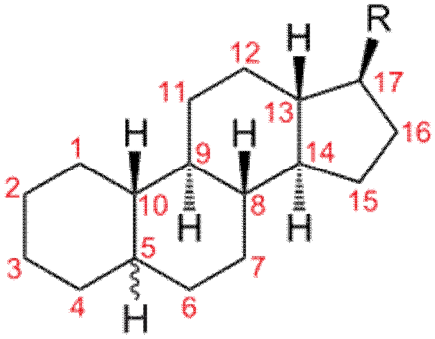
IUPAC recommended ring lettering (left) and atom numbering (right) of cholestane, a prototypical steroid skeleton. The four rings A-D form the gonane nucleus of the steroid.



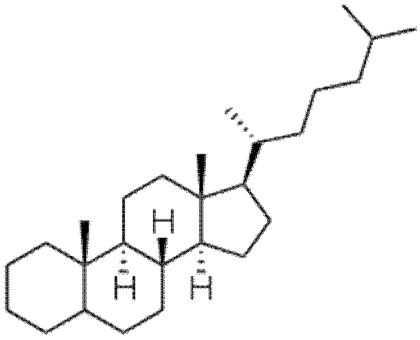
Stick model of the steroid lanosterol. The total number of carbons (30) reflects its triterpenoid origin.

3.1 Structure of Steroid

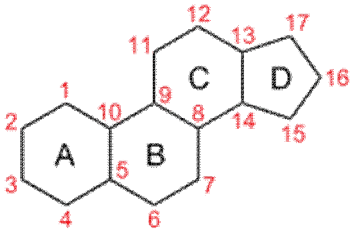
Steroids are a class of organic compounds with a chemical structure that contains the core of gonane or a skeleton derived therefrom. Usually, methyl groups are present at the carbons C-10 and C-13. At carbon C-17 an alkyl side chain may also be present.



The basic skeleton of a steroid, with standard stereo orientations. R is a side-chain.



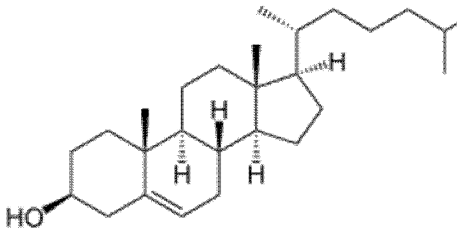
Cholestane, a typical steroid



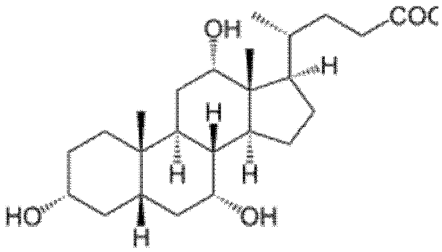
Numbering of carbon atoms in gonane

Gonane is the simplest possible steroid and is composed of seventeen carbon atoms, bonded together to form four fused rings. The three cyclohexane rings (designated as rings A, B, and C in the figure above right) form the skeleton of phenanthrene; ring D has a cyclopentane structure. Hence, together they are called cyclopentaphenanthrene.

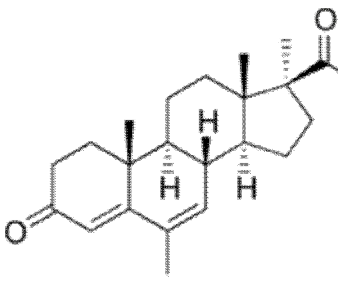
Commonly, steroids have a methyl group at the carbons C-10 and C-13 and an alkyl side chain at carbon C-17. Further, they vary by the configuration of the side chain, the number of additional methyl groups and the functional groups attached to the rings. For example the hydroxyl group at position C-3 in sterols.



Cholesterol



Cholic acid



Medrogestone

3.2 Classification

3.2.1 Taxonomical/Functional Classification

Some of the common categories of steroids:

1. Animal steroids

a. Insect steroids: These include Ecdysteroids such as ecdysterone

b. Vertebrate steroids (steroid hormones)

Sex steroids are a subset of sex hormones that produce sex differences or support reproduction. They include androgens, estrogens, and progestagens.

Corticosteroids include glucocorticoids and mineralocorticoids. Glucocorticoids regulate many aspects of metabolism and immune function, whereas mineralocorticoids help maintain blood volume and control renal excretion of electrolytes. Most medical 'steroid' drugs are corticosteroids.

Anabolic steroids are a class of steroids that interact with androgen receptors to increase muscle and bone synthesis. There are natural and synthetic anabolic steroids. In popular language, the word "steroids" usually refers to anabolic steroids.

Cholesterol, which modulates the fluidity of cell membranes and is the principal constituent of the plaques implicated in atherosclerosis.

2. Plant steroids: Phytosterols, Brassinosteroids

3. Fungus steroids: Ergosterols

3.2.2 Structural Classification
This is based upon the chemical composition of the steroids. Examples from this classification include:

Class	Examples	Number of carbon atoms
Cholestanes	cholesterol	27
Cholanes	cholic acid	24
Pregnanes	progesterone	21
Androstanes	testosterone	19
Estranes	estradiol	18

Gonane (or steroid nucleus) is the parent (17-carbon tetracyclic) hydrocarbon molecule without any alkyl sidechains.

Self Assessment Exercise
1. Describe the structure of gonane
2. What is the biological importance of corticosteroids

3.3 Metabolism of Steroid
Steroids include estrogen, cortisol, progesterone, and testosterone. Estrogen and progesterone are made primarily in the ovary and in the placenta during pregnancy, and testosterone in the testes. Testosterone is also converted into estrogen to regulate the supply of each, in the bodies of both females and males. Certain neurons and glia in the central nervous system (CNS) express the enzymes that are required for the local synthesis of pregnane neurosteroids, either *de novo* or from peripherally-derived sources. The rate-limiting step of steroid synthesis is the conversion of cholesterol to pregnenolone, which occurs inside the mitochondrion.

