Introduction

Why organic chemistry? This must seem to be a strange question to be asking at the beginning of the website, but I want you to think at this point why you have this interest in chemistry, especially organic chemistry.

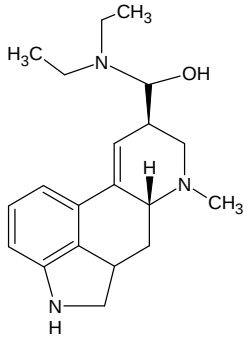
Is it because you have an interest, wish you had done better at 'A' level, fancy studying this subject at university or want to take up chemistry as a career?!

How to use this website

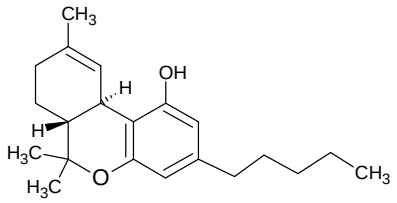
It not expected that you should read all of the sections, but firstly to decide which areas interest you most, take those on board and read as much about that area. I have given many different links so that you can explore your chosen part, hopefully that will inspire you to go on.

For me it was a passion, a passion that was given to me at the age of 14 in my science classes in school by a very special teacher. When I left school I was directed into a job in a bank, but fortunately I did not take up that offer, instead I found my first job as a laboratory assistant washing up glassware and preparing experiments. It was here that I learnt my craft, and it was at this juncture that I found this need to find out how things worked and behaved. Do not feel that you need to understand the structures portrayed in this introduction at the moment, just marvel in their beauty.

I was lucky in that I was born in the fifties and my inquisitive years, my teens, were in the sixties and seventies. Many things were going on then that would be major headlines, 'the swinging sixties' and all that went with that, psychedelic drugs, LSD {figure 1} marijuana {figure 1}, the Vietnam War (Agent Orange {figure 2}), thalidomide {figure 3} and of course the moon landings.



Lysergic acid diethylamide:
LSD



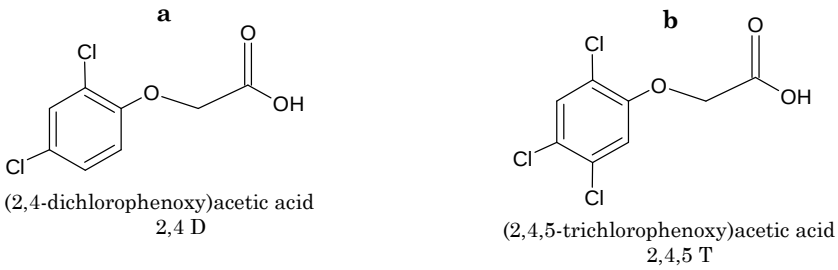
Δ^9–tetrahydrocannabinol
Cannabis

Figure 1

How could anyone fail to be in awe of these events that would unfold, and to be curious about the origins and make-up of the components of these events?

We now know that LSD has little or no value for medical research. Although initial observations on the benefits of LSD were favourable; empirical data developed subsequently proved less promising. Its use in scientific research has been extensive and its use has been widespread. Although the study of LSD and other hallucinogens increased the awareness of how chemicals could affect the mind, its use in psychotherapy has largely been shown to be false. It produces no aphrodisiac effects, does not increase creativity, and has no lasting positive effect in treating alcoholics or criminals. It does not produce a 'model psychosis', and does not cause immediate personality changes. However, drug studies have confirmed that the powerful hallucinogenic effects of this drug can produce profound adverse reactions, such as acute panic reactions, psychotic crises, and "flashbacks", especially in users ill-equipped to deal with such disturbances.

Agent Orange[1] is the code name for a powerful herbicide and defoliant used by the U.S. military in its Herbicidal Warfare program during the Vietnam War. An estimated 80,000 m^3 of this agent was deployed in South Vietnam.



(2,4-dichlorophenoxy)acetic acid
2,4 D

(2,4,5-trichlorophenoxy)acetic acid
2,4,5 T

Figure 2

2

Agent Orange consisted of a 50:50 mixture of 2, 4 D and 2, 4, 5 T. (see structures {Figure 2a and 2b}) and its usage from 1961 to 1971 was by far the most used of the so-called "Rainbow Herbicides". Breakdown of Agent Orange (as well as Agents Purple, Pink, and Green) released dioxins, (which were a contaminant of these compounds) and it is the dioxins[3] which have caused the health problems for those exposed during the Vietnam War. Agents Blue and White were part of the same program but did not produce dioxins.

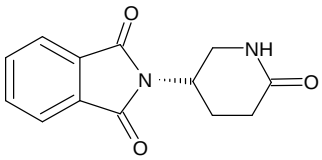
Agent Orange has been a contentious issue right up to the present day[4]; lawyers are still dealing with cases in many countries.

