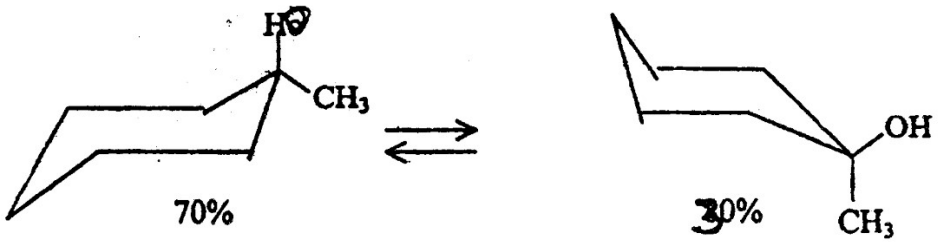
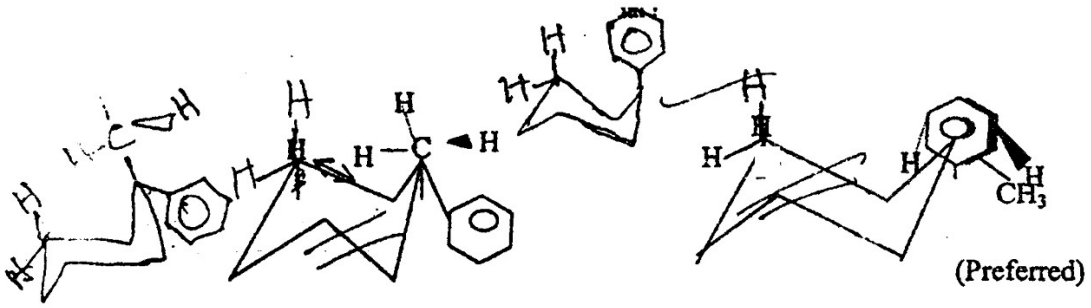


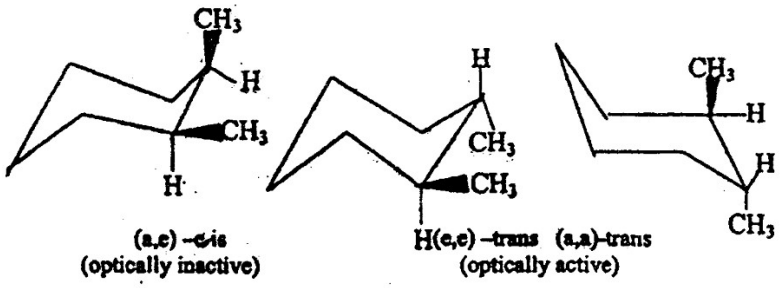
In certain cases, the conformer with bulky axial substituent predominates (e.g) 1-methyl 1-phenyl cyclohexane.



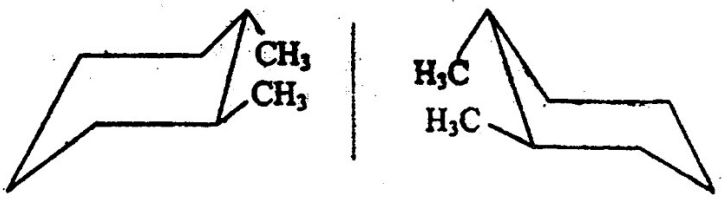
The preferred conformer has the phenyl group with an orientation such that there is no significant 1.3 interaction as in the other (less preferred)

1.2 Disubstituted Cyclohexanes

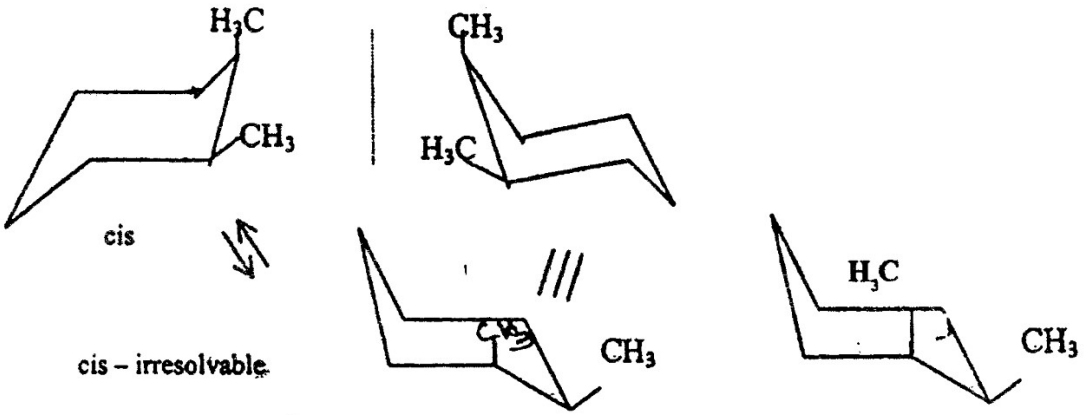
Three different conformers exist for 1,2 dimethyl cyclohexane since cis and trans isomers are possible when the two groups are taking (a,e) positions and diaxial or diequatorial positions respectively.



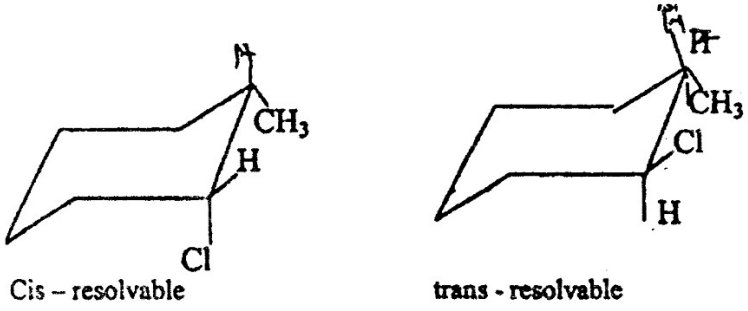
The trans form is optically active and exists as a pair of enantiomers. The trans forms of the enantiomers are most stable when both the groups are equatorial, hence the diequatorial form constitutes 99% of the mixture.



The diequatorial form does not undergo flipping to form the diaxial form, since the latter has 4 gauche-butane interactions compared to just one in the former.

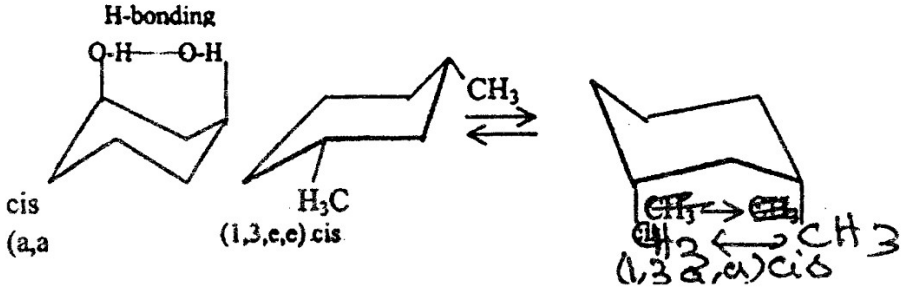


The 1,2-cis isomers also constitute a pair of enantiomers which are readily interconvertible, hence irresolvable, unlike the 1,2 trans form. However, when the two substituents are different at 1,2 position both the cis and trans forms are resolvable.



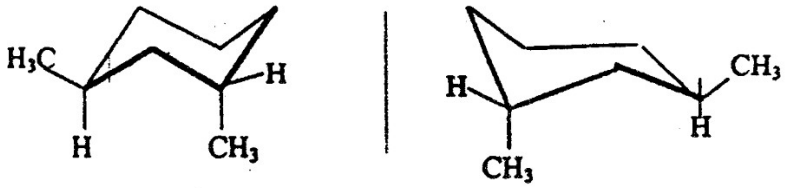
1.3 Disubstitutedcyclohexanes

The 1,3 derivatives can exist in three distinct stereoisomeric forms, viz, the + and - forms of the trans isomer and the cis form which is meso. The cis form has 2 conformers the diequatorial and diaxial, the former being the predominant for most of the substituents. The diequatorial conformer of 1,3 diaxial (Me/Me) interaction. Hence the diaxial form is almost nonexistent with a population of just 1 in 10,000 at 25°C. But cyclohexane 1,3 diol prefers to exist in the diaxial form rather than the diequatorial form due to intramolecular hydrogen bonding stabilization.

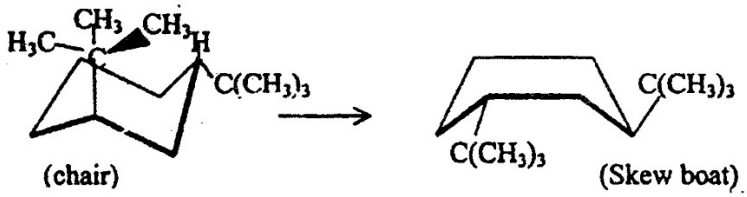


However, both the conformers have a plane of symmetry and they represent the meso forms.

The trans isomer has an (e,a) conformation which is less preferred over the cis conformations, as the interaction between the two methyl groups in (e,a) conformation is more than that in the (e,e) form.



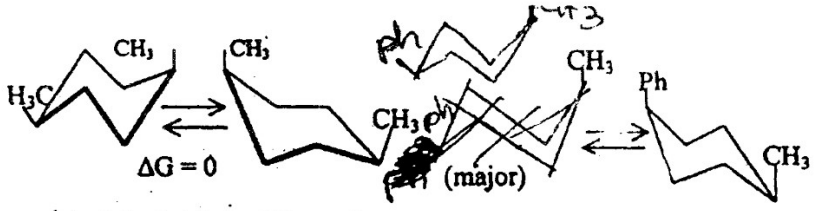
In trans 1,3 - ditertiarybutylcyclohexane, the ring is twisted in a 'skew boat' form in order to avoid the substituent taking the axial position.



Any of these trans conformer can exist in d & l forms and hence resolvable, unlike the cis form which is non-resolvable. However when both the substituents are different, both cis as well as transconformers are resolvable.

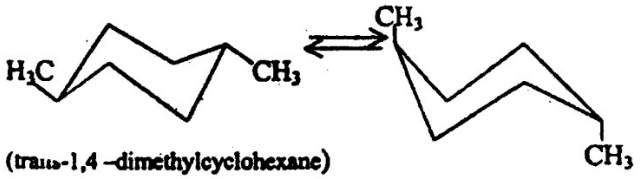
1,4-Disubstitution

The substitution leads to the cis and trans isomers similar to 1,2 disubstitution. The cis isomer exists in two identical conformers, (a,e) or (e,a). When the substituents are identical, But when the substitnents different, it gives rise to two unequally populated (a,e) conformers, the predominant being the one where bulkier group is at the equatorial position.



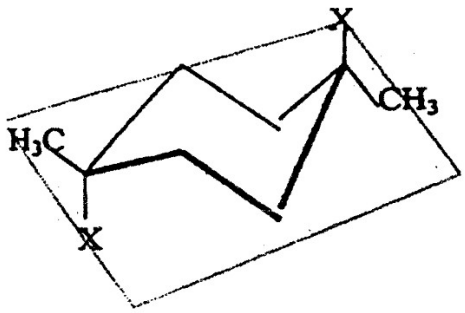
(cis –1,4 –dimethylcyclohexane)

In the trans isomer, two distinct conformers, the diaxial and diequatorial forms are possible, the predominant being the diequatorial.

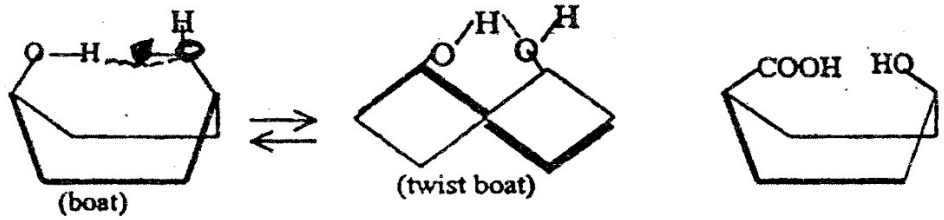


(trans-1,4 –dimethylcyclohexane)

The diaxial form is destabilized by four gauche interactions and the trans isomer is always more preferred over the cis as it has no gauche interactions with the (e,e) form. However, (1,4) conformers of cyclohexanes are all achiral even when both the groups are different, due to the presence of a vertical plane of symmetry passing through the C1 - C4 axis.



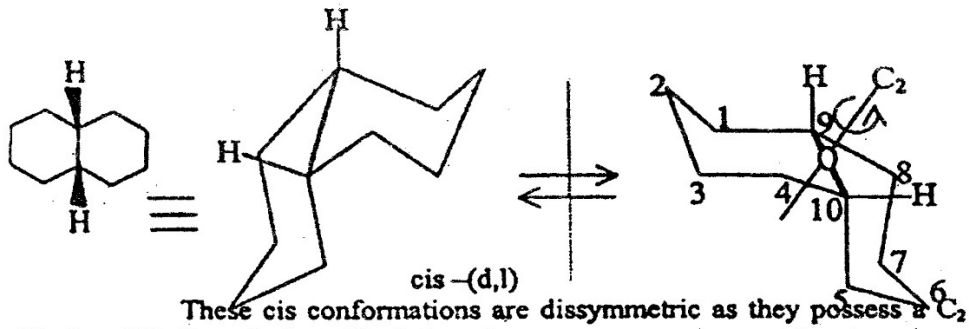
When intramolecular H-bonding is possible between groups at 1,4 positions the cyclohexane ring may assume a boat form preferably a twist boat which is stabilized due to hydrogen bonding, ~~as in~~



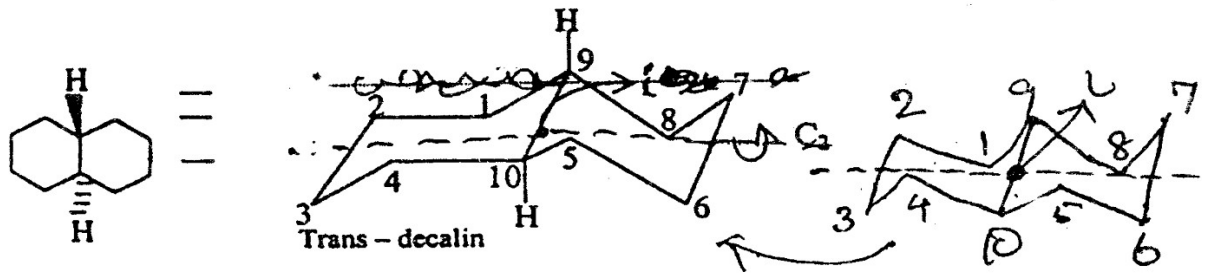
The cis-4-hydroxycyclohexanecarboxylic acid also assumes the boat conformation which facilitates easy lactonisation whereas the trans form does not form any lactone.

Conformations of Fused Ring Systems

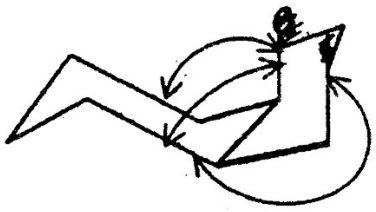
Decalins : Decalin is bicyclo-4,4,0-decane, existing in two diastereoisomeric forms, based on the type of ring fusion. A cis fusion of two cyclohexane chairs (ie) along the (e,a) bonds leads to cis –decalin where the (a,e) bonds are flexible and interchangeable giving rise to two conformers, which are mirror images of each other.



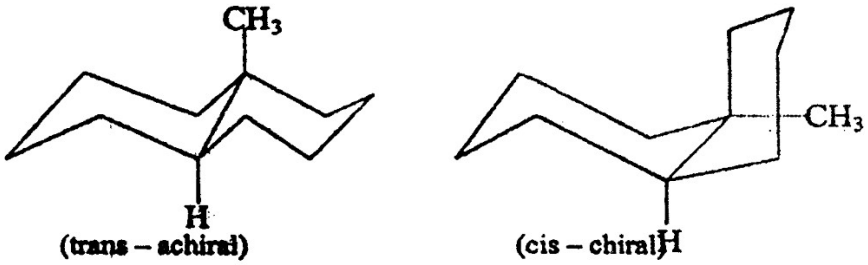
These cis conformations are dissymmetric as they possess a C_2 bond along the midpoint of C_9-C_{10} axis, but chiral since they are nonsuperimposable mirror images of each other and enantiomers. A trans fusion along the (e,e) bonds of the two cyclohexane chairs leads to trans-decalin which has a rigid conformation.



This conformation has a C_2 axis passing along the C2 - C3, $C_9 - C_{10}$ and $C_6 - C_7$ bonds, in addition to an inversion centre (i), hence achiral. There is no additional gauche-butane interactions due to trans-fusion. But in cis decalin there are three gauche-butane interactions, as shown. Hence the cis conformer is destabilized to the extent of (3× 3.35) =10.05 K.J.mol^{-1}, compared to the trans form.



On introduction of an angular methyl group at the C_9 or C_{10} position, the trans conformer acquires four additional gauche interactions since the CH_3 group is axial with respect to each ring but the cis conformer gets 2 additional gauche interactions. On the whole the trans conformer has four gauche interactions but the cis form has five such interactions, thereby making the former more stable by 3.35 KJ mol^{-1}.

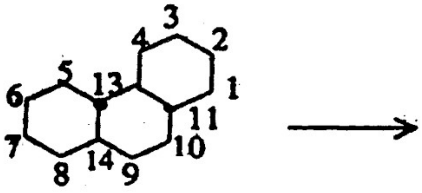


(trans – achiral) (cis – chiral)

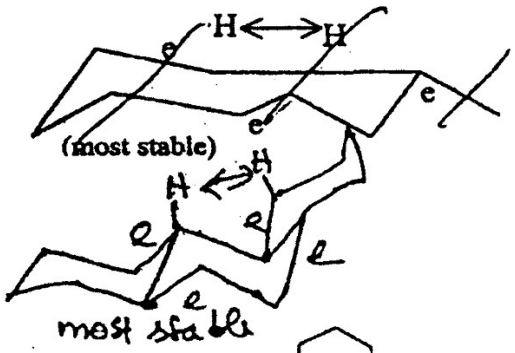
The trans-9-methyldecalin possesses a plane of symmetry and is achiral. But the cis form is chiral and due to rapid interconversion of the (a,e) positions, a racemic mixture results.

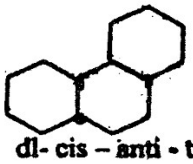
Perhydrophenanthrene

It has three cyclohexane rings fused together either Cis or trans with respect to each ring. The molecule has ten sterioisomeric forms four pairs of enantiomers and two meso forms, as it contains two equivalent pairs of chiral centers along the four bridged carbons. The different conformers are represented as under:

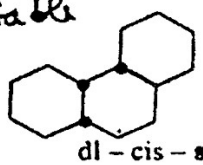


dl – trans – anti trans 2

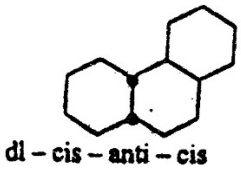




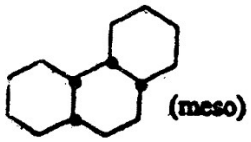
dl- cis – anti - trans



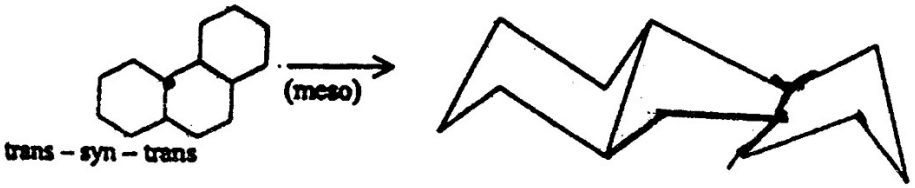
dl – cis – syn - trans



dl – cis – anti – cis



cis – syn - cis



trans – syn – trans

A heavy dot indicates the hydrogen in front of the plane and the absence of the dot denotes a hydrogen behind the plane. The prefixes cis and trans indicates the type of sterco chemistry at the points of ring fusion and the suffixes syn & anti refers to the orientation of the terminal rings with respect to each other. When any two rings are trans fused, the entire system becomes rigid and no ring inversion could occur.

The trans – anti-trans conformers are the most stable in which the central ring is trans fused with the other rings by four equatorial bonds and the system has the minimum energy (3.35KJ mol^{-1}) due to just one gauche interaction resulting from the C_4 and C_5 Hs. The trans-syn-trans conformer is the least stable with maximum energy (23.4KJmol^{-1}). Since it is not possible to have both the ring junctions trans and the C_{12} & C_{13} hydrogens syn to each other all at the same time, the central ring must necessarily take up a boat conformation in the trans-syn-trans conformer, hence it is least stable.

All other conformers have intermediate stability due to the gauche interactions and the additional 4,5 interactions.

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Scott Christian College
Nagercoil.

* * * *

UNIT – III
ALKALOIDS

A-1 Introduction:

It would be difficult to given an exact definition for alkaloids. The definition for alkaloids underwent different changes, rather incorporated various changes and finally rested with the following definition.

"Basic nitrogenous plant products, mostly optically active and possessing nitrogen heterocycles as their structural units, with a pronounced physiological action".

This definition too is inadequate to include all the alkaloids. Because there are compounds, which satisfy this definition, but are not included under alkalorids.

(i) Caffeine, which fully statisfies the above definition is not included in alkaloids.

(ii) Thiamine, is a heterocyclic nitrogenous base, but is not included in alkaloids. The simple reason, it is universally distributed in living matter.

A2. Occurrence:

Alkaloids are widely distributed in higher plants particularly the dicotyledons in abudance in the families Apoecynacease, Papaveraceae etc. Because of their basic nature, they are found as salts of plant acids like acetic, oxalic, citrio, etc. alkaloids of solanum and veