Alkaloids

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1. General Characteristics of Alkaloids

The general characteristics of **alkaloids** may be grouped together in *two* categories, namely:

(*a*) Physical characteristics, and

(*b*) Chemical characteristics.

These *two* categories shall now be discussed individually in the sections that follows:

1.2 Physical Characteristics

First and foremost, let us consider the solubility of alkaloids both in water and organic solvents along with some typical examples. In fact, a comprehensive knowledge of the solubility of complete range of alkaloids and their corresponding salts is of utmost pharmaceutical importance because of their extremely specific and potent pharmacological actions.

It is pertinent to mention here that in general the solubilities of different alkaloids and their respective salts usually exhibit considerable variation, which may be attributed from their extremely complex and varied chemical structures. However, it has been observed that the free alkaloid bases as such are invariably found to be fairly soluble in organic solvents, such as: either, chloroform, relatively non-polar solvents (hexane, benzene, petroleum ether), immiscible solvent, lower alcohols (methanol, ethanol); but they are either practically insoluble or very sparingly soluble in water.

Interestingly, the alkaloidal salts are almost freely soluble in water, relatively less soluble in alcohol and mostly either insoluble or sparingly soluble in organic solvents:

Examples Atropine sulphate and **morphine hydrochloride** are much more soluble in water than their corresponding bases *i.e.*, **atropine** and **morphine.**

However, there are a few exceptions to the above stated generalizations, namely:

(*i*) Certain **alkaloid** bases are water soluble, but these may be solely regarded as exceptions rather than any specific rule, such as: **ephedrine, colchicine, pilocarpine;** the **quaternary alkaloid-base** like **berberine** and **tubocurarine; caffeine-base** readily extracted from tea with water.

(*ii*) **Narceine** and **pilocarpine** are insoluble in organic solvents, whereas morphine is sparingly soluble in organic solvents *viz*., solubility in either 1:5000.

(*iii*) Certain alkaloidal salts, for instance: **lobeline hydrochloride** and **apoatropine hydrochloride** are found to be soluble in organic solvent like chloroform.

(*iv*) Some alkaloidal salts are sparingly soluble in water whereas others are extremely watersoluble, such as: **Quinine sulphate**-soluble in 1:1000 parts of water, **Quinine hydrochloride** soluble in 1:1 part of water. The physical characteristics of some potent **alkaloids,** such as: mp, optical rotation and solubility are enlisted below so as to have a glimps of the distinct variation in the observed parameters:

S.No.	Alkaloid	mp (°C)	Optical rotation	Solubility
1.	Ajmaline	150-160	$[\alpha]_D^{20}$ + 144°	Chloroform, ether, ethanol, methanol
2.	Atropine	144-116	–	Benzene, chloroform, ether
3.	Berberine	145	–	Water
4.	Colchicine	142-150	$[\alpha]_D^{17}$ – 429°	Water, chloroform, ethanol
5.	Ephedrine	79	–	Water, ethanol, ether, chloroform, oils
6.	Hyoscyamine	108.5	$[\alpha]_D^{20}$ – 21.0°	Ethanol, dilute acids
7.	Morphine	197	$[\alpha]_D^{25}$ – 132°	Sparingly soluble in ethanol, chloroform, amyl alcohol,
8.	Physostigmine	105-106	$[\alpha]_D^{25}$ – 120°	Benzene, chloroform, oils
9.	Quinine	177	$[\alpha]_D^{17}$ – 117°	Chloroform, ether
10.	Reserpine	264-265 (dec.)	$[\alpha]_D^{23}$ – 118°	Chloroform, ethyl acetate, benzene.
11.	Strychnine	275-285	$[\alpha]_D^{18}$ – 104.3°	Chloroform, methanol, benzene
12.	Taxol	213-216 (dec.)	$[\alpha]_D^{20}$ – 49°	Methanol
13.	Vinblastine	211-216	$[\alpha]_D^{20}$ + 42°	Chloroform, ethanol
14.	Yohimbine	234	$[\alpha]_D^{20}$ + 108°	Chloroform, ethanol, benzene

1.3 Chemical Characteristics

The general chemical characteristics of the **alkaloids** are so broadly spread out, therefore, they shall be treated individually under the following heads, namely.

