Alkaloids

Group of natural products which contain basic nitrogen (not always true)

Alkaloids are produced by a large variety of fungi, plants, and microorganisms; metabolic routes to alkaloids greatly vary.

Many alkaloids have pronounced biological and pharmacological properties and are used as medications or recreational drugs.

The history of alkaloids dates back to the beginnings of modern chemistry (or even further). Several plants produce large amounts of alkaloids and the extraction process is relatively simple (basic properties and formation of salts)

Alkaloids can be classified by different means: Origin (plant source), structural properties (ring motifs, indole...)
Historical facts of alkaloid chemistry

1804 Sertürner isolated morphine from opium

1818 Isolation of strychnine by Pelletier and Caventou

1820 Isolation of quinine by Pelletier and Caventou

Friedrich Sertürner  Pierre Joseph Pelletier
Strychnine is highly toxic; isolated from Strychnos nux-vomica; Long history as poison; today commonly used as pesticide (birds and rodents); causes muscular convulsions and death through asphyxia

One of the most prominent alkaloids; used as recreational drug for several thousand of years; isolated from *Papaver somniferum* (mainly Afghanistan) extremely important for medication of pain.

Extremely important antimalarial drug with bitter taste; isolated from the bark of the cinchona tree; indirectly responsible for the development of chemical industry (Perkin’s mauveine synthesis)
Other milestone achievements (isolation of alkaloids)

Atropine (1819); caffeine (1820); nicotine (1828);

Atropine; isolated from deadly nightshade (*Atropa belladonna*); variety of biological effects. Competitive antagonist of muscarinic acetylcholine receptor. Counteracts toxic effects of organophosphate toxins (sarin, tabun...); dilates pupils of the eyes.

Bitter crystalline ingredient found in a variety of plants; acts as stimulant of the central nervous system.

Found in many plants of the nightshade family; most prominent alkaloid of tabacco; nicotinic acetylcholine receptor agonist → increases the level of neurotransmitters and has stimulating and relaxing properties (depending on the blood concentration); increases blood pressure and heart rate.
Other milestone achievements (isolation of alkaloids)

Colchicine (1833); sparteine (1851); cocaine (1860)

Highly toxic constituent of the autumn crocus; used to treat swellings and gout; important tubulin binding anticancer drug

Antiarrhythmic agent and sodium channel blocker; isolated from lupin plants; plays important role in organic chemistry as chiral base

Obtained from leaves of the coca plant; Topical anesthetic; Powerful nervous system stimulant; induces euphoria, feeling of well-being...; serious side effects if used over prolonged period of time
Early syntheses of alkaloids

In 1886, Ladenburg achieved the first total synthesis of a natural product.
Ladenburg’s synthesis of Coniin

Original:

Modified:
In 1901, Willstätter achieved the first synthesis of tropinone (parent compound of important alkaloids such as atropine and cocaine) via a tedious pathway.
In 1917, (ten years after Collie’s pioneering work on polyketides), Robinson proposed a biochemical pathway for tropinone. Until today, Robinson’s synthesis of tropinone is considered the ideal synthesis.

Robinson also proposed biosynthetic pathways (without the knowledge of biochemistry or biological process!) of terpenes, alkaloids and polyketides – because of his reputation, scientists started to believe in his (and consequently in Collie’s) ideas.
**Tropane alkaloids**

Alkaloids possessing the tropane skeleton are common in various plants.

As most of the tropane alkaloids possess pronounced biological properties, plants with high content of tropane alkaloids have been used in herbal folk medicine, for recreational drug use, and as poison.

The most prominent members of plants producing tropane alkaloids are *Solanaceae* (nightshade or potato family) and *Erythroxylaceae*. 
Deadly Nightshade (*Atropa belladonna*)

Long history as poisonous plant; perennial herbaceous plant, endemic in Europe, North Africa and Western Asia.

Name derived from Atropos, one of the three Greek goddesses of Fate.
Deadly Nightshade (*Atropa belladonna*)

Deadly nightshade is one of the most poisonous plants. Two to five berries or one leaf are lethal to an adult human. Cattle and rabbits can eat the plants without experiencing toxic effects; however, the alkaloids survive in the meat for a few hours and can cause troubles if consumed by humans.

Used as herbal medicine: pain reliever; muslce relaxant; anti-inflammatory properties; menstrual problems; motion sickness...