1

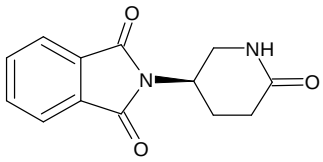
2 http://www.cancer.org/docroot/PED/content/PED_1_3x_Agent_Orange_and_Cancer.asp

3 http://www.chm.bris.ac.uk/motm/dioxin/dioxin-hp.htm

4 http://www1.va.gov/Agentorange/



2-[(3*S*)-6-oxopiperidin-3-yl]-1*H*-isoindole-1,3(2*H*)-dione



2-[(3*R*)-6-oxopiperidin-3-yl]-1*H*-isoindole-1,3(2*H*)-dione

Thalidomide

Figure 3

Thalidomide is racemic {Figure 3} – it contains both left and right handed isomers in equal amounts. The (R) enantiomer is effective against morning sickness. The (S) is teratogenic[3] and causes birth defects. The enantiomers can interconvert in vivo – that is, if a human is given pure (R)-thalidomide or (S)-thalidomide, both isomers can be found in the blood – therefore, administering only one enantiomer will not prevent the teratogenic effect. The mechanism of its biological action is under debate, the current thinking suggests that it inserts itself (intercalation)[3] into the DNA into the G-C rich areas.

Soon after its disuse, an Israeli doctor discovered anti-inflammatory effects of thalidomide and began to look for uses of the medication despite its teratogenic[5] effects[6]. On July 16, 1998, the FDA[7] approved the use of thalidomide for the treatment of lesions associated with erythema nodosum leprosum (Leprosy), but because of thalidomide's potential for causing birth defects, the distribution of thalidomide was permitted only under tightly controlled conditions. Thalidomide has had a revival of interest, and researchers, continue to work with the drug.

Today organic compounds available come from many sources, essential oils from plants, chemicals from oil and coal. Many millions of compounds have been made; they come in all sizes[8], shapes[9] and colours[10].

We could spend an enormous amount of time on the important discoveries that have happened since these days, but my space is limited.

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[5] http://www.medterms.com/script/main/art.asp?articlekey=9334

[6] http://www.thalidomide.ca/en/information/re_mechanism.html

[7] http://www.fda.gov/

[8] http://www.cem.msu.edu/~reusch/VirtualText/polymers.htm

[9] http://www.nanotech-now.com/nanotube-buckyball-sites.htm

[10] http://www.cirad.fr/en/actualite/communique.php?id=959

Later we will look at the terpenes and a small amount of their chemistry, I would however, like to show that these substances have played an important roll from earliest times. As far back as the sixteenth century many compounds were discovered and used by extraction from plants. This use took the form of: **Tinctures** (alcoholic extracts of herbs) e.g. tincture of pennyroyal, an oil used in aromatherapy, {figure 5} was used in a crude way to induce an abortion, **Tisanes** (Hot-water extracts of herbs), e.g. Bergamot used in Earl Grey tea. {Figure 4}, Along with the chemically related compound 6, 7-dihydroxy bergamottin, it is believed to be responsible for the grapefruit juice effect in which the consumption of the juice affects the metabolism of a variety of pharmaceutical drugs. **Decoctions**, (long-term boiled extract of usually roots or bark): **Macerates** (cold infusions of plants with a high mucilage content (i.e. contain high amounts of exopolysaccharide). e.g. in wine making where the grapes are steeped in water.

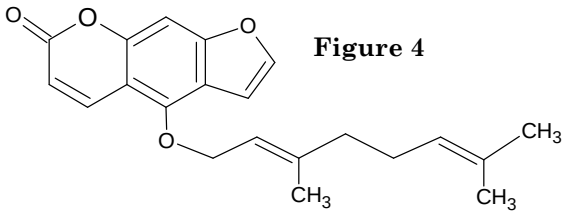


Figure 4

4-{[(2*E*)-3,7-dimethylocta-2,6-dien-1-yl]oxy}-7*H*-furo[3,2-*g*]chromen-7-one
Bergamottin

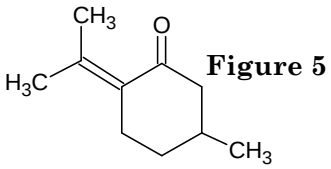
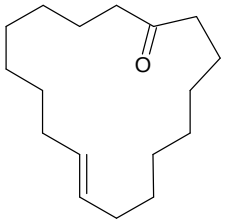


Figure 5

5-methyl-2-(1-methylethylidene)cyclohexanone
Pulegone, in tincture of Pennyroyal

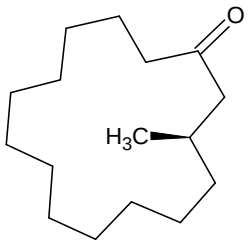
Natural products are also used in perfumery, in fact Chanel no 5 used to contain the secretions of the perineal glands of the civet[11] cat (the glands are found near the anus of the animal and are used to mark territory), civet musk {figure 6} is a powerful fixative, (makes the scent last longer). The Chanel Company claims that, starting in 1998; natural civet has been replaced with a synthetic substitute. If we compare this with deer musk {figure 7} we can see a resemblance in their structures.

