Phenylalanine, Tyrosine and From Dihydro Phenylalanine Derived Alkaloids

Phenethylamines are compounds found in many plants.

We will see some protoalkaloids such as mescaline, cathinone and ephedrine. These alkaloids have very significant effects.

Since these compounds are metabolized in the intestine and liver, they always pose a risk of high blood pressure.

It can also create serious problems for patients treated with MAO inhibitors: They can cause migraine, the results and effects can be dangerous due to the place where they are metabolized...

ISOKINOLINE ALKALOIDES

Examined under 20 groups

Tetrahydroisoquinolein Alkaloids

Benzyl isoquinolein and Pavin Alkaloids

Bisbenzyl isoquinoline Alkaloids

Aporphine Alkaloids

Proaporphine Alkaloids

Oxoaporphine Alkaloids

Kularine Alkaloids

Dibenzopyrocholine Alkaloids

Protoberberine Alkaloids

Protopine Alkaloids

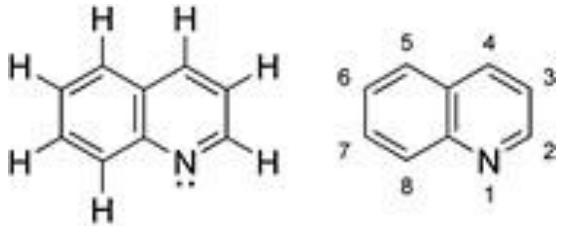
11) Phthalyl isoquinoline Alkaloids
12) Benzophenatridine Alkaloids
13) Spirobenzyl isoquinoline Alkaloids
14) Protephanin Alkaloids
15) Phenylethyl Isoquinoline Alkaloids
16) Isoquinolone Alkaloids
17) Phenyl tetrahydro Isoquinoline Alkaloids
18) Phenantroquinolysis and Phenanthroindolizine Alkaloids
19) Ipeca Alkaloids
20) Morphine Alkaloids

There are many alkaloids in the nature.
They are known as Qinoline and isoquinoline alkaloids.

Apart from phenylethylamines, there are 5 main alkaloid groups, which are formed as a result of the reactions of precursors with amino acids, according to the shape of the final structure.
Simple tetrahydro isoquinoline
Benzyl tetrahydroisoquinoline
Phenylethylisoquinoline
Amaryllidaceae
Monoterpenic isoquinoline alk.
Alkaloids derived from phenylalanine and tyrosine metabolism, the main structure is isoquinoline structure.
Alkaloids of H. Ephedra derived from phenylethylamines.
Other groups, Benzopyridine isomers

Biosynthesis of Isoquinoline alkaloids:

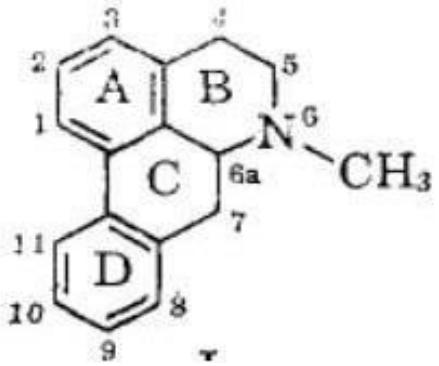
- From *phenylalanine* of *tyrosine* *Phenylethylamine* derivatives and *phnylacetaldehyde* derivatives are obtained which are condensed to give Isoquinoline alkaloids.
- Morphine (and codeine, thebaine) is also formed from tyrosine (2 molecules) and in the biosynthetic pathway Norlaudanosoline is a key intermediate.



- Quinoline; is one of the benzopyridine isomers. It carries nitrogen in the α position. The isomer in the β position is called isoquinoline.
- The quinoline ring system is involved in the structure of many alkaloids (However, the quinoline ring is independent in kına kına-chinchona alkaloids).

Aporphine alkaloids

All the aporphine alkaloids are based on the 4H-dibenzo *quinoline structure* *or its 3-methyl derivative* commonly known as the aporphine nucleus. The numbering system is as indicated, so as to conform with the "Ring Index"



ISOQUINOLINE alkaloids

Largest group of alkaloids

Derived from the amino acids Tyrosine and Phenylalanine

- Anti-microbial
- Chologogue/choleretic
- Enzyme inhibitor
- Antitumor
- Pain suppressant
- Cough suppressant
- Hypnotic
- Relaxant
- Antispasmodic

Isoquinoline alkaloids
Benzyl Tetrahydroisoquinoline

1.Simple Benzylisoquinolines
Papaverine

2.Bisbenzyltetrahydroisoquinolines
Curare etc

3.Aporfins
Apomorphine

4. Protoberberine and its derivatives
Hydrastis canadensis
Sangunaria canadenisis
Papaver rhoeas
Others; *Jateorrhiza palmata*

5.Morphinan alkaloids
Papaver; Opium alkaloids

Morphine/Morphinan Alkaloids

Isoquinoline alkaloids, especially, found in the family Papaveraceae,
Genera: Argemone, Glaucium, Baccania, Chelidonium, Papaver, etc.

However, thebaine was found almost in 10 Papaver species, but there are 100 or more Papaver species (P. bracteatum, P. orientale); morphine was found only in P. somniferum and P. setigerum

Structurally true morphinan alkaloids are characteristic for Papaver species.
These alkaloids are also not very common.
Structures; Benzyltetrahydroisoquinoline derivatives.
They derive from tyrosine metabolism...
Morphine is formed by the demethylation of codeine.
It is also synthesized via oripavine (3-demethylthebaine) (thebaine, oripavine, morphinone, morphine, respectively, in the synthesis pathway).

OPIUM (TF)-AFYON

Papaver somniferum (Papaveraceae) has one of the capsule type fruits of the varieties known as Turkish Poppy, contain dried latex (milk).

It is also registered in many pharmacopoeias.

Just for galenic prep.

Used in the preparation, there is no direct use.

The fruit is a flattened spherical capsule. There are secretory channels in the capsule mesocarp. These channels contain a latex. When the capsule is green, it is made a incision transversely in the early morning. The air-dried form of the drug gives latex. Drog is known as OPIUM/Opium. Raw opium must contain at least 10% morphine and 2% codeine.

History

- 1805.....Isolation of Morphine from Opium
- 1817.....Strychnine
- 1819.....Caffeine
- 1826.....Coniin was isolated

- **People's interest in the poppy plant dates back to 4500 years ago.**
- **It is thought that it was first used in the Neolithic age, in the polished stone age.**
- **Later, its use in religious ceremonies and for medical purposes in Crete, in the eastern part of the Mediterranean, was taken from here to Egypt and Cyprus.**
- **It is used as jewellery, needles and jewelry-like objects, in the temple and tomb decorations in Egypt in earlier periods.**
- **Traces were found in marble vases (1500 BC) Similar objects were also found in Anatolia.**
- **Assyrians are thought to know this plant.**
- **The Sumerians called this plant the Joy plant-plant of happiness.**
- **It was used as a pain reliever in India, China, Egypt, Greece, and Rome.**
- **Dioscorides was also described**
- **Introduced to the east by the Arabs - Used in pain relief and dysentery.**

Poppy is one of the important cultural plants of our country.
Both the alkaloids in their capsules and oil is used.
Alkaloids such as papaverine, thebaine and codeine, especially morphine in the capsule bark, are important pharmaceutical raw materials.

In addition, morphine and the heroin are widely used as drugs in the world, although it is prohibited.

- Poppy has been cultivated in Anatolia since the Hittite period. For the first time in 1933, the agriculture was taken under state control and production continued until 1971 with the laws and regulations enacted from time to time.
- In 1971, the cultivation of poppy was banned in Turkey with the government decree numbered 2654.

- Production was allowed again in 1974, but capsule drawing was prohibited.
- A factory was established in Bolvadin district of Afyon in 1976 to obtain alkaloids from dry capsules.
- The factory started partial production in 1981 and full capacity production in 1983. Between these years, poppy capsule stocks have increased continuously, and TMO (Soil Crops Office) has been in a difficult situation. For this reason, the poppy cultivation areas have been narrowed.