Often used in combination with opium for medical reasons

Deadly nightshade was also used as recreational drug (very problematic as side effects are severe!)
Deadly Nightshade (*Atropa belladonna*)

Deadly nightshade played an important role in medieval witchcraft and folklore; in combination with morphine (*Papaver somniferum*) and other plants as „flying ointments“ and other potions.

Highly potent poison; commonly used in ancient Rome (Claudius, maybe Augustus) and many other cultures.

Main alkaloids: hyoscyamine, hyoscine
Jimson weed / Thornapple / Datura (datura stramonium)

Bushy annual plant; endemic in Europe and North America – other members of the family are also found in Asia. Highly poisonous plant; cultivated for the isolation of alkaloids for medical purposes. Main ingredients: hyoscyamine and hyoscine.

Has been used as recreational drug (smoking), potions (see deadly nightshade) and poison (especially in India; *Datura metel*)
Henbane (Hyoscyamus)

Small genus of flowering plants; belong to the nightshade family; Poisonous plants with high content of hyoscyamine and hyoscine
Hyoscyamine, Hyoscine, Atropine

Hyoscyamine is a tropane ester; both enantiomeric forms are found in nature; (-)-hyoscyamine shown. Both isomers are biologically active;

A racemic mixture of hyoscyamine is called atropine. Atropine and hyoscyamine are marketed as drugs.

Hyoscine is also known under the synonym scopolamine (truth drug); similar biological properties as atropine;
base-catalysed or heat-initiated
keto-enol tautomerism

(-)-hyoscyamine
double bond of enol and aromatic ring in conjugation

(+)-hyoscyamine

hydrolysis

nucleophilic attack of 3α-hydroxyl onto either carbon of epoxide

(-)-hyoscine

scopine

(±)-oscine
The biological activity is related to the structural similarity to acetylcholine which acts as neurotransmitter. Tropane alkaloids bind to the muscarinic acetylcholine receptors.

- Antispasmodic action of gastrointestinal tract
- Antisecretory effect controlling salivary secretion (important during surgery)
• Mydriatic effects on the pupil of the eye

• Used to treat motion sickness

• Atropine is used as antidote in poisoning with compounds inhibiting the acetylcholin receptors (organophosphates)

• In combination with opioids (morphine...), atropine induces „twilight sleep“ – drug was used for small surgeries and childbirth.
Coca plant (*Erythroxylum coca*)

Small shrubs native to the Andes regions; several different species are known.

The coca plant has been in cultivation for several thousand years – first indications date back as far as 8000 years. Coca leaves have been found in 3000 year old mummies.

Usually, leaves have been chewed in combination with lime to increase solubility of the alkaloids. In the Inca period, the consumption of coca leaves was restricted to high priests and favoured individuals. After the Spanish colonialization, coca leaves were further distributed.
Coca leaves contain a vast number of alkaloids; cocaine is the best known natural product.

Cocaine is a stimulating, appetite suppressing local anesthetic. Highly addictive because of interactions with the mesolimbic reward pathway (increase of dopamine production in brain).

Blockage of dopamine transporter protein, responsible for active transport of neurotransmitter from cells into presynaptic neuron; dopamine accumulates and has prolonged effect on nerve cells.
Side effects of chronic use of Cocaine

**Brain:**
- Increased risk of strokes
- Reduced attention
- Insatiable hunger
- Insomnia/Hypersomnia
- Lethargy

**Systemic:**
- Fever
- Eosinophilia

**Nose:**
- Rhinorrhea (discharge)

**Teeth:**
- Bruxism (abrasion)

**Lungs:**
- Hemoptysis
- Bronchospasm
- Dyspnea
- Infiltrates
- Eosinophilia
- Chest pain
- Asthma

**Heart:**
- Increased risk of infarction

**Skin:**
- Pruritus
Among others, coca leaves also contain the following alkaloids:

- Cinnamoylcocaine (cinnamylcocaine)
- Tropacocaine
- Methylecgonine
- Hygrolineline
- β-Truxilline
Steady NERVES

HELLO! MARY
WHAT TIME WILL—
SAY WHAT'S THAT NOISE
HOW CAN YOU STAND IT?

OH! THAT'S THE
CHILDREN PLAYING—
SINCE I HAVE BEEN
TAKING NERVINE
NOTHING BOTHERS ME

When you are restless, sleepless, nervous, try
Dr. Miles Nervine
Your money back if it fails to relieve you. At your drug store. Small package 25 cents. Large package $1.00.