[11] http://science.jrank.org/pages/1514/Civets.html



(9*Z*)-cycloheptadec-9-en-1-one
civetone: civet musk

Figure 6



(3*R*)-3-methylcyclopentadecanone
muscone: deer musk

Figure 7

Eucalyptus oil is an important essential oil (cineole based {figure 8}) used in the perfume industry, it is also active as an antiseptic as a decongestant and even an anti-inflammatory agent. It has also had a use as an insect repellent, and is used in the flavouring industry for chewing gum (non cineole {figures 9-13}).

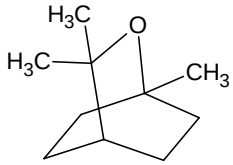


Figure 8

1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane
Eucalyptol **Cineole**

Eucalyptus is a mixture of many essential oils and compounds; hence it is a widely used substance.

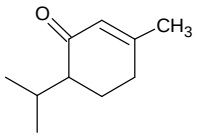


Figure 9

6-isopropyl-3-methylcyclohex-2-en-1-one
Piperitone used in the production of
menthol and thymol

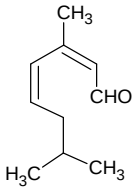
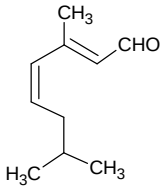


Figure 11



Citral

Lemon odour and anti-bacterial

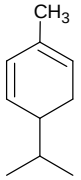
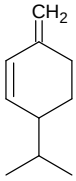


Figure 10



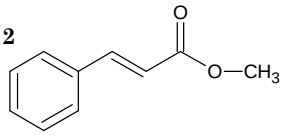
5-isopropyl-2-methylcyclohexa-1,3-diene

3-isopropyl-6-methylenecyclohexene

α and β Phellandrene

used as fragrances

Figure 12



methyl (2*E*)-3-phenylacrylate
Methyl cinnamate
Perfume industry imparts cinnamon
and strawberry smells

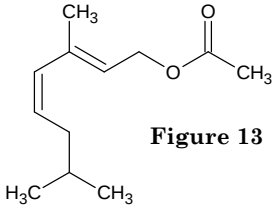


Figure 13

(2*E*,4*Z*)-3,7-dimethylocta-2,4-dien-1-yl acetate
Geranyl acetate fruit and floral aroma

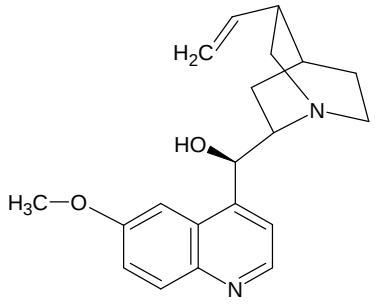
Organic chemistry, Alkaloids and the Pharmaceutical Industry

The use of alkaloids[12] also goes back to the sixteenth century; many compounds which had potent effects were alkaloids: Quinine {figure 14} was one that was used by the Quechua Indians; they used it to stop shivering that was brought on by the cold.

The quinine came from the bark of the cinchona tree. It was first used for the treatment of malaria in the seventeenth century by a Jesuit Priest called Agostino Salumbrino who trained in Lima. He sent the bark back to Rome to test its use on malaria that had broken out there. Many cardinals, several popes and many citizens had died from the effects of malaria.

Salumbrino had observed the effects the bark had from the Indians and thought it might help to subdue the shivering that occurred with malaria, although his reasoning was incorrect the substance turned out to be correct for this disease.

[12] True alkaloids: The basic unit in the biogenesis of the true alkaloids are amino acids. The non-nitrogen containing rings or side chains are derived from terpene units and/or acetate, while methionine is responsible for the addition of methyl groups to nitrogen atoms.

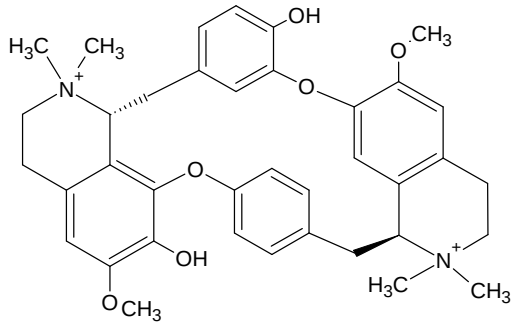


(*R*)-(6-methoxyquinolin-4-yl)(5-vinyl-1-azabicyclo[2.2.2]oct-2-yl)methanol
Quinine

Figure 14

The best form of quinine was first found in 1737 by Charles Marie de La Condamine, and large scale use of the drug didn't occur until 1850.

Curare[13] from the curare vine (*Chondrodendron tomentosum)*[14] is used by the South American Indians to immobilise their prey. Most of the Indians food lives in the trees and using blowpipes or poison tipped arrows the animals are shot, the curare works rapidly and the animals relax their grip and fall from the trees.