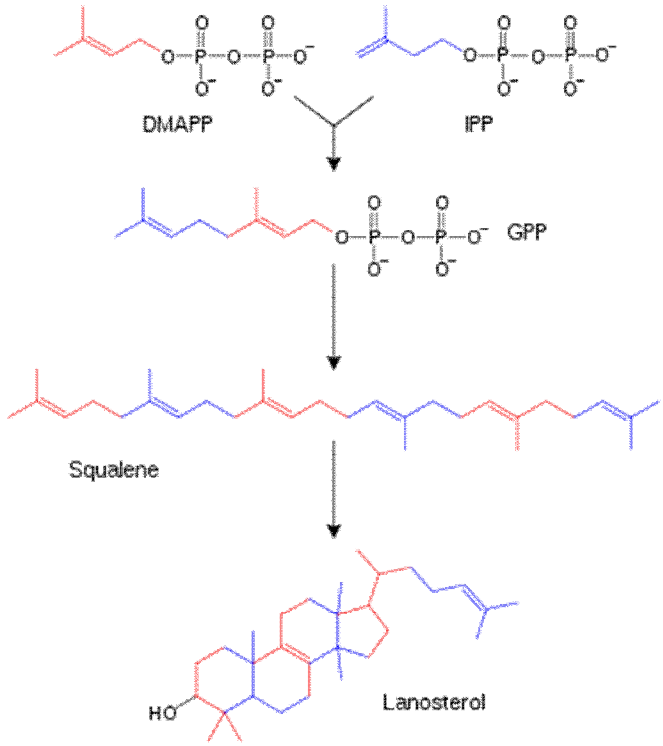
Steroid metabolism is the complete set of chemical reactions in organisms that produce, modify, and consume steroids. These metabolic pathways include:

- steroid synthesis – the manufacture of steroids from simpler precursors
- steroidogenesis – the interconversion of different types of steroids
- steroid degradation.

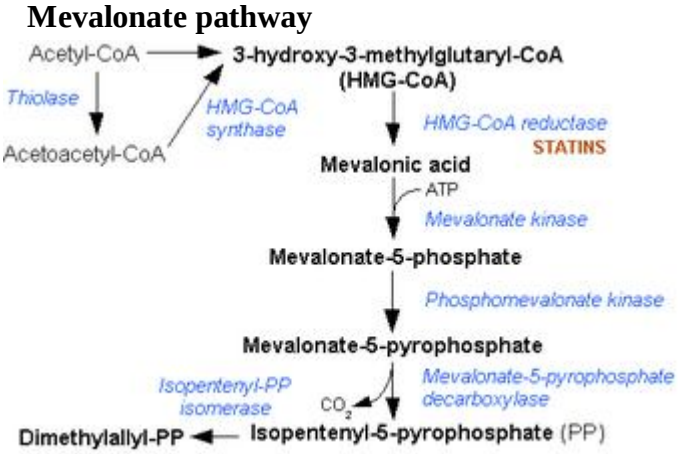
3.3.1 Steroid synthesis
Steroid biosynthesis is an anabolic metabolic pathway that produces steroids from simple precursors. This pathway is carried out in different ways in animals than in many other

organisms, making the pathway a common target for antibiotics and other anti-infective drugs. In addition, steroid metabolism in humans is the target of cholesterol-lowering drugs such as statins.

It starts in the mevalonate pathway in humans, with Acetyl-CoA as building blocks, which form DMAPP and IPP. In following steps, DMAPP and IPP form lanosterol, the first steroid.



Simplified version of latter part of steroid synthesis pathway, where the intermediates isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP) form geranyl pyrophosphate (GPP), squalene and, finally, lanosterol, the first steroid in the pathways.



Mevalonate pathway
The mevalonate pathway or HMG-CoA reductase pathway starts with and ends with dimethylallyl pyrophosphate (DMAPP) and isopentenyl pyrophosphate (IPP).

Several key enzymes can be activated through DNA transcriptional regulation on activation of SREBP (Sterol Regulatory Element-Binding Protein-1 and -2). This intracellular sensor detects low cholesterol levels and stimulates endogenous production by the HMG-CoA reductase pathway, as well as increasing lipoprotein uptake by up-regulating the LDL receptor. Regulation of this pathway is also achieved by controlling the rate of translation of the mRNA, degradation of reductase and phosphorylation.

Pharmacology
A number of drugs target the *mevalonate pathway*:

- Statins (used for elevated cholesterol levels)
- Bisphosphonates (used in treatment of various bone-degenerative diseases)