There are two subspecies of Papaver somniferum.

P. somniferum subsp. spontaneum (in Open Poppy-Anatolia)(When the capsules mature, they are opened with holes from the top and the seeds are poured into the soil from there.)

P. somniferum subsp. anatolicum (Blind poppy-in Anatolia)(Capsules do not open at maturity)

P. somniferum subsp. anatolicum

album (white flower)

nigrum (with purple flowers)

setgerum (dark purple flowers)

glabrum (with red-purple flowers)

The plant is cultured in Turkey, Australia, France, Spain, India, Pakistan, Iran and Mexico.

In Turkey, mostly P. somniferum subsp. anatolicum, var. album (with white flowers) and var. nigrum (purple-flowered) varieties are planted.

Since the plant has been cultivated in Anatolia for thousands of years, the species grown are the ones that give the best product.

If we draw a line between

Ankara and Mersin; Eskişehir, Bilecik, Kütahya, Uşak, Afyon, Isparta, Burdur, Denizli (Drogist Region-to the west of the line-single-edged knife)

Amasya, Tokat, Çorum, Malatya (Soft Region - 4-5 bladed knife to the east of the line)

Obtaining opium begins early in the morning with the drawing of the capsules, which are just beginning to mature.

The line depth should reach the mesocarp, but the capsule should not be torn. The latex, which flows out when the capsule is scratched and collects as droplets outside the capsule, is fluid and light in color at first, darkens and turns brown towards the evening. Raw opium is a mass ranging from yellow to brown to black, with a special odor, elastic when fresh and hardens when dried.

- The darkened opium is collected by scraping with the help of wide-faced knives called perception knives. It is made into lumps, wrapped in poppy leaves and left to dry.
- According to the laws in Turkey, the Council of Ministers decides in which provinces poppy cultivation will take place.
- While poppy cultivation was allowed in 30-35 provinces before, cultivation areas decreased and in 1972 it was limited to 4 provinces.
- Since the autumn of 1972, a decree has been issued stating that poppy cultivation will not be carried out in Turkey.
- In 1974, the cultivation of poppy was allowed again, provided that the capsules were not scratched. The capsules were previously stored and sold abroad. Afterwards, the export was stopped and the capsules were started to be processed in the Afyon-Bolvadin Alkaloid Factory.

The alkaloid amount in Opium is between 10-25%.
Of the 25 alkaloids obtained from this drug, the some of them are used in pharmacy: morphine, codeine, thebaine, papaverine, laudanin, narcotine (noscapine), and narsein. They are alkaloids with a benzyl isoquinoline group.
Most opium contains morphine, varying between 5-25%.
Codeine is about 0.5-3%.
Thebaine is between 0.2-1%.
Papaverine is between 0.5-1.3%.
It has the highest narcotine amount after morphine, 2-10%.

Identification

Morphine: Powdered drug is wetted with ammonia, consumed with chloroform, if chloroform is evaporated and concentrated sulfuric acid is placed on it, a red color is observed.

Codeine: dissolved in concentrated sulphuric acid, dark blue color if dissolved in acid, and ferric chloride added.

Papaverine: If potassium ferric cyanide is added, formolluster sulfuric acid with formol is added, a green-blue color is observed.

Isolation

Powdered drug is wetted with lime milk Ca(OH)2. Meconic acid precipitates as calcium meconate, calcium morphinate remains in solution because it dissolves in water. It is filtered, and ammonium chloride and morphine precipitate in the base form.

Opium (TF)-Afyon
Poppy: *Papaver somniferum-Haşhaş*

- Papaveraceae

Opium in small amounts, respiratory stimulator, in high doses it stops, in small amounts it relieves pain. It is used for severe pain.

Before 1800: Herbs and herbal extracts were used
1805: Morphine isolated from opium (structure determined in 1935, synthesized in 1952)

Papaver somniferum (Papaveraceae)-is obtained from the capsule type fruits of poppy varieties and defined as dried latex (milk).

The fruit is a flattened spherical capsule. There are secretory channels in the capsule mesocarp.

These channels contain a latex. When the capsule is green, it is drawn transversely in the early morning.

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