Tubocurarine

Figure 15

The alkaloid works by blocking the signals in the brain which tell the muscles to move - thereby rendering the whole body immobile to the point of becoming virtually paralyzed. It's not a toxin - and the effects generally wear off in about 90 minutes, in fact the curare will only work if introduced into the bloodstream and because it is not a toxin and cannot be introduced through the stomach the food is very safe to eat.

In 1942 curare and d-tubocurarine {figure 15} were introduced into clinical anaesthesia, being the starting point for modern surgery. Today it is still sold as a prescription drug that is used as a general anaesthetic and muscle relaxant in various types of surgeries (during which breathing can be controlled with machines).

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[13] http://www.rain-tree.com/curare.htm

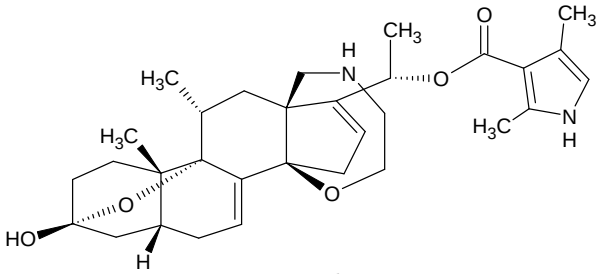
[14] http://www.blueplanetbiomes.org/curare.htm

While I am talking about interesting alkaloids, I found a particularly nasty alkaloid, which is also a toxin which is used for poisoning blowgun darts; it is used by the Noanamá Chocó and Emberá Chocó Indians of western Colombia for use in hunting. The substance is called Batrachotoxin {figure 16}. It is one of the most potent poisons and there is no known antidote. The lethal dose is said to be between 1-2 µg/kg of body weight. It is fifteen times more potent than curare in its effects. This substance comes from a frog called the dart frog, a member of the family Dendrobatidae, the frog doesn't make the poison but it comes from insects that the frog eats.

Dendrobates tinctorius[15]

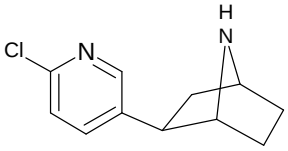
Epipedobates tricolor

Another frog of the same family Epipedobates tricolour produces a painkiller 200-time as potent as morphine, called epibatidine {figure 17}.



Batrachotoxin

Figure 16



2-(6-chloropyridin-3-yl)-7-azabicyclo[2.2.1]heptane
Epibatidine

Figure 17

Epibatidine[16] seems to have little or no side-effects as it is not an opioid and is not related to morphine. {Figure 18} The chance of epibatidine ever being used as a medicinal agent is quite low because of its high toxicity. However, new analogues of epibatidine have been and are still being synthesized.

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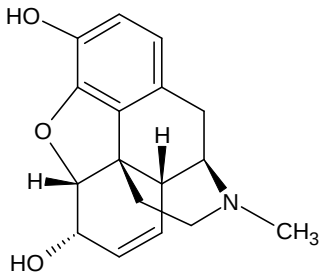
[15] http://en.wikipedia.org/wiki/Poison_dart_frog

[16] http://www.phc.vcu.edu/Feature/oldfeature/epi/:Matthew J. Dowd

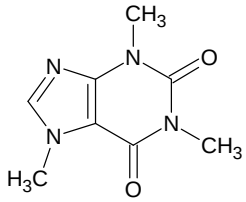


morphine

Figure 18

One of the most common alkaloids that most of us drink every day is caffeine[17] {figure 19}. Many foods or drinks contain this stimulant. In the plant it acts as a natural pesticide and will kill many insects that feed on the plant. In humans the caffeine is metabolised into three compounds, paraxanthine {figure 20} theobromine {figure 21} and theophylline {figure 22}. Each substance affects the body in a different way. E.g. Paraxanthine promotes lipolysis - breakdown of fat stored in the fat cells. Theobromine - dilates blood vessels and is a diuretic. Theophylline – relaxes smooth muscle. Each of these substances is used in its own right as a medication for treatment of specific diseases.

Caffeine in moderate amounts (200–300 mg per day) is a beneficial compound as it stimulates and makes one mentally alert, however, taken in large amounts it can cause many unwanted side effects - nervousness, irritability, anxiety, muscle twitching, insomnia, headaches, hyperventilation and heart palpitations.



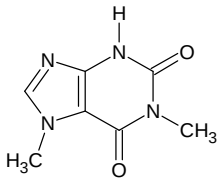
1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,6-dione

Caffeine

Figure 19

Caffeine may also cause the body to lose calcium, and that can lead to bone loss over time. Drinking caffeine-containing soft drinks and coffee instead of milk can have an even greater impact on bone density and the risk of developing osteoporosis.

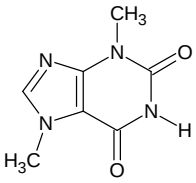
[17] http://www.cosic.org/background-on-caffeine



1,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione

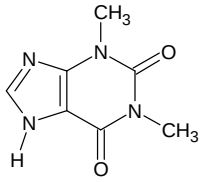
Paraxanthine

Figure 20



Theobromine

Figure 21



1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione

Theophylline

Figure 22

Many plants have been the source of vital drugs for many conditions, - cancer, high blood pressure, antipsychotic drugs to name but a few. Some of the anti cancer drugs come from the most amazing sources. E.g. The Yew tree (*Taxus baccata* Linnaeus) produces two specific drugs for treating cancer, Paclitaxel[18] (Pacific Yew {figure 23}) and Docetaxel[19] (European Yew {figure 24}). We can see there is a difference between the two compounds, substitution of a benzene group in Paclitaxel for i-Butyl in Docetaxel. These drugs are used as mitotic[20] inhibitors used in cancer chemotherapy and have been used for lung, ovarian, breast cancer, head and neck cancer, and advanced forms of Kaposi's sarcoma[21].

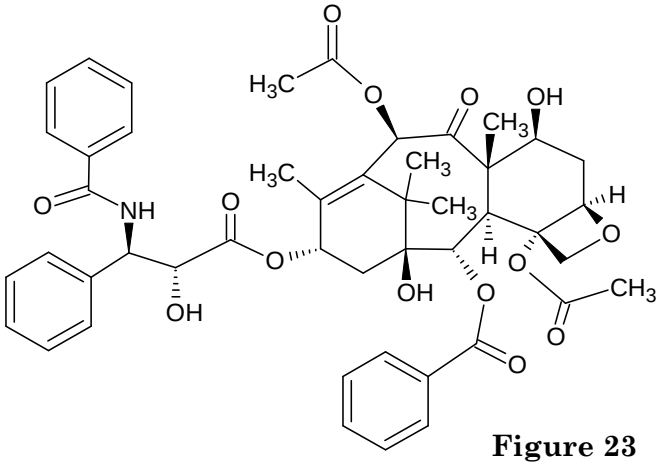


Figure 23

Paclitaxel: from Pacific Yew Tree

very rare tree

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[18] http://www.cancerbackup.org.uk/Treatments/Chemotherapy/Individualdrugs/Paclitaxel

[19] http://www.cancerbackup.org.uk/Treatments/Chemotherapy/Individualdrugs/Docetaxel

[20] http://www.cancer.gov/Templates/db_alpha.aspx?CdrID=46705

[21] http://www.cancer.org/docroot/cri/content/cri_2_4_1x_what_is_kaposis_sarcoma_21.asp

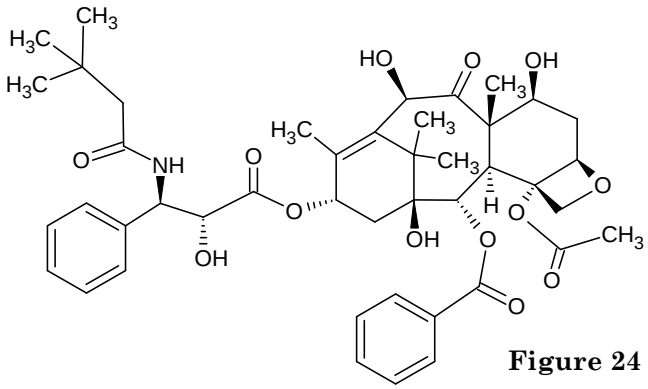


Figure 24

Docetaxel: from European Yew Tree

Another interesting source of chemotherapy drugs comes from the Madagascan periwinkle plant. These two substances are also mitotic inhibitors; Vinblastin {figure 25} and Vincristane {figure 26}. The Madagascar periwinkle (Catharanthus roseus), is the source of the Vinblastin and Vincristane, these alkaloids are used respectively in the treatment of Hodgkin's disease and pediatric leukaemia. As an anti-mitotic drug - it stops mitosis of the cancer cells in metaphase.

Madagascan Periwinkle (Catharanthus roseus)

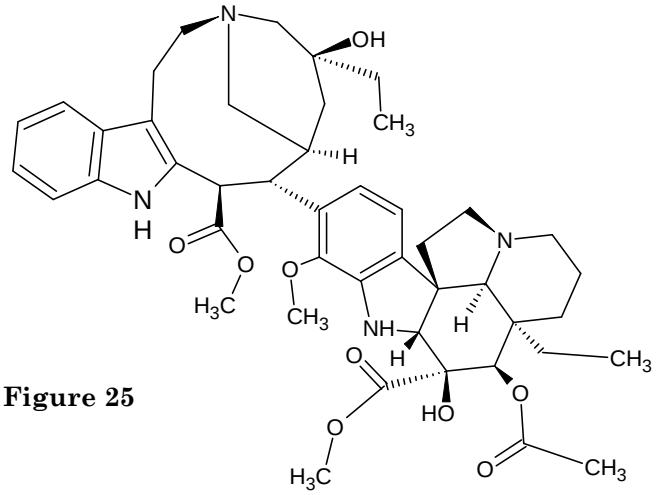


Figure 25

Vinblastin

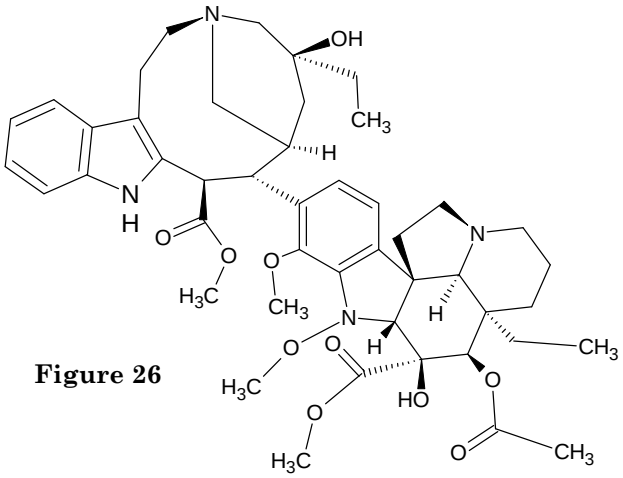


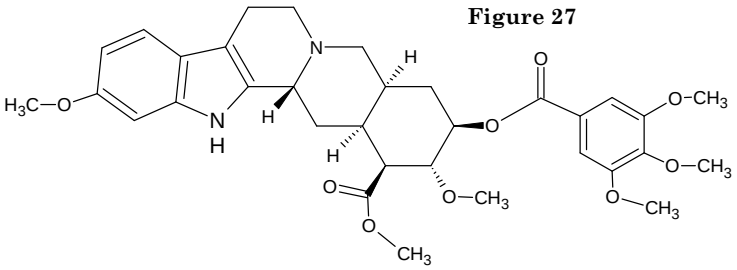
Figure 26

Vincristine

Reserpine is a drug that comes from the Rauwolfia serpentine (snakeroot) plant which is used as an antihypertensive drug {figure 27}. It is also used as an antipsychotic and tranquilizing drug. It marketed under the name Serpina.

Along with hypertension high cholesterol is a major problem in this century. Many products now have anti-cholesterol put in them; one that immediately comes to mind is Benecol[22]. This substance is a plant sterol[23] {figure 28} usually in the form of the ester {Figure 29}

Figure 27



Reserpine

methyl-11,17α-dimethoxy-18β-[(3,4,5-trimethoxybenzoyloxy]-3β,20a-yohimban-16β-carboxylate

Reserpine (1952) antipsycotic, tranquilizing and antihypertensive drug

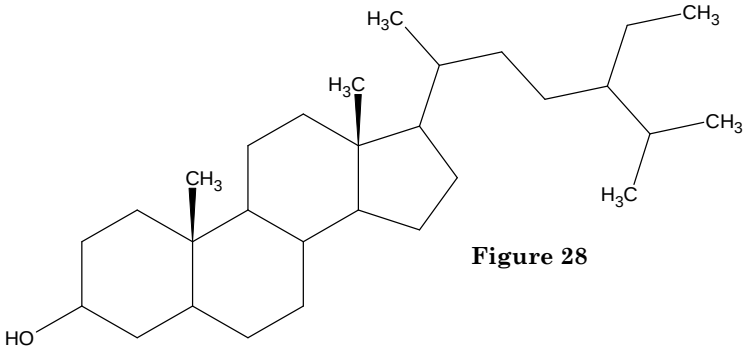


Figure 28

Sitostanol

[22] http://www.benecol.co.uk/new/how-benecol-works.htm

[23] http://www.bda.uk.com/foodfacts/070606_PlantStanolsAndSterols.pdf

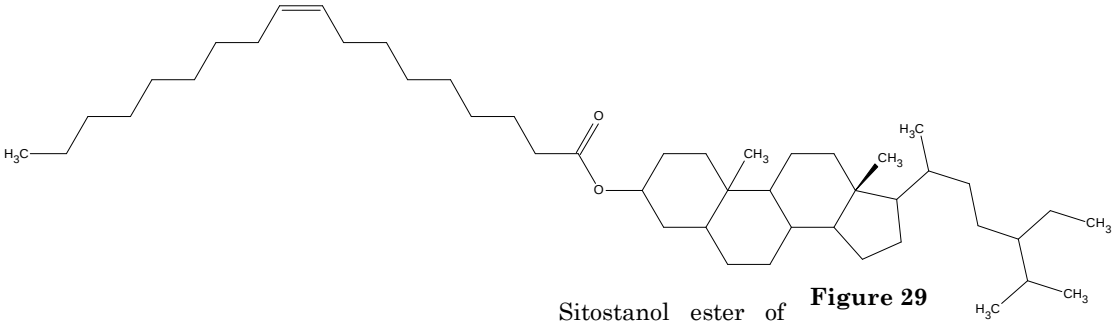


Figure 29

Sitostanol ester of oleic acid

Cardiovascular disease is still the leading cause of death in both men and women in the United Kingdom. A healthy and varied diet including functional foods including plant sterols, plant stanols, and oats can play a significant role in improving heart health.