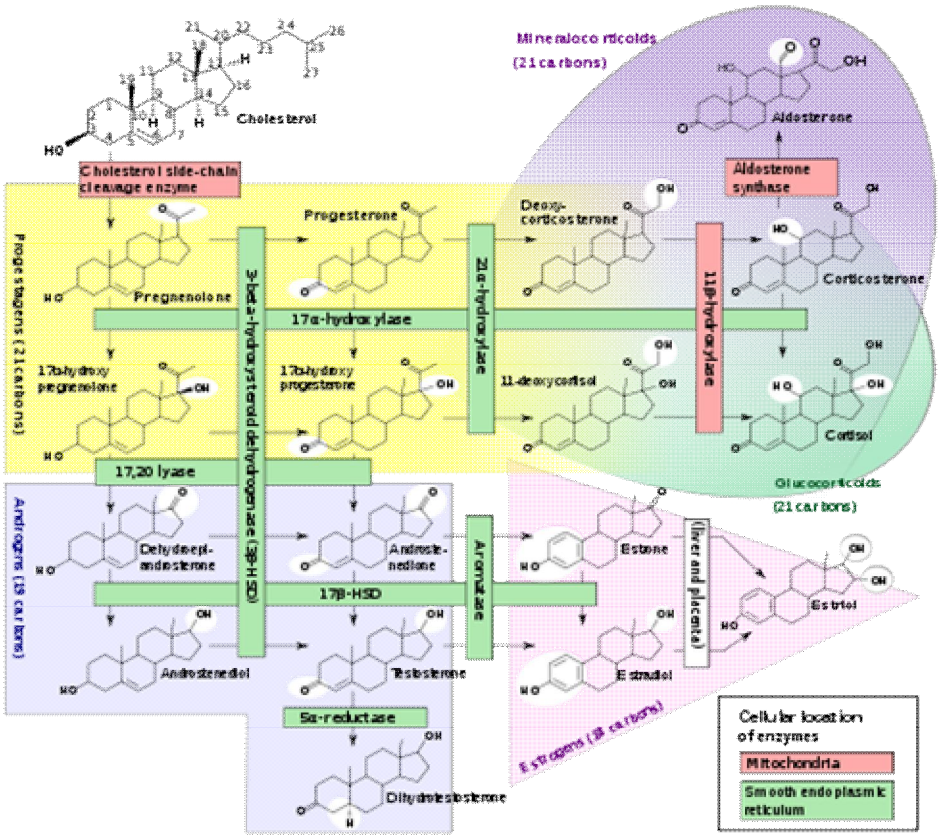
Plants and bacteria
In plants and bacteria, the non-mevalonate pathway uses pyruvate and glyceraldehyde 3-phosphate as substrates.

DMAPP to lanosterol
Isopentenyl pyrophosphate and dimethylallyl pyrophosphate donate isoprene units, which are assembled and modified to form terpenes and isoprenoids, which are a large class of lipids that include the carotenoids, and form the largest class of plant natural products.

Here, the isoprene units are joined together to make squalene and then folded up and formed into a set of rings to make lanosterol. Lanosterol can then be converted into other steroids such as cholesterol and ergosterol.

3.3.2 Steroidogenesis
Steroidogenesis is the biological process by which steroids are generated from cholesterol and transformed into other steroids. The pathways of steroidogenesis differ between different species, but the pathways of human steroidogenesis are shown in the figure.

Lanosterol can then be converted into other steroids such as cholesterol and ergosterol.



Human Steroidogenesis

Products of steroidogenesis include:

i. androgens: testosterone
ii. estrogens and progesterone
iii. corticoids: cortisol and aldosterone

3.3.3 Degradation and Elimination of Steroids

Steroids are oxidized mainly by cytochrome P450 oxidase enzymes, such as CYP3A4. These reactions introduce oxygen into the steroid ring and allow the structure to be broken up by other enzymes, to form bile acids as final products. These bile acids can then be eliminated through secretion from the liver in the bile. The expression of this oxidase gene can be up-regulated by the steroid sensor PXR when there is a high blood concentration of steroids.

4.0 Conclusion

Sterols are special forms of steroids, with a hydroxyl group at position-3 and a skeleton derived from cholestane. They can be classified based on their functions as well as their structures. Their metabolic pathways include steroid synthesis, steroidogenesis and steroid degradation.

5.0 Summary

In summary, we have learnt that

i. Steroids are a class of organic compounds with a chemical structure that contains the core of gonane or a skeleton derived therefrom.
ii. Gonane is the simplest possible steroid and is composed of seventeen carbon atoms, bonded together to form four fused rings.
iii. Steroids are produced in plants and animals as well as micro-organism
iv. Examples of steroids include oestrogen, progesterone, corticosterone, ergosterol and cholesterol

6.0 Tutor Marked Assignment

1. What are steroids?
2. State the classes of steroids based on functions
3. Briefly describe steroidogenesis

7.0 Further Reading

Paul M Dewick (2002). *Medicinal Natural Products. A Biosynthetic Approach. Second Edition*. Wiley. ISBN 0471496405.

Plemenkov VV (2001). *Introduction to the Chemistry of Natural Compounds*. Kazan.

Module 3: Alkaloids

Unit 1: Nature of Alkaloids

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1.0 Introduction

Many alkaloids are toxic to other organisms. They often have pharmacological effects and are used as medications, as recreational drugs, or in entheogenic rituals. Examples are the local anesthetic and stimulant, cocaine; the stimulant, caffeine; nicotine; the analgesic, morphine; the antibacterial, berberine; the anticancer compound, vincrinstine; the antihypertension agent, resepine; the cholinomimeric, galatamine; the spasmolysis agent, atropine; the vasodilator, vincamine; the anti-arhythmia compound, quinidine; the anti-asthma therapeutic, ephedrine; and the antimalarial drug, quinine. Although alkaloids act on a diversity of metabolic systems in humans and other animals, they almost uniformly invoke a bitter taste.

2.0 Objectives

At the end of this unit, students should be able to
i. Know what alkaloids are
ii. Understand the properties of alkaloids
iii. Know modes of extraction of alkaloids
iv. Comprehend the applications of alkaloids in human endeavour

3.0 Definiton of Alkaloid

Alkaloid is a group of naturally occurring chemical compounds which mostly contain basic nitrogen atoms. This group also includes some related compounds with neutral and even weakly acidic properties. Also some synthetic compounds of similar structure are attributed to alkaloids. In addition to carbon, hydrogen and nitrogen, alkaloids may also contain oxygen, sulfur and more rarely other elements such as chlorine, bromine and phosphorus.

3.1 History of Alkaloid

Alkaloid-containing plants were used by humans since ancient times for therapeutic and recreational purposes. For example, medicinal plants have been known in the Mesopotamia at least around 2000 BC. The *Odyssey* of Homer referred to a gift given to Helen by the Egyptian queen, a drug bringing oblivion. It is believed that the gift was an opium-containing drug. A Chinese book on houseplants written in 1st-3rd centuries BC mentioned a medical use of Ephedra and opium poppies. Also, coca leaves were used by South American Indians since ancient times.