[A] N-in the Molecule Besides, the other normal elements *e.g.*, carbon, hydrogen, oxygen, the alkaloids must essentially contain at least one N-atom. The number of N-atoms vary from the bear minimum one in a molecule *e.g.*, **cocaine**, to even five in a molecule *e.g.*, **ergotamine**. It has been observed that these N-atoms are normally present as a part of the **heterocyclic ring** in the alkaloid molecule *e.g.*, **quinine, reserpine, strychnine, vinblastine** and **yohimbine;** whereas there are certain alkaloids that contain the N-atom in the aliphatic side chain *e.g.*, **ephedrine, mescaline.**

Invariably, the alkaloids contain the N-atom in the **tertiary-amine form** (R_3N) *e.g.*, **morphine, reserpine;** lesser in the **secondary-amine form** (R_2NH) *e.g.*, **ephedrine;** and very rarely in the **primary-amine form** (RNH_2) *e.g.*, **nor-pseudo-ephedrine.** Furthermore, whenever N-atom occurs either in the *tertiary*- or *secondary*-form, it essentially constitutes as an integral part of the ringsystem, precisely the heterocyclic ring system.

Noticeably, the tertiary N-atoms wherein only two of the bonds are involved in a ring, the methyl moiety is usually found as the third component, for instance: N-methyl group in **morphine, cocaine, colchicine, dextro methorphan, codeine, physostigmine, vinblastine, vindesine** etc. Hence, methyl moiety seems to be the only **alkyl group** that has been found to be substituted on the **N-atom.**

However, in some very specific cases, the N-atom occurs in the **quaternary ammonium form** ($R_4N^+ \ . \ X^-$) *e.g.*, **tubocurarine chloride** [see section 7.1.5 (c)]. Nevertheless, the quaternary ammonium compounds are logically and technically not regarded as alkaloids by virtue of the following *two* particular reasons, namely:

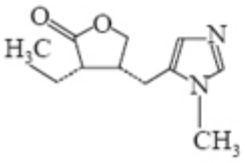
(*i*) N-atom does not possess a H-atom, and

(*ii*) Chemical properties are quite different.

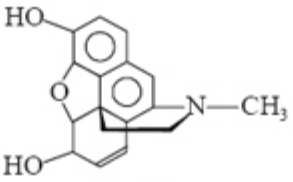
As a matter of convenience, they are legitimately grouped along with the *alkaloids*.

[B] O-in the Molecule In addition to the common elements C, H and N, a variety of **alkaloids** normally contains O-atom. Invariably, these specific alkaloids are found in the solid state, with a few exceptions where the oxygenated alkaloids usually occur as non-volatile liquids, such as: **pilocarpine.**

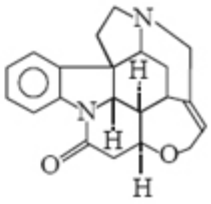
[C] Basicity (Alkalinity) In general, the **alkaloids** are basic (alkaline) in reaction, by virtue of the presence of N-atom present in the molecule. Hence, these are prone to the formation of their respective salts with various acids.



Pilocarpine
(Liquid, mp34°C)



Morphine
(Solid, mp197°C)



Strychnine
(Solid, mp 268–270°)

Degree of Basicity: The degree of basicity of the **alkaloids** mostly depends upon the prevailing influence caused due to the electrostatic status of the N-atom present in the alkaloid molecule, for instance, the number of N-atom present in the alkaloid, whether the N-atom is located in the ring or in the side-chain, the presence of alkyl group (*e.g.*, methyl) to the N-atom etc.

Another vital factor, which establishes the degree of basicity of an alkaloid, is the presence of *pri*-, *sec*-, *tert*-, or *quaternary* N-atom or atoms in it. In fact, such apparent differences in the degree of basicity arising from the various structural features, are eventually reflected by the different dissociation constant values (*i.e.*, pKa values) with regard to various alkaloids as stated below:

S.No.	Alkaloid	pKa Values
1	Berberine	2.47 ($K = 3.35 \times 10^{-3}$)
2	Colchicine	12.35 (at 20°C)
3	Emetine	$pK_1 = 5.77$; $pK_2 = 6.64$
4	Morphine	9.85
5	Papaverine	8.07 (at 25°C)
6	Physostigmine	$pKa_1 = 6.12$; $pKa_2 = 12.24$;
7	Quinine	$pK_1 = 5.07$ (at 18°C); $pK_2 = 9.7$;
8	Reserpine	6.6
9	Vinblastine sulphate	$pKa_1 = 5.4$; $pKa_2 = 7.4$;
10	Vincristine	5.0 ; 7.4 (in 33% DMF)

Salient Features

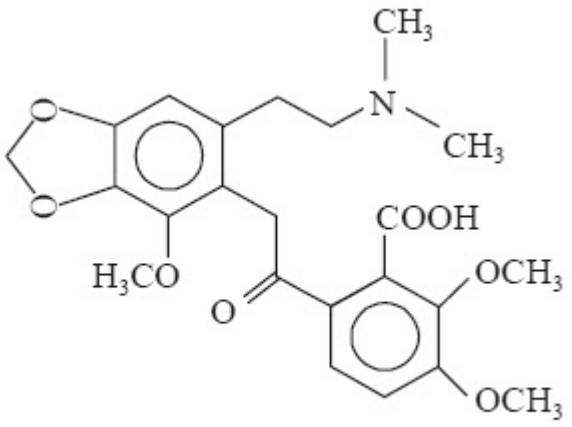
1. The weaker bases, *i.e.*, **alkaloids** having low pKa values, shall require a more acidic medium to form their respective salts with the corresponding acid.

2. The strongly basic **alkaloids** *i.e.*, those possessing high pKa values, shall require comparatively low acidic medium to form their respective salts with the acid.

Note: In a medium at a weakly acidic pH certain strongly basic alkaloids would be easily converted to their respective salt by interaction with the corresponding acid, whereas the alkaloids which are relatively weaker bases having lower pKa values shall still remain in their free-base form. Such a critical situation is skillfully exploited for the separation of a specific alkaloid or a group of alkaloids having closely identical pKa values, from other alkaloids that essentially possess either very low or very high pKa values.

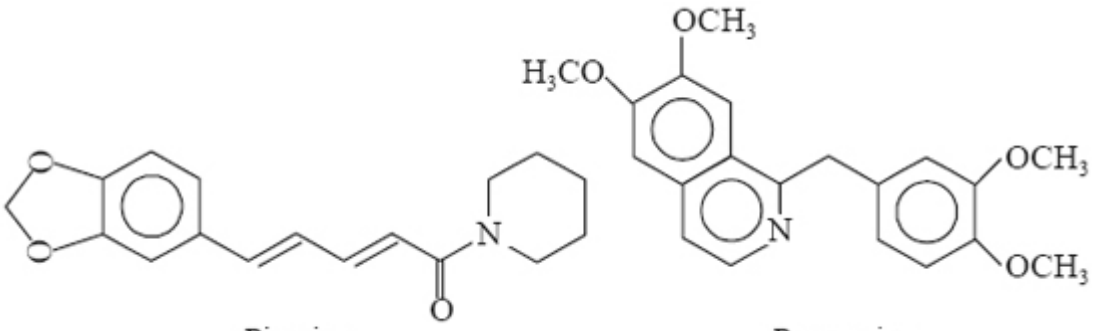
3. The **alkaloids** are usually neutrallized with acids to form salts that may be converted to the corresponding **free-base** by the cautious addition of selective weak bases, such as, ammonia, calcium hydroxide or sodium carbonate. The usage of either NaOH or KOH solutions must be avoided so as to prevent the decomposition or destruction of highly sensitive alkaloids.

4. **Amphoteric alkaloids:** There are some **alkaloids** which are amphoteric in nature *i.e.*, they are neither acidic nor basic in character; this is due to the presence of phenolic (–OH) moiety in **Morphine,** or the presence of carboxylic (–COOH) function in **Narceine,** as shown below:

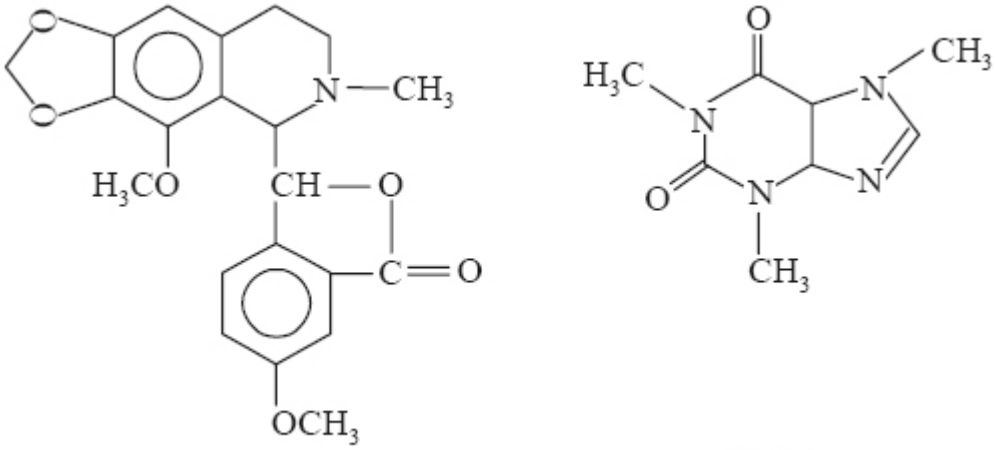


Narceine

5. **Unstable alkaloidal salts:** There exists some specific **alkaloids** that inherently possess *weakbasic properties* and their salts are not so stable, for instance: **piperine, papaverine, narceine, narcotine,** and **caffeine.**

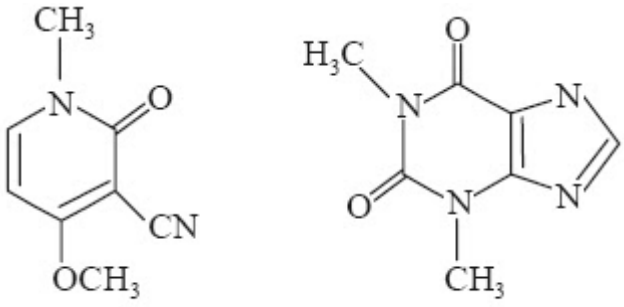


Piperine Papaverine



Narcotine Caffeine

6. **Neutral or slightly acidic alkaloids:** There are a few typical naturally occurring **alkaloids** that almost behave as either neutral or slightly acidic character, namely: ricinine and theophylline, as depicted below:



Ricinine Theopylline

[D] Precipitation by Specific Reagents A good number of **alkaloids** obtained from various plant sources invariably give a distinct precipitate with certain specific reagents to an extent as small as *one microgram*. Based on these observations, these **alkaloid-precipitating reagents** are sometimes employed for either detecting the presence or absence of alkaloids in:

(*a*) Crude extracts or plant materials, and

(*b*) For ascertaining whether a specific extraction procedure has exhausted completely the alkaloidal contents or not.

However, a negative test *i.e.*, the absence of precipitation, may infer that the alkaloids are absent. It is pertinent to mention here that a positive test may not always indicate the presence of alkaloids, but may also be due to the presence of other plant constituents, such as: purines, proteins, betaines and ammonium salts etc. Therefore, it is always desired to rule out the possibility of a *false-test* by alkalifying the acidic solution with dilute ammonium hydroxide and subsequently extracting the liberated alkaloid with chloroform. The residue thus obtained, after the removal of the solvent (chloroform), is tested with the **alkaloid-precipitating reagents.** Now, if the test is positive, the presence of an alkaloid is almost confirmed.

Microcrystalline precipitates of alkaloids: Alkaloids, alike other amines, usually form *doublesalts* with salts of heavy metals, such as, gold (Au), mercury (Hg) and platinum (Pt). The resulting double salts are found to be possessing characteristic microcrystalline structures. It has been observed that under controlled and specific experimental parameters *viz*., profile of mixing and gradual evaporation, a drop of an alkaloidal solution reacting with a drop of an appropriate alkaloidalprecipitating reagent, such as: chloroplatinic acid (H_2PtCl_6) or chlorauric acid ($HAu\ .\ Cl_4$), on a microscopic-glass slide, gives rise to microcrystalline products having specific and characteristic shapes and structures solely based upon the manner of aggregation.* It may, however, be exploited skillfully as a convenient means of rapid-microscopical identification of an **alkaloid**.

The various reagents that are invariably used either for the testing of **alkaloids** by precipitation or by the formation of microcrystalline complexes (salts) are as stated below along with their individual compositions, namely:

(*i*) **Mayer's Reagent (Potassium-Mercuric Iodide Test Solution):**

Mercuric chloride = 1.36 g

Potassium Iodide = 3.00 g

Distilled water to make = 100.00 ml

(*ii*) **Wagner's Reagent (Potassium Triiodide):**

Iodine = 1.3 g

Potassium = 2.0 g

Distilled water to make = 100.00 ml

(*iii*) **Kraut's Reagent (Modified Dragendorff's Reagent or Potassium Bismuth Iodide):**

Bismuth Nitrate = 8.0 g

Nitric Acid = 20.0 ml

Potassium Iodide = 27.2 g

Distilled water to make = 100.00 ml

(*iv*) **Marme's Reagent (Potassium-Cadmium Iodide Reagent):**

Cadmium Iodide = 10.0 g

Potassium Iodide = 20.0 g

Distilled water to make = 100.00 ml

(*v*) **Scheibler's Reagent (Phosphotungstic Acid Reagent):**

Sodium Tungstate = 20.0 g

Disodium Phosphate = 70.0 g

Distilled water to make = 100.00 ml

Note: Acidify with nitric acid to litmus paper.

(*vi*) **Hager's Reagent:**

A saturated solution of *Picric Acid.*

(*vii*) **Sonnenschein's Reagent (Phosphomolybdic Acid):**

A 1% (w/v) solution of phosphomolybdic acid in ethanol.

(*viii*) **Bertrand's Reagent (Silicotungstic Acid):**

A 1% (w/v) solution of silicotungstic acid in distilled water.

(*ix*) **Reineckate salt solution:**

Ammonium Reineckate = 1.0 g

$NH_4 [Cr . (NH_3)_2 (SCN)_4$

Hydroxylamine HCl = 0.3 g

Ethanol = 100.00 ml

Note: Filter and store in a refrigerator.

[E] Colour Reactions with Specific Reagents Broadly speaking the colour reactions of the **alkaloids** are rather unspecific; however, they are certainly very sensitive so much so that even alkaloids present in microgram quantities invariably afford immediate and instant response. The ultimate development of a characteristic colour reaction is solely dependent upon either the

dehydration or the oxidation of the alkaloid. Generally, a large number of these reagents essentially consist of concentrated sulphuric acid along with certain specific added compounds, such as, sulphomolybdic acid, formaldehyde, sulphovanadic acid, potassium arsenate, hydrogen peroxide, and selenious acid.

A number of such **specific reagents** shall be described in the section that follows:

(*a*) **Froehd's reagent:** Dissolve 5 mg of molybdic acid or sodium molybdate in 5 ml of pure concentrated H_2SO_4.

Note: The reagent should be freshly prepared before use.

(*b*) **Erdmann's reagent:** A mixture of 10 drops of concentrates HNO_3, and 100 ml of water are added to 20 ml of pure concentrated H_2SO_4.

(*c*) **Marqui's reagent:** A mixture of 2-3 drops of formaldehyde solution (40%) with 3 ml of concentrated H_2SO_4.

(*d*) **Mandalin's reagent:** Dissolve 1 g of finely powdered ammonium vanadate in 200 g of pure conc. H_2SO_4.

(*e*) **Mecke's Reagent:** Dissolve 1 g of selenious acid in 200 g of pure concentrated H_2SO_4.

(*f*) **Modified Dragendroff's reagent:** Dissolve 1.6 g of bismuth subnitrate in 60 ml of 20% glacial acetic acid, add to it 5 ml of 40% aqueous solution of KI, 5ml of glacial acetic acid and make up the volume to 100 ml of water.

(*g*) **Rosenthaler's reagent:** Dissolve 1 g of potassium arsenates in 100 g of pure concentrated H_2SO_4.

(*h*) **Schaer's reagent:** Mix carefully 1 volume of pure 30% H_2O_2 with 10 volumes of concentrated H_2SO_4.

Note: The reagent is always prepared afresh, before use.

Interestingly, there are some instances where in the intensity of the colour so produced is in *linear proportion* under standardized experimental parameters. Therefore, such specific colour reactions may be used exclusively for the quantitative determination of certain groups of **alkaloids**, such as:

(*i*) **For Ergot Alkaloids:** The blue colour produced by the ergot alkaloids with the **Van Urk Reagent** (or **Ehrlich Reagent**) *i.e.*, *para*-dimethylaminobenzaldehyde in 65% H_2SO_4, is employed for the quantitative estimation of **ergot alkaloids.**

(*ii*) **For Belladona Alkaloids:** The violet colour caused by the belladona alkaloids with fuming HNO_3 and alcoholic KOH solution is employed for their assay.

[F] Stability of Alkaloids Alkaloids, in general, are not very stable. They normally undergo degradation or decomposition on being exposed to air, light, moisture and heat, besides chemical reagents. A few typical examples of alkaloids *vis-a-vis* their stability are stated below, namely:

(*i*) Ergotamine gets destroyed by prolonged treatment with alkali, whereas strychnine can stand such vigorous action.

(*ii*) An aqueous solution of alkaloids undergo rapid decomposition or degradation as compared to their solid forms.

(*iii*) Storage of **alkaloids** in pure form or their dry extracts is usually done in a vacuum desiccator over a dehydrating agent *e.g.*, phosphorous pentoxide (P_2O_5) or calcium chloride ($CaCl_2$) anhydrous for their better stability.

(*iv*) During the course of extraction of **alkaloids** followed by isolation, the solvent is preferably removed effectively by distillation under vacuum** (or reduced atmospheric pressure) or by subjecting it to evaporation in a Rotary Thin-Film Evaporator under vacuum so that the desired product is not exposed to excessive heat, thus avoiding decomposition.

(*v*) **Alkaloids**, are stored in amber-coloured glass bottles preferably in a vacuum desiccator.

[G] Acid salts of Alkaloids A plethora of **alkaloids** are strongly alkaline in nature and most of them form well-defined salts. However, in certain instances the basicity of an **alkaloid** is quite weak and feeble, and hence the formation of the corresponding salts with either acetic or other weak acids is practically insignificant and rare. The salts formed with stronger acids *e.g.*, HCl, H_2SO_4 etc., get decomposed in the presence of water to liberate the free base and the acid. It has been observed that only a few of the alkaloids form carbonates, and consequently either the alkali carbonates or the alkali hydrogen carbonates are invariably used to liberate them from the aqueous solutions of their corresponding salts.

Alkaloids, in general, containing either one or more than one N-atom usually behave as **monoacidic bases;** and, therefore, form only one series of salts with acids as designated by '*BA*' (where: B = base; and A = acid). It is pertinent to mention here that **quinine** in particular and the **cinchona alkaloids** in general are an exception to the earlier concept and found to behave as *diacidic bases*. Besides, a number of alkaloids to behave as monoacidic bases, even though they contain two N-atoms in their molecule. It is worthwhile to mention here that the

basicities of the alkaloids is of utmost importance with regard to their quantitative volumetric estimation.

In common practice the salts of alkaloids are prepared by using cold and dilute solutions of the mineral acid specifically, *e.g.*, **morphine hydrochloride, atropine sulphate, quinine sulphate, ephedrine hydrochloride** etc. It may be pointed out that the use of concentrated mineral acids, or heating an alkaloid even with a dilute acid under pressure may ultimately lead to profound changes in them. Noticeably, the concentrated mineral acids invariably give rise to characteristic colour changes, that are usually used as a means of identification and characterization of the alkaloids. In addition to the complete decomposition of **alkaloids** by strong acids to result the various colour changes, the chemical changes caused by the mineral acids on them may be categorized into *three* different types, namely:

(*a*) **Dehydration:** Dehydration of **alkaloids** give rise to either *anhydro*- or *apo*- alkaloids, such as:

Apomorphine obtained from **Morphine**

Apoatropine obtained from **Atropine**

(*b*) **Demethoxylation:** The removal or elimination of the methoxyl groups from the alkaloids by treatment with either concentrated HCl or HI to produce methyl chloride (CH3Cl) or methyl iodide

(CH_3I) while giving rise to the corresponding *hydroxy base*. The methoxyl group (s) are present in a variety of alkaloids, for instance: **codeine, quinine, narcotine** and **papaverine.**

Example:

NARCOTINE + 3HI -> NORNARCOTINE + 3CH3I

(*c*) **Hydrolysis:** A good number of **naturally occurring alkaloids** are obtained as *esters*. They easily undergo hydrolysis on being heated with either alkalies or mineral acids thereby resulting into the formation of the corresponding acids along with respective alcohols or phenols of the alkaloids.

A few typical examples are as give below:

(*i*) ATROPINE + H2O -> TROPINE + TROPIC ACID

(*ii*) COCAINE + 2H2O -> ECGONINE + BENZOIC ACID + METHANOL

[H] Action of Alkalies The action of alkalies *e.g.*, NaOH and KOH on the **alkaloids** are found to be varying in nature as enumerated below:

(*a*) Dilute alkaline solutions of KOH or NaOH normally decompose most alkaloidal salts and finally liberate the free alkaloids.

(*b*) Certain alkaloids containing phenolic hydroxyl groups *e.g.*, **morphine,** on being treated with alkaline solutions yield, their corresponding soluble sodium or potassium salts.

(*c*) The ester alkaloids usually undergo hydrolysis on being treated with dilute alkalies, such as: atropine, cocaine.

(*d*) **Racemic Isomeride:** The action of alkali hydroxides on **hyoscyamine** in alcohol gives rise to the racemic isomeride atropine.

(*e*) Fusion of alkaloids with dry KOH or NaOH by the application of heat ultimately leads to drastic decomposition of the former thereby yielding ultimately the simple heterocyclic bases, for instance: pyridine, quinoline, pyrrolidine etc.

(*f*) Simple fusion of **alkaloids** with alkali hydroxides may give rise to distinct and visible colour changes.

[I] Pharmacological Activity The **alkaloids** exhibit a wide-spectrum and complete diversity of complex structures which ultimately is responsible for their extra ordinary broad-range of pharmacological activities covering both the cardio-vascular and central nervous system. It has been observed beyond any reasonable doubt that most alkaloids usually exert certain specific and definite pharmacological action. Moreover, a small quantity of an alkaloid (0.1–1.0 mg) may bring about a marked and pronounced pharmacological action on various organs and tissues both of animal and human origin. However, the potency of an individual alkaloid varies from one another widely and profusely.

A few typical pharmacological actions of some **alkaloids** are stated below showing their broadspectrum of activities, namely:

S.No.	Alkaloid	Pharmacological Action
1	**Morphine**	Narcotic analgesic
2	**Codeine**	Expectorant, analgesic
3	**Brucine**	CNS-Stimulants
4	**Strychnine**	CNS-Stimulants
5	**Ergotamine**	Uterine muscle contractions
6	**Atropine**	Mydriatics
7	**Homotropine**	Mydriatics
8	**Pilocarpine**	Myotics
9	**Physostigmine**	Myotics
10	**Ephedrine**	Hypertensive
11	**Reserpine**	Hypotensive
12	**Quinine**	Antimalarial
13	**Caffeine**	CNS-stimulant
14	**Tubocurarine**	Neuromuscular blocking action
15	**Emetine**	Antiprotozoal action
16	**Hyoscyamine**	Relief of spasms of urinary tract
17	**Cocaine**	CNS-stimulant
18	**Colchicine**	Anti-gout
19	**Lobeline**	Treatment of asthma
20	**Arecoline**	Parasympathomimetic action
21	**Protoveratrine A**	For management of hypertension in pregnancy
22	**Conessine**	Antiprotozoal and antiamoebic
23	**Vasicine**	Expectorant and bronchodilator
24	**Vinblastine**	Antineoplastic
25	**Vincristine**	Antineoplastic
26	**Piperine**	Carminative, stomachic
27	**Heroin**	Narcotic analgesic
28	**Hyoscine**	Motion sickness (sedation)
29	**Theophylline**	Smooth musele relaxant
30	**Aconitine**	Treatment of neuralgia, sciatica, rheumatism and inflammation.