DR. MILES' NERVINE
LIQUID AND
EFFERVESCENT TABLETS

BURNETT'S
COCOAINE
FOR THE HAIR.
CURES DANDRUFF, SOOTHS ALL
IRRITATION OF THE SCALP, MAKES
THE HAIR GROW AND GIVES A BEAUTI-
FUL LUSTRE.
Blosser's Cigarettes

ACTIVE INGREDIENTS: Each Cigarette Contains Stramonium (Total Stramonium Alkaloids 0.012 grains), with Cubeb, Yerba Santa and Eucalyptus.

For the Relief of the Paroxysms of Bronchial Asthma, to Allay the Discomforts of Excessive Secretion due to Hay Fever, and to Ease Nasal and Bronchial Congestion due to Colds. Promotes easier breathing.

For Directions See Opposite Side

Contents: 24 Cigarettes—Price 50c

THE BLOSSER COMPANY, Sole Distributors
Atlanta, Georgia, U.S.A.

London, England

Coca-Cola Syrup and Extract

For Soda Water and other Carbonated Beverages.

This "Intellectual Beverage" and Temperance Drink contains the valuable Tonic and Nerve Stimulant properties of the Coca plant and Cola (or Kola) nuts, and makes not only a delicious, exhilarating, refreshing and invigorating Beverage, (dispensed from the soda water fountain or in other carbonated beverages), but a valuable Brain Tonic, and a cure for all nervous affections — Sick Head-Ache, Neuralgia, Hysteria, Melancholy, &c.

The peculiar flavor of Coca-Cola delights every palate; it is dispensed from the soda fountain in same manner as any of the fruit syrups.

J. S. Pemberton;
Chemist,
Sole Proprietor, Atlanta, Ga.
PARKER'S TONIC
THE GREAT HEALTH & STRENGTH
RESTORER.

CURES COUGHS, CONSUMPTION, ASTHMA.
BY REJUVENATING THE BLOOD.

Are you weary in Brain and Body
AVOID INTOXICANTS AND RELY ON PARKER'S TONIC

COCAIN TOOTHACHE DROPS
Instantaneous Cure!
PRICE 15 CENTS.
Prepared by the
LLOYD MANUFACTURING CO.
219 HUDSON AVE., ALBANY, N. Y.
For sale by all Druggists.
(Registered March 1885.)
See other side.
Rapoport’s Synthesis of Cocaine – Part 1

Rapoport’s Synthesis of Cocaine – Part 2

Pearson’s Synthesis of Cocaine

Scheme 1. Retrosynthesis of Cocaine

Pyridine alkaloids - biosynthesis

E1: L-tryptophan 2,3-dioxygenase (L-Trp-specific)
E2: indoleamine 2,3-dioxygenase (broad specificity)
E3: kynurenine formamidase
E4: kynurenine 3-monooxygenase
E5: kynureninase
E6: 3-hydroxyanthranilate 3,4-dioxygenase
E7: aminocarboxymuconate-semialdehyde decarboxylase
E8: quinolinic acid phosphoribosyltransferase
enamine as nucleophile

dihydroxy-acetone P

E2

keto–enol–keto
tautomerism

tautomerism to amine,
then imine formation

E2

–H₂O

FAD

E1

L-Asp

iminoaspartic acid

E1: aspartate oxidase
E2: quinolinate synthase

nicotinic acid

quinolinic acid
Nicotine

Most prominent alkaloid isolated from plants of the genus *Nicotiana* (Solanaceae)
Several different species; *Nicotiana tabacum* is cultivated for the production of tobacco.

*N. tabacum* is an annual herbal plant originally endemic to indigenous and tropical America.
Tabacco was originally used by Native Americans for religious, medicinal, and ceremonial purposes. Soon after the discovery of America, tabacco was brought to Europe. First reports as early as 1518.

Earliest picture of Spaniard smoking a pipe
Main alkaloid in tobacco is nicotine, a highly toxic and highly addictive alkaloid.

Nicotine is a potent parasympathomimetic alkaloid (stimulates parasympathetic nervous system). The alkaloid increases levels of neurotransmitters and dopamine (reward pathway)

Nicotine acts as stimulant and relaxant:

• Causes release of glucose and adrenaline (→ stimulation)

• Reduces appetite

• Enhances concentration and alertness (increased level of acetylcholine)

• Increases blood pressure

• In high concentrations, nicotine has a pain-killing effect
Nicotine binds to acetylcholine receptors because of structural similarities with the neurotransmitter.

Cigarette smoke contains a vast number of highly toxic and cancerogenic compounds which are responsible for the serious side effects and health issues of smoking.

Despite the toxicity of nicotine, it is nearly impossible to suffer from lethal overdose as cigarette smoke only contains small amounts of the alkaloid (approximately 1 mg of nicotine is absorbed from one cigarette).
Side effects of Nicotine

Blood
- Increased clotting tendency

Lungs
- Bronchospasm

Muscular
- Tremor
- Pain

Gastrointestinal
- Nausea
- Dry mouth
- Dyspepsia
- Diarrhea
- Heartburn

Joints
- Pain

Central
- Lightheadedness
- Headache
- Sleep disturbances
- Abnormal dreams
- Irritability
- Dizziness

Heart
- Increased or decreased heart rate
- Increased blood pressure
- Tachycardia
- More (or less) arrhythmias
- Coronary artery constriction

Endocrine
- Hyperinsulinemia
- Insulin resistance
Tyrosine derived alkaloids - Catecholamines

L-Tyr \[\text{tyrosine hydroxylase} \rightarrow \text{dopa} \] E4
\[\text{tetrahydrobiopterin} \rightarrow \text{oxygenase} \rightarrow \text{dopamine (norepinephrine)} \] E5
\[\text{dopamine} \rightarrow \text{mesocainine} \] E6

E1: aromatic L-amino acid decarboxylase (tyrosine decarboxylase; DOPA decarboxylase)
E2: tyramine N-methyltransferase
E3: N-methyltyramine N-methyltransferase
E4: tyrosine hydroxylase
E5: dopamine β-monooxygenase
E6: phenylethanolamine N-methyltransferase
**Catecholamines**

Dopamine, noradrenaline and adrenaline are important neurotransmitters. Produced in adrenal glands and nervous tissue.

Adrenaline (epinephrine) plays a major role in the regulation of the heart rate and the blood pressure. Additionally, adrenaline releases glucose and increases metabolic rate and alertness (stress hormone).

Catecholamines interact with adrenergic receptors in the body:

α-Receptors: effect on vascular, uterine and intestinal muscles

β-Receptors: inhibitory effect on smooth muscles but stimulatory effect on heart muscle

Several drugs act as selective β-receptor antagonist (beta blocker) and reduce effect of stress on the body (mainly heart muscle. Thus, those compounds protect patients from suffering a heart attack.
Example of commercial beta-blockers:
Morphine and related alkaloids:

- Morphine (1), $R = H$
- Codeine (2), $R = \text{Me}$
- Thebaine (3), $R = \text{Me}$
- Oripavine (4), $R = H$
E1: aromatic amino acid decarboxylase (DOPA decarboxylase)
E2: norcoclaurine synthase
E3: norcoclaurine 6-O-methyltransferase
E4: (RS)-coclaurine N-methyltransferase
E5: (S)-N-methylcoclaurine 3'-hydroxylase
E6: (RS)-3'-hydroxy-N-methylcoclaurine 4'-O-methyltransferase
E7: 1,2-dehydroreticuline synthase
E8: 1,2-dehydroreticuline reductase
one-electron oxidation of phenol groups to give resonance-stabilized radicals

\[ (R)\text{-reticuline} \rightarrow \text{O}_{2} \text{ NADPH E1} \rightarrow \text{radical coupling} \rightarrow \text{salutaridine} \]

S\(_{N}\)2' nucleophilic attack with acetate as leaving group

\[ \text{thebaine} \rightarrow \text{esterification provides better leaving group} \rightarrow \text{salutaridinol} \]

demethylation of thebaine via hydroxylation, cleaving off methyl as formaldehyde

\[ \text{neopinone} \rightarrow \text{oripavine} \rightarrow \text{morphinone} \]

demethylation

demethylation
demethylation of thebaine via hydroxylation, cleaving off methyl as formaldehyde

demethylation

keto-enol tautomerism favoured by conjugation

demethylation of codeine; probably via oxidation of methyl to hydroxymethyl and cleavage of formaldehyde

stereospecific reduction of carbonyl

stereospecific reduction of carbonyl

E1: salutaridine synthase
E2: salutaridine:NADPH 7-oxidoreductase
E3: salutaridinol 7-O-acetyltransferase
E4: codeinone reductase
Origin of Morphine: *Papaver somniferum* and related poppy plants.

More than 700 different members of this plant family are known.

*Papaver lateritium*
Origin of Morphine: *Papaver somniferum* and related poppy plants.

*Papaver radicatum*  
*Papaver somniferum*
Origin of Morphine: *Papaver somniferum* and related poppy plants.

*Papaver somniferum*  
*Papaver hybridum*
Opium – Historic Aspects:

First indication of the cultivation of poppy plants can be traced back to the Stone Age. Poppy seed was found in ancient settlements in the Bodensee area (Switzerland). Interestingly, the species found in these settlements was not endemic in Switzerland – one of the earliest examples of international trade...

Poppy plants need warm climate for the production of narcotics)

Poppy plants and poppy seeds were common and highly valued „food additives“ in Mesopotamia, Ancient Rome and Greece. The plant was used for nutrition, medicinal treatments and „religious“ rites.
Morphine – Biological Activity:

Morphine acts as agonist for morphine receptors (mainly $\mu$-opioid receptor), predominantly in the central nervous system but also in muscle cells

- used to treat acute and chronic pain
- traditionally used for the treatment of acute pulmonary edema
- releases symptoms of shortness of breath
- used as analgetic (3 to 4 hours, maximum 6 hours)
- substitution therapy for drug addicts (if buprenorphine or methadone does not give satisfactory results)
- muscle relaxant
- euphoria
Morphine – Biological Activity:

**Side effects:**
- strongly addictive
- strong increase in dosage needed for desired results
- possible respiratory depression and apnoea
- renal failure (toxic metabolites)
- raised intracranial pressure
- euphoria
- nightmares and depression
Cultivation of *Papaver somniferum*; Production of Opium
Origin of Morphine: *Papaver somniferum* and related poppy plants.

Harvest of raw opium:
Origin of Morphine: *Papaver somniferum* and related poppy plants.
Poppy Plants in Ancient Art:

Goddess Gazi  
(Kreta, minoic period)

Dionysos  
Greek vase
Poppy Plants in Ancient Art:

Demeter with wheat and poppy plants
In the early 1900’s, Bayer wanted to stop the production of aspirin because other pain killers, such as heroin and cocaine were cheaper and more effective. Between 1910 and 1920, aspirin became more popular because heroin was slowly banned from the market.
Not so long ago...
Not so long ago...
Early Syntheses of Morphine and Codeine

Gates – 1952; part 1

1. PhCOCl, py
2. NaNO₂, AcOH
(65%)

1. NCCH₂CO₂Et
2. K₃Fe(CN)₆
3. KOH
(81%)

1. Me₂SO₄, K₂CO₃
2. KOH
3. NaNO₂
4. H₂, Pd/C
5. FeCl₃
(59%)

Cu-Cr, H₂
27 atm, 130 °C
(50%)

1. NaOH, N₂H₄
2. MeI, NaH
3. LAH
(79%)

20
Early Syntheses of Morphine and Codeine

Gates – 1952; part 2

\[
\begin{align*}
&\text{1. dibenzoyl tartaric acid} \\
&\text{2. } \text{H}_2\text{SO}_4, \text{H}_2\text{O} \\
&\text{3. tBuOK, Ph}_2\text{CO} \\
\end{align*}
\]

1. dibenzoyl tartaric acid
2. H\textsubscript{2}SO\textsubscript{4}, H\textsubscript{2}O
3. tBuOK, Ph\textsubscript{2}CO

\[
\begin{align*}
\text{20} & \rightarrow \text{MeO} \quad \text{Br} \\
\text{NMe} & \quad \text{HO} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{Br} \\
\text{21} & \quad \text{H} \\
\text{NMe} & \quad \text{HO} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{Br} \\
\text{22} & \quad \text{Br} \\
\text{NMe} & \quad \text{HO} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{Br} \\
\text{23} & \quad \text{Br} \\
\text{NMe} & \quad \text{HO} \\
\text{ArNHN} & \quad \text{HO} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{Br} \\
\text{24} & \quad \text{Br} \\
\text{NMe} & \quad \text{HO} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{Br} \\
\text{25} & \quad \text{Br} \\
\text{NMe} & \quad \text{HO} \\
\text{O} & \quad \text{Br} \\
\text{5} & \quad \text{NMe} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{Br} \\
\text{26} & \quad \text{Br} \\
\text{NMe} & \quad \text{HO} \\
\text{ArNHN} & \quad \text{HO} \\
\text{O} & \quad \text{Br} \\
\text{5} & \quad \text{NMe} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{Br} \\
\text{27} & \quad \text{Br} \\
\text{NMe} & \quad \text{HO} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{Br} \\
\text{morphine (1)} & \\
\text{NMe} & \quad \text{HO} \\
\end{align*}
\]
Early Syntheses of Morphine and Codeine

Rice – 1980

1. $\text{Li}, \text{NH}_3$, THF, $t\text{BuOH}$
2. PhOCHO, EtOAc, $\Delta$
3. $(\text{CH}_2\text{OH})_2$, THF, MeSO$_3$H
4. CH$_3$CONHBr, 0 °C

1. MeOH, HCl, reflux; NH$_3$, H$_2$O, iPrOH
2. H$_2$, Pd/C, HOAc, HCHO

1. Br$_2$, HOAc
2. NaOH, CHCl$_3$
3. H$_2$, HOAc, HCHO

5 steps see ref. xx

36%
Hudlicky (2007)

1. MeNH₂, K₂CO₃, -40 °C
2. (Boc)₂O, NEt₃, MeOH
3. TBSCl, imidazole, -78 °C

47%

44%

n-Bu₃P, DIAD, THF, 48, 0 °C
55%

PPh₃CHBr, t-BuOK, THF, -60 °C
49%

Pd(OAc)₂, Ag₂CO₃, dppf, toluene, 110 °C
82%

Pd(OAc)₂, Ag₂CO₃, dppp, toluene, 110 °C
44%

1. TBAF, THF
2. IBX, DMF
3. NaBH₄, CeCl₃, MeOH
72%

1. TFA, CH₂Cl₂
2. Hg(OAc)₂, NEt₃, MeOH
3. LAH
15%

ent-codeine (ent-2)
Morphine binds to opioid receptors in the brain. The natural substrates for those receptors are opioid peptides, including endorphins, dynorphins, endomorphins. The natural substrates are by a terminal tyrosine unit, mimicked by the morphine structure.
Diels–Alder reaction

Grignard reagent attacks ketone stereospecifically from less-hindered side

demethylation with strong base
Colchicine:

Highly toxic natural product isolated from the autumn crocus (*Colchicum autumnale*). Traditionally used to treat gout and swellings. Used as herbal remedies by ancient cultures (Ancient Egypt 1500 BC); first isolated in 1820 by Pelletier and Caventou

Approved to treat gout – also used in the treatment of various forms of cancer (inhibits tubulin polymerization)
(S)-demecolcine

$E_1$: autumnaline oxidase

**Oxidative coupling**

Homomorphinan skeleton

Isoandroscybine

R = Me, O-methylandroscybine (R = H, androscybine)

**Cleavage of cyclopropane** generates 7-membered tropolone ring; remaining ring carbon becomes N-formyl group

**Oxidation leading to formation of cyclopropane ring and generation of radical**

**Oxidation of enamine** (enamine); may proceed through iminium, followed by iminium–enamine tautomerism

**Oxidative demethylation**

Deacetylcolchicine

**Amide formation**

Colchicine
Morphine, Galanthamine-type alkaloids and Amaryllidaceae alkaloids:

- L-Phe (via cinnamic acids with side-chain cleavage)
- via imine and reduction
- norbelladine
- 4'-O-methyllnorbelladine

Pathway:
- L-Phe → tyramine (via imine and reduction)
- norbelladine → 4'-O-methyllnorbelladine (SAM, E1)
E1: catechol O-methyltransferase
\[ \text{(R)-reticuline} \rightarrow \text{salutaridine} \rightarrow \text{morphine} \]

\[ \text{4'-O-methylnorbelladine} \rightarrow \text{galanthamine} \]
Galanthamine (also galantamine):

Isolated from several plant of the genus *Narcissus* and *Galanthus* (Amaryllidaceae family). Content varies; usually between 0.05% and 0.2% of bulbs.

Galanthamine is used to treat Alzheimer’s disease as it raises the acetylcholine level in the brain by selectively (and reversibly) inhibiting acetylcholinesterase.
Pancratistatin:

Isolated by Pettit from Spider Lily (native to Hawaii); exhibits strong anti-cancer activities. Pancratistatin induces apoptosis in cancer cells while normal cells are not affected. The natural product attacks mitochondrial RNA but the exact mechanism is not known.

Several total syntheses; pancratistatin is currently in clinical trials (phosphate for better water solubility).
Reaction conditions: (a) 6-iodopiperonol, NaH, Cl$_3$CCN, 0 °C; (b) TfOH, THF, 0 °C, 75% (over 2 steps); (c) L-Selectride, CH$_2$Cl$_2$, -78 °C; (d) BnONH$_2$:HCl, pyr., 96% (over 2 steps); (e) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, 0 °C; (f) HF-pyridine, THF, 84% (over 2 steps); (g) TPAP, NMO, 4 A MS; (h) 1-amino-2-phenylaziridine, EtOH, 0 °C, 83% (over 2 steps); (i) Ph$_3$SnH, AIBN, C$_6$H$_6$, reflux, 78%; (j) Sml$_2$, then TFAA, 88%; (k) PCC, CH$_2$Cl$_2$, 83%; (l) BF$_3$:OEt$_2$; (m) K$_2$CO$_3$, MeOH, 88% (over 2 steps). Reaction conditions and yields for reactions (c) to (h) correspond to the ether series.
Reaction conditions: (a) E. coli JM109 (pDTG601A), 4 g/L; (b) i) DMP, acetone, TsOH, rt, ii) NHCO₂Me, NaIO₄, rt, 70%; (c) borate 77 Pd(PPh₃)₄, aq. Na₂CO₃, PhH, reflux, 30%; (d) TTMSS, AIBN, PhH, reflux, 80%; (e) NaBH₄, CeCl₃, MeOH, 0 °C, 80%; (f) BzOH, Bu₃P, DEAD, THF, rt, 65%; (g) i) Dowex 50X8-100, MeOH, rt, ii) Ac₂O, pyr., DMAP, rt, 70%; (h) Tf₂O, DMAP, CH₂Cl₂, 0 °C, 40%; (i) i) Amberlyst A21, MeOH, MeOH; ii) LiCl, DMF, 120 °C, 20%.
Purine alkaloids

Caffeine, theobromine, and theophylline are the most prominent members of the purine alkaloids.
Origin of Life?

The original spark of life may have begun in a "warm little pond, with all sorts of ammonia and phosphoric salts, lights, heat, electricity, etc. present, so that a protein compound was chemically formed ready to undergo still more complex changes.

Charles Darwin, 1871
Caffeine

Stimulating psychactive drug

First research was initiated by Goethe who asked Runge to investigate coffee beans

1820  Caffeine was isolated by Runge
1821  Independently isolated by Pelletier and Caventou
1895  Structure proof and first total synthesis by Emil Fischer
Caffeine is the main alkaloid in coffee beans; can also be isolated from the tea bush, kola nut...

Coffee contains approximately 0.9 – 2.6% caffeine, one cup of coffee is equivalent to 100 -240 mg caffeine. Caffeine overdose starts with approximately 1 g; lethal dose approximately 10 g

Caffeine is an important ingredient in many beverages and is produced chemically on large scale.
Adenine monophosphate (AMP) is converted to inosine monophosphate (IMP) via the purine biosynthetic pathway. IMP is further converted to guanosine monophosphate (GMP) with the help of NAD+. 7-Methylguanosine (GMP) is converted to 7-methyl guanosine monophosphate (XMP) by SAM. XMP is hydrolyzed to 7-methyl xanthine by E3. 7-Methyl xanthine is further converted to caffeine (1,3,7-trimethylxanthine) and theobromine (3,7-dimethylxanthine) by E6 and E7, respectively. The mechanism involves the displacement of the purine leaving group by D-ribose in the presence of SAM. Enzymes involved are:

- **E1**: AMP deaminase
- **E2**: IMP dehydrogenase
- **E3**: 5'-nucleotidase
- **E4**: xanthosine 7-N-methyltransferase
- **E5**: 7-methylxanthosine nucleosidase
- **E6**: 7-methylxanthine 3-N-methyltransferase (theobromine synthase)
- **E7**: theobromine 1-N-methyltransferase (caffeine synthase)
Health effects of caffeine

Positive effects
- increased attention and alertness, decreased fatigue
- lower risk of cardiovascular disease
- lower risk of diabetes
- increased metabolic rate

Negative effects
- anxiety and addiction
- increased vasoconstriction and blood pressure
- reduced control of fine motor movements
- stimulation of urination

Diagram showing a human body with highlighted sections for positive and negative effects.
Caffeine overdose?

Effect of caffeine on central nervous system of insects is more pronounced than in humans...