Studies of alkaloids began in the 19th century. In 1804, the German chemist Friedrich Sertürner isolated from opium a "soporific principle" (Latin: *principium somniferum*), which he called "morphium" in honor of Morpheus, the Greek god of dreams; in German and some other Central-European languages, this is still the name of the drug. The term "morphine", used in English and French, was given by the French physicist Joseph Louis Gay-Lussac).

A significant contribution to the chemistry of alkaloids in the early years of its development was made by the French researchers Pierre Joseph Pelletier and Joseph Bienaimé Caventou who discovered quinine (1820) and strychnine (1818). Several other alkaloids were discovered around

that time, including xanthine (1817), atropine (1819), caffeine (1820), coniine (1827), nicotine (1828), colchicine (1833), sparteine (1851) and cocaine (1860).

The first complete synthesis of an alkaloid was achieved in 1886 by the German chemist Albert Ladenburg. He produced coniine by reacting 2-methylpyridine with acetaldehyde and reducing the resulting 2-propenyl pyridine with sodium. The development of the chemistry of alkaloids was accelerated by the emergence of spectroscopic and chromatographic methods in the 20th century, so that by 2008 more than 12,000 alkaloids had been identified.

3.2 Properties of Alkaloid

Most alkaloids contain oxygen; those compounds are usually colorless crystals at ambient conditions. Oxygen-free alkaloids, such as nicotine or coniine, are typically volatile, colorless, oily liquids. Some alkaloids are colored, like berberine (yellow) and sanguinarine (orange).

Most alkaloid are weak bases, but some are amphoteric, for example theobromine and theophylline. Most alkaloids are poorly soluble in water but readily dissolve in organic solvents, such as diethyl ether, chloroform and 1,2-dichloroethane. However, caffeine dissolves well in boiling water. With acids, alkaloids form salts of various strengths. Those salts are usually soluble in water and alcohol and poorly soluble in most organic solvents. Exceptions include scopolamine hydrobromide which is soluble in organic solvents and water-soluble quinine sulfate.

Most alkaloids have a bitter flavor. It is believed that plants evolved the ability to produce these bitter substances, many of which are poisonous, in order to protect themselves from animals; however, animals in turn evolved the ability to detoxify alkaloids.[Some alkaloids can produce developmental defects in the offspring of animals that consume them but cannot detoxify them. A characteristic example is the alkaloid cyclopamine, which is present in the leaves of corn lily. During the 1950s, up to 25% lambs born by sheep that had grazed on corn lily suffered serious facial defects. Those defects ranged from deformed jaws to cyclopia. After decades of research, in 1980s, the substance that was responsible for the deformities was identified as the alkaloid 11-deoxyjervine, which was renamed cyclopamine.

3.3 Distribution in Nature

bvThe alkaloid content in plants is usually within a few percent and is inhomogeneous over the plant tissues. Depending on the type of plants, the maximum concentration is observed in the leaves (black henbane), fruits or seeds (Strychnine tree), root (*Rauwolfia serpentina*) or bark (cinchona). Furthermore, different tissues of the same plants may contain different alkaloids.

Beside plants, alkaloids are found in certain types of fungi, such as psilocybin in the fungus of the genus Psilocybe, and in animals, such as bufotenin in the skin of some toads. Many marine organisms also contain alkaloids. Some amines, such as adrenaline and serotonin, which play an important role in higher animals, are similar to alkaloids in their structure and biosynthesis and are sometimes called alkaloids.

3.4 Extraction

Because of the structural diversity of alkaloids, there is no single method of their extraction from natural raw materials. Most methods exploit the property of most alkaloids to be soluble in organic solvents but not in water, and the opposite tendency of their salts.

Most plants contain several alkaloids. Their mixture is extracted first and then individual alkaloids are separated. Plants are thoroughly ground before extraction. Most alkaloids are present in the raw plants in the form of salts of organic acids. The extracted alkaloids may remain as salts or change into bases. Base extraction is achieved by processing the raw material with alkaline solutions and extracting the alkaloid bases with organic solvents, such as 1,2-dichloroethane, chloroform, diethyl ether or benzene. Then, the impurities are dissolved by weak acids; this converts alkaloid bases into salts which are washed away with water. If necessary, an aqueous solution of alkaloid salts is again made alkaline and treated with an organic solvent. The process is repeated until the desired purity is achieved.

In the acidic extraction, the raw plant material is processed by a weak acidic solution (e.g., acetic acid in water, ethanol or methanol). A base is then added to convert alkaloids to basic forms which are extracted with organic solvent (if the extraction was performed with alcohol, it is removed first, and the remainder is dissolved in water). The solution is purified as described above.

Alkaloids are separated from their mixture using their different solubility in certain solvents and different reactivity with certain reagents or by distillation.

Self Assessment Exercise

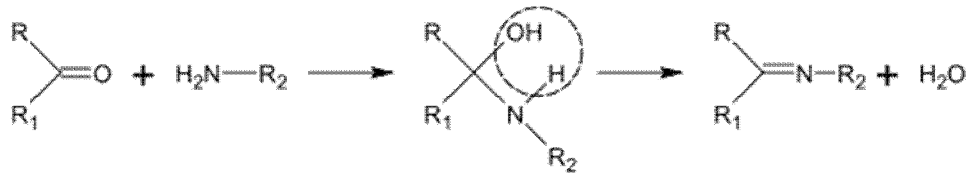
1. List five properties of alkaloids
2. How is alkaloid distributed in nature?

3.5 Biosynthesis of Alkaloids

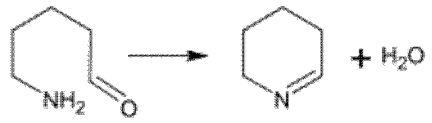
Biological precursors of most alkaloids are amino acids, such as ornithine, lysine, phenylalanine, tyrosine, tryptophan, histidine, aspartic acid and anthranilic acid. Nicotinic acid can be synthesized from tryptophan or aspartic acid. Ways of alkaloid biosynthesis are too numerous and cannot be easily classified. However, there are a few typical reactions involved in the biosynthesis of various classes of alkaloids, including synthesis of Schiff bases and Mannich reaction.

3.5.1 Synthesis of Schiff bases

Schiff bases can be obtained by reacting amines with ketones or aldehydes. These reactions are a common method of producing C=N bonds.

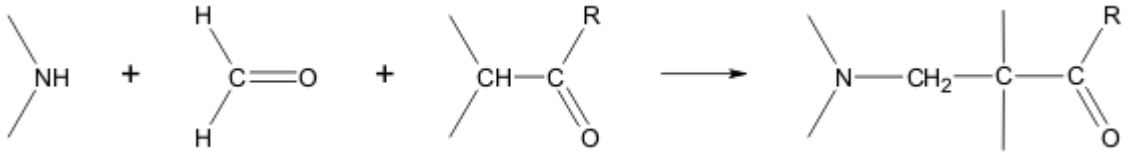


In the biosynthesis of alkaloids, such reactions may take place within a molecule, such as in the synthesis of piperidine:

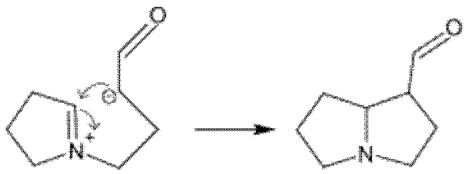


3.5.2 Mannich reaction

An integral component of the Mannich reaction, in addition to an amine and a carbonyl compound, is a carbanion, which plays the role of the nucleophile in the nucleophilic addition to the ion formed by the reaction of the amine and the carbonyl.



The Mannich reaction can proceed both intermolecularly and intramolecularly:

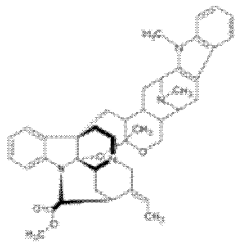


3.5.3 Dimer alkaloids

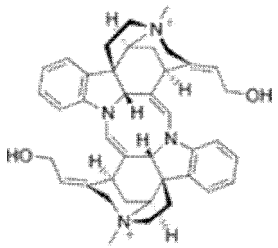
In addition to the described above monomeric alkaloids, there are also dimeric, and even trimeric and tetrameric alkaloids formed upon condensation of two, three and four monomeric alkaloids. Dimeric alkaloids are usually formed from monomers of the same type through the following mechanisms:

- Mannich reaction, resulting in, e.g., voacamine
- Michael reaction (villalstonine).
- Condensation of aldehydes with amines (toxiferine).
- Oxidative addition of phenols (dauricine, tubocurarine).
- Lactonization (carpaine).

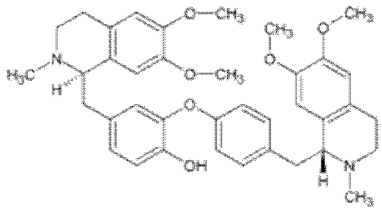
Voacamine



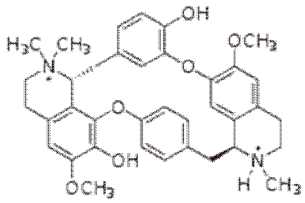
Villalstonine



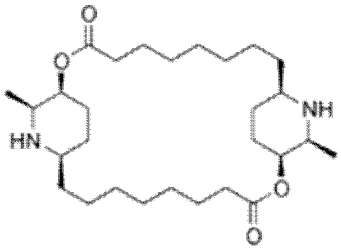
Toxiferine



Dauricine



Tubocurarine



Carpaine

3.6 The biological role of Alkaloids

The role of alkaloids for living organisms which produce them is still unclear. Initially, it was assumed that the alkaloids are the final products of nitrogen metabolism in plants, as urea in mammals. Most of the known functions of alkaloids are related to protection. For example, aporphine alkaloid liriodenine produced by the tulip tree protects it from parasitic mushrooms. In addition, presence of alkaloids in the plant prevents insects and chordate animals from eating it. However, some animals adapted to alkaloids and even use them in their own metabolism. Such

alkaloid-related substances as serotonin, dopamine and histamine are important neurotransmitters in animals. Alkaloids are also known to regulate plant growth.

3.7 Applications of Alkaloids

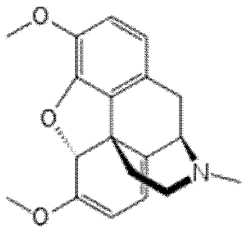
3.7.1 In medicine

Medical use of alkaloid plants has a long history, and thus when the first alkaloids were synthesized in the 19th century, they immediately found application in clinical practice. Many alkaloids are still used in medicine, usually in the form of salts, including the following:

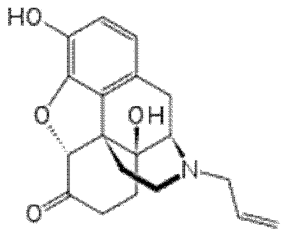
Alkaloid	Action
Ajmaline	antiarrhythmic
Atropine, scopolamine, hyoscyamine	anticholinergic
Vinblastine, vincristine	antitumor
Vincamine	vasodilating, antihypertensive
Codeine	cough medicine
Cocaine	anesthetic
Colchicine	remedy for gout
Morphine	analgesic
Reserpine	antihypertensive
Tubocurarine	Muscle relaxant
Physostigmine	inhibitor of acetylcholinesterase
Quinidine	antiarrhythmic
Quinine	antipyretics, antimalarial
Emetine	antiprotozoal agent
Ergot alkaloids	sympathomimetic, vasodilator, antihypertensive

Many synthetic and semisynthetic drugs are structural modifications of the alkaloids, which were designed to enhance or change the primary effect of the drug and reduce unwanted side effects.

For example, naloxone, an opioid receptor antagonist, is a derivative of thebaine which is present in opium.



Thebaine



Naloxone

3.7.2 In agriculture

Prior to the development of a wide range of relatively low-toxic synthetic pesticides, some alkaloids, such as salts of nicotine and anabasine, were used as insecticides. Their use was limited by their high toxicity to humans.

3.7.3 Use as psychoactive drugs

Preparations of plants containing alkaloids and their extracts, and later pure alkaloids have long been used as psychoactive substances. Cocaine and cathinone are stimulants of the central nervous system. Mescaline and many of indole alkaloids (such as psilocybin, dimethyltryptamine and ibogaine) have hallucinogenic effect. Morphine and codeine are strong narcotic pain killers.

There are alkaloids that do not have strong psychoactive effect themselves, but are precursors for semi-synthetic psychoactive drugs. For example, ephedrine and pseudoephedrine are used to produce methcathinone and methamphetamine.

4.0 Conclusion

Alkaloids are produced by a large variety of organisms, including bacteria, fungi, plants, and animals and are part of the group of natural products (also called secondary metabolites). Many alkaloids can be purified from crude extracts by acid-base extraction. The boundary between alkaloids and other nitrogen-containing natural compounds is not clear-cut. Compounds like amino acid peptides, proteins, nucleotides, nucleic acid, amines and antibiotics are usually not called alkaloids. Natural compounds containing nitrogen in the exocyclic position (mescaline, serotonin, dopamine, etc.) are usually attributed to amines rather than alkaloids.

5.0 Summary

i. Alkaloid is a group of naturally occurring chemical compounds which mostly contain basic nitrogen atoms.

ii. Most alkaloids are weak bases, but some are amphoteric, for example theobromine and theophylline.

iii. Alkaloids are found mostly in plants, marine organisms and in some fungi such as genus Psilosybe.

iv. Alkaloids are of widespread importance especially in medicine and agriculture.

6.0 Tutor Marked Assignment

1. In tabular form, state 10 examples of alkaloids and their therapeutic importance.
2. Describe the modes of extraction of alkaloids.
3. With examples, describe the properties of alkaloids.

7.0 Further Reading

Tadeusz, A. (2007): *Alkaloids - secrets of life*. Amsterdam: Elsevier.

Fattorusso, E and Taglialatela-Scafati, O. (2008): *Modern Alkaloids: Structure, Isolation, Synthesis and Biology*. Wiley-VCH.

Manfred, H. (2002): *Alkaloids: Nature's Curse or Blessing?*. Wiley-VCH.

Orekhov, A. P. (1955): *Chemistry alkaloids*, Academic Publisher (2nd ed.). USSR.

Module 3: Alkaloids

Unit 1: Classification of Alkaloids

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1.0 Introduction

Compared with most other classes of natural compounds, alkaloids are characterized by a great structural diversity and there is no uniform classification of alkaloids. Historically, first classification methods combined alkaloids by the common natural source, e.g., a certain type of plants. This classification was justified by the lack of knowledge about the chemical structure of alkaloids and is now considered obsolete.

2.0 Objectives

At the end of this unit, students should be able to
i. Understand the diversity of alkaloids
ii. Know the major classes of alkaloids
iii. Examples of alkaloids in each group

3.0 Major Classes of Alkaloids

Alkaloids are often divided into the following major groups:

1. "True alkaloids", which contain nitrogen in the heterocycle and originate from amino acids. Their characteristic examples are atropine, nicotine and morphine. This group also includes some alkaloids which beside nitrogen heterocycle contain terpene (e.g. evonine) or peptide fragments (e.g. ergotamine). This group also includes piperidine alkaloids coniine and coniceine although they do not originate from amino acids.

2. "Protoalkaloids", which contain nitrogen and also originate from amino acids. Examples include mescaline, adrenaline and ephedrine.

3. Polyamine alkaloids – derivatives of putrescine, spermidine and spermine.

4. Peptide and cyclopeptide alkaloids.

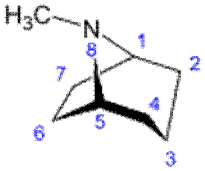
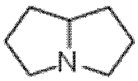
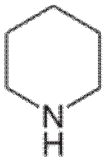
5. Pseudalkaloids – alkaloid-like compounds which do not originate from amino acids. This group includes, terpene-like and steroid-like alkaloids, as well as purine-like alkaloids such as caffeine, theobromine and theophylline. Some authors classify as pseudoalkaloids such compounds such as ephedrine and cathinone. Those originate from the amino acid phenylalanine, but acquire their nitrogen atom not from the amino acid but through transamination.

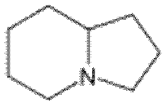
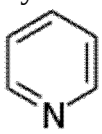
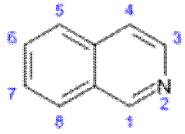
Some alkaloids do not have the carbon skeleton characteristic of their group. So, galantamine and homoaporphines do not contain isoquinoline fragment, but are generally attributed to isoquinoline alkaloids.

Self Assessment Exercise

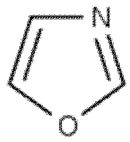
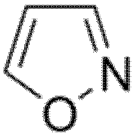
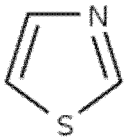
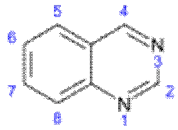
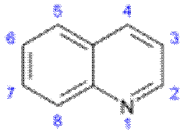
1. Highlight the five major classes of alkaloids
2. Describe with examples the true alkaloids

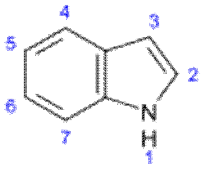
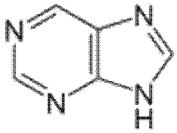
3.1 Main Classes of Alkaloids

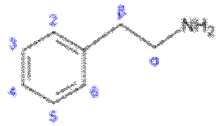
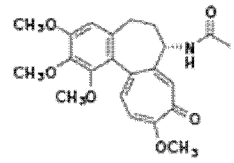
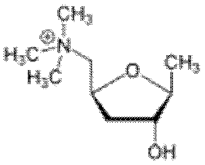
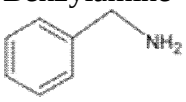
Class	Major groups	Main synthesis steps	Examples
Alkaloids with nitrogen heterocycles (true alkaloids)			
Pyrrolidine derivatives[41] 		Ornithine or arginine → putrescine → N-methylputrescine → N-methyl-Δ^1-pyrroline	Cuscohygrine, hygrine, hygroline, stachydrine
Tropane derivatives[44] 	Atropine group Substitution in positions 3, 6 or 7	Ornithine or arginine → putrescine → N-methylputrescine → N-methyl-Δ^1-pyrroline	Atropine, scopolamine, hyoscyamine
	Cocaine group Substitution in positions 2 and 3		Cocaine, ecgonine
Pyrrolizidine derivatives 	Non-esters	In plants: ornithine or arginine → putrescine → homospermidine → retronecine [42]	Retronecine, heliotridine, laburnine
	Complex esters of monocarboxylic acids		Indicine, lindelophin, sarracine
	Macrocyclic diesters		Platyphylline, trichodesmine
	1-aminopyrrolizidines (lolines)	In fungi: L-proline + L-homoserine → *N*-(3-amino-3-carboxypropyl)proline → norloline	Loline, *N*-formylloline, *N*-acetylloline
Piperidine derivatives 		Lysine → cadaverine → Δ^1-piperideine	Sedamine, lobeline, anaferine, piperine
		Octanoic acid → coniceine → coniine	Coniine, coniceine
Quinolizidine derivatives	Lupinine group	Lysine → cadaverine → Δ^1-piperideine	Lupinine, nupharidin

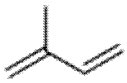
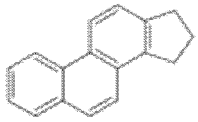
	Cytisine group		Cytisine
	Sparteine group		Sparteine, lupanine, anahygrine
	Matrine group		Matrine, oxymatrine, allomatridine
	Ormosanine group		Ormosanine, piptantine
Indolizidine derivatives 		Lysine → δ-semialdehyde of α-aminoadipic acid → pipecolic acid → 1 indolizidinone	Swainsonine, castanospermine
	Simple derivatives of pyridine		Trigonelline, ricinine, arecoline
Pyridine derivatives 	Polycyclic noncondensing pyridine derivatives	Nicotinic acid → dihydronicotinic acid → 1,2-dihydropyridine	Nicotine, nornicotine, anabasine, anatabine
	Polycyclic condensed pyridine derivatives		Actinidine, gentianine, pediculinine
	Sesquiterpene pyridine derivatives	Nicotinic acid, isoleucine	Evonine, hippocrateine, triptonine
	Simple derivatives of isoquinoline		Salsoline, lophocerine
	Derivatives of 1- and 3-isoquinolines		N-methylcoridaldine, noroxyhydrastinine
	Derivatives of 1- and 4-phenyltetrahydroisoquinolines		Cryptostilin
Isoquinoline derivatives and related alkaloids [69]	Derivatives of 5-naftil-isoquinoline	Tyrosine or phenylalanine → dopamine or tyramine (for alkaloids Amarillis)	Ancistrocladine
	Derivatives of 1- and 2-benzyl-izoquinolines		Papaverine, laudanosine, sendaverine
	Cularine group		Cularine, yagonine
	Pavines and isopavines		Argemonine, amurensin
	Benzopyrrocolines		Cryptaustoline
	Protoberberines		Berberine, canadine,

			ophiocarpine, mecambridine, corydaline
	Phtalidisoquinolines		Hydrastine, narcotine (Noscapine)
	Spirobenzylisoquinolines		Fumaricine
	Ipecacuanha alkaloids		Emetine, protoemetine, ipecoside
	Benzophenanthridines		Sanguinarine, oxynitidine, corynoloxine
	Aporphines		Glaucine, coridine, liriodenine
	Proaporphines		Pronuciferine, glaziovine
	Homoaporphines		Kreysiginine, multifloramine
	Homoproaporphines		Bulbocodine
	Morphines		Morphine, codeine, thebaine, sinomenine
	Homomorphines		Kreysiginine, androcymbine
	Tropoloisoquinolines		Imerubrine
	Azofluoranthenes		Rufescine, imeluteine
	Amaryllis alkaloids		Lycorine, ambelline, tazettine, galantamine, montanine
	Erythrite alkaloids		Erysodine, erythroidine
	Phenanthrene derivatives		Atherosperminine
	Protopins		Protopine, oxomuramine, corycavidine
	Aristolactam		Doriflavin
Oxazole derivatives[92]		Tyrosine → tyramine	Annuloline, halfordinol, texaline, texamine

 Isoxazole derivatives			
 Thiazole derivatives		Ibotenic acid → Muscimol	Ibotenic acid, Muscimol
 Quinazoline derivatives		1-Deoxy-D-xylulose 5-phosphate (DOXP), tyrosine, cysteine	Nostocyclamide, thiostreptone
 Acridine derivatives	3,4-Dihydro-4-quinazolone derivatives	Anthranilic acid or phenylalanine or ornithine	Febrifugine
	1,4-Dihydro-4-quinazolone derivatives		Glycorine, arborine, glycosminine
	Pyrrolidine and piperidine quinazoline derivatives		Vazicine (peganine)
 Quinoline derivatives		Anthranilic acid	Rutacridone, acronicine
	Simple derivatives of quinoline derivatives of 2 - quinolones and 4-quinolone	Anthranilic acid → 3-carboxyquinoline	Cusparine, echinopsine, evocarpine
	Tricyclic terpenoids		Flindersine
	Furanoquinoline derivatives		Dictamnine, fagarine, skimmianine
	Quinines	Tryptophan → tryptamine → strictosidine (with secologanin) → korinanteal → cinhoninon	Quinine quinidine cinchonine, cinhonidine
	Non-isoprene indole alkaloids		
Indole derivatives	Simple indole derivatives	Tryptophan → tryptamine or 5-	Serotonin, psilocybin,

		hydroxitriptofan	dimethyltryptamine (DMT), bufotenin
	Simple derivatives of β-carboline		Harman, harmine, harmaline, eleagnine
	Pyrroloindole alkaloids		Physostigmine (eserine), etheramine, physovenine, eptastigmine
		Semiterpenoid indole alkaloids	
	Ergot alkaloids	Tryptophan → chanoclavine → agroclavine → elimoclavine → paspalic acid → lysergic acid	Ergotamine, ergobasine, ergosine
		Monoterpenoid indole alkaloids	
	Corynanthe type alkaloids		Ajmalicine, sarpagine, vobasine, ajmaline, yohimbine, reserpine, mitragynine, group strychnine and (Strychnine brucine, aquamicine, vomicine)
		Tryptophan → tryptamine → strictosidine (with secologanin)	
	Iboga-type alkaloids		Ibogamine, ibogaine, voacangine
	Aspidosperma-type alkaloids		Vincamine, vincotine, aspidospermine
Imidazole derivatives 		Directly from histidine	Histamine, pilocarpine, pilosine, stevensine
Purine derivatives 		Xanthosine (formed in purine biosynthesis) → 7 methylxantosine → 7-methyl xanthine → theobromine →	Caffeine theobromine theophylline saxitoxin

	caffeine	
Alkaloids with nitrogen in the side chain (protoalkaloids)		
β-Phenylethylamine derivatives 	Tyrosine or phenylalanine → dioxyphenilalanine → dopamine → adrenaline and mescaline tyrosine → tyramine phenylalanine → 1-phenylpropane-1,2-dione → cathinone → ephedrine and pseudoephedrine	Tyramine, ephedrine, pseudoephedrine, mescaline, cathinone, catecholamines (adrenaline, noradrenaline, dopamine)
Colchicine alkaloids 	Tyrosine or phenylalanine → dopamine → autumnaline → colchicine	Colchicine, colchamine
Muscarine 	Glutamic acid → 3-ketoglutamic acid → muscarine (with pyruvic acid)	Muscarine, allomuscarine, epimuscarine, epiallomuscarine
Benzylamine 	Phenylalanine with valine, leucine or isoleucine	Capsaicin, dihydrocapsaicin, nordihydrocapsaicin
Polyamines alkaloids		
Putrescine derivatives 		Paucine
Spermidine derivatives 	ornithine → putrescine → spermidine → spermine	Lunarine, codonocarpine
Spermine derivatives		Verbascenine, aphelandrine

Peptide (cyclopeptide) alkaloids			
Peptide alkaloids with a 13-membered cycle	Numularine C type		Numularine C, numularine S
	Ziziphin type		Ziziphin A, sativanine H
	Frangulanine type		Frangulanine, scutianine J
	Scutianine A type		Scutianine A
Peptide alkaloids with a 14-membered cycle	Integerrine type	From different amino acids	Integerrine, discarine D
	Amphibine F type		Amphibine F, spinanine A
	Amfibine B type		Amphibine B, lotusine C
Peptide alkaloids with a 15-membered cycle	Mucronine A type		Mucronine A
Pseudoalkaloids (terpenes and steroids)			
Diterpenes 	Licoctonine type	Mevalonic acid → izopentenilpyrophosfate → geranyl pyrophosphate	Aconitine, delphinine
Steroids 		Cholesterol, arginine	Solasodine, solanidine, veralkamine

4.0 Conclusion

Recent classification of alkaloids are based on similarity of the carbon skeleton (e.g., indole, isoquinoline and pyridine-like) or biogenetic precursor (ornithine, lysine, tyrosine, tryptophan, etc.). However, they require compromises in borderline cases; for example, nicotine contains a pyridine fragment from nicotinamide and pyrrolidine part from ornithine and therefore can be assigned to both classes.

5.0 Summary

There are five classes of alkaloids based on functions. These are:

1. "True alkaloids", which contain nitrogen in the heterocycle and originate from amino acids. e.g. evonine and ergotamine).

2. "Protoalkaloids", which contain nitrogen and also originate from amino acids. Examples include mescaline, adrenaline and ephedrine.

3. Polyamine alkaloids – derivatives of putrescine, spermidine and spermine.

4. Peptide and cyclopeptide alkaloids.

5. Pseudalkaloids – alkaloid-like compounds which do not originate from amino acids. E.g caffeine, theobromine and theophylline.

6.0 Tutor Marked Assignment

1. With the aid of relevant examples, describe the major classes of alkaloids

7.0 Further Reading

Tadeusz, A. (2007): *Alkaloids - secrets of life*. Amsterdam: Elsevier.

Fattorusso, E. and Taglialatela-Scafati, O. (2008): *Modern Alkaloids: Structure, Isolation, Synthesis and Biology*. Wiley-VCH.

Manfred, H. (2002): *Alkaloids: Nature's Curse or Blessing?*. Wiley-VCH.

Orekhov, A. P. (1955): *Chemistry alkaloids* (Acad. 2 ed.). M.: USSR.