Low density lipoprotein (LDL) cholesterol is most probably the agent for Cardio-Vascular-Disease (CVD), and that management of the LDL should be the priority. The current thinking is for a level of 3mmol/L for the amount of LDL in the blood. Diet and lifestyle have a major influence on the amount of LDL in the blood, hence a low cholesterol diet should be adhered to.

The importance of diet in the maintenance of heart health demands the lowering of the LDL's. Plant sterols are structurally similar to cholesterol[24] {figure 30} apart from an extra side chain. The saturated derivatives of plant sterols are plant stanols. The plant stanols are usually esterified – usually adding a fatty acid, typically oleic acid. Plant stanol esters make it easy to incorporate in a variety of foods. This fatty acid gets broken off the plant stanol in the digestive tract, where the free plant stanol can block the cholesterol absorption. The main type of plant stanol ester is sitostanol ester {figure 29}.

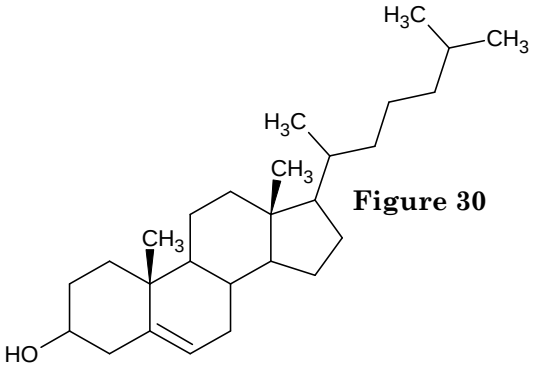


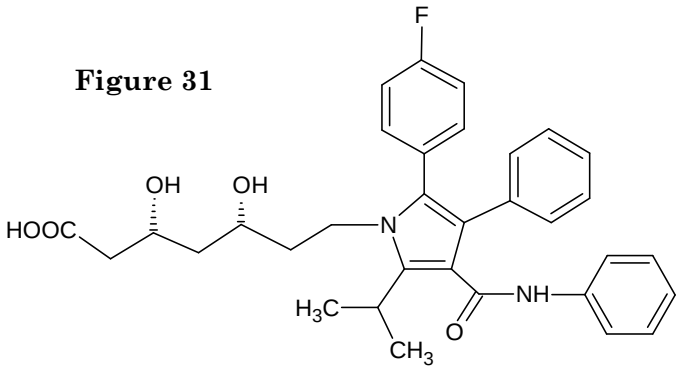
Figure 30

Cholesterol

Additional benefit is also achieved when plant stanol ester is used in conjunction with statin {figure 31} therapy.

[24] http://www.patient.co.uk/showdoc/23068704/

Figure 31

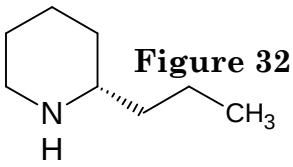


Lipitor

Organic chemistry and the poisoned

Finally, because of my love of the crime novel and Agatha Christie books I would like to look at that of the poisoner and the poisoned. There have been many examples of the poisoned in literature, e.g. Socrates who was a classical Greek Philosopher, was poisoned with hemlock {figure 32}. Socrates lived in Athens and his pursuit of virtue and his strict adherence to truth clashed with the current course of Athenian politics and society. He was very much a critic of the social and moral behaviour; it was this that led to his imprisonment and poisoning.

Figure 32



Coniine

Coniine the active ingredient in hemlock is a neurotoxin and reacts like curare in that it results in paralysis and then death.

Pope Clement VII (Born 1478; died 25 September, 1534) was poisoned by the death cap mushroom (Angelus):

Death Cap (*Amanita phalloides)*

The active agent in the mushroom is α-amanitin {figure 33}. It is from a family of cyclic octapeptides called amanitins. Poisoning by the amanitins is characterized by a long latent period (6-48 hours) during which the patient shows no symptoms. Then the patient who has eaten the mushrooms will get sudden, severe seizures of abdominal pain, persistent

vomiting and watery diarrhoea, extreme thirst, and lack of urine production. The person may appear to recover for a short time, but this period will generally be followed by a rapid and severe loss of strength, and painful restlessness. Death will occur usually after about 6 days in most cases of irreversible liver, kidney, cardiac and skeletal muscle damage.

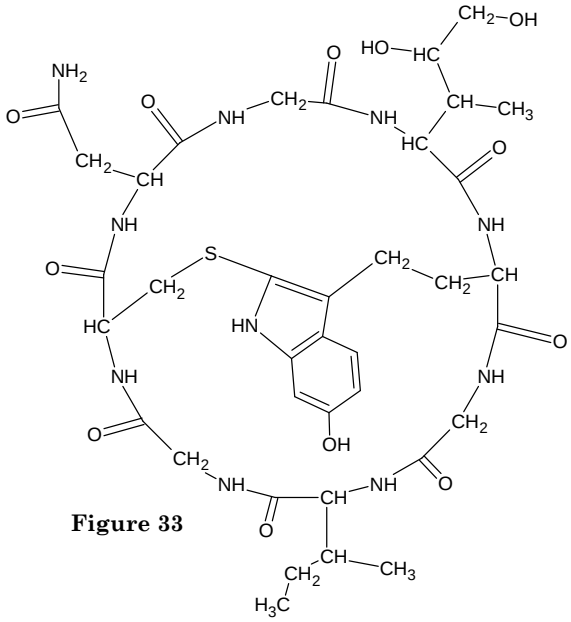


Figure 33

α-amanitin

Fictional poisoning, that in the novels by Agatha Christie are many and varied, Christie preferred poison, it was in her words not "messy". During the Great War she worked in a dispensary which gave her a working knowledge of toxicology – it was by far her most favourite weapon of murder.

Her list of poisons include: Strychnine {figure 34}, Stropanthine, eserine {figure 35}, oxalic acid, aconitine or aconite {figure 36}, in some novels it is referred to as datura[25] because the poison comes from specific plants, digitalin[26] from foxgloves, nicotine {figure 37}, taxine[27], and chloral {figure 38}.

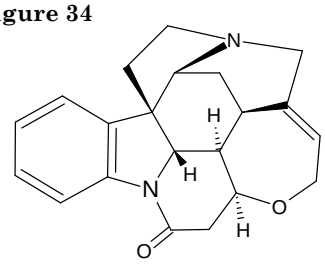
Pictures of the Datura plant not sure which variety this is?

[25] http://en.wikipedia.org/wiki/Datura

[26] http://www.plant-identification.co.uk/skye/scrophulariaceae/digitalis-purpurea.htm

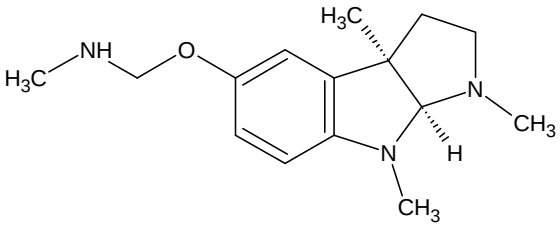
[27] See figures 23 and 24

Figure 34



Strychnine

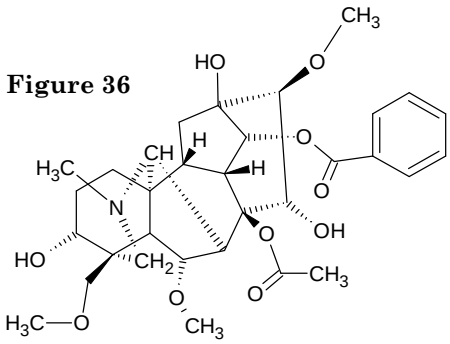
Figure 35



Eserine: from the calabar bean

In her book 'Cards on the Table' infection of a shaving brush with anthrax is the chosen dispenser. A similar application i.e. a shaving smoothing cream was used in 'The Cretan Bull'[28] and in 'A Caribbean Mystery' a face cream, the agent in question in both cases was atropine sulphate. The poison gave the recipients nightmares and paranoia, of course now her job would have been easier with the use of a few drops of DMSO[29] in the creams; finally in 'A Sad Cypress' the nurse uses apomorphine hydrochloride {figure 39} (a powerful emetic) to treat herself after she and the intended victim eat sandwiches laced with morphine hydrochloride[30].

Figure 36



Aconite

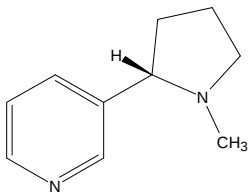


Figure 37

3-[(2*S*)-1-methylpyrrolidin-2-yl]pyridine
Nicotine

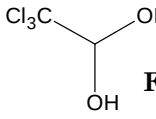


Figure 38

Chloral hydrate

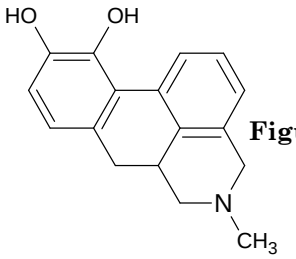


Figure 39

Apomorphine

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[28] Labours of Hercules

[29] An idea given to me by Dr D D Ball, it has the ability of helping substance through the skin barrier.

[30] http://www.nda.ox.ac.uk/wfsa/html/u03/u03_016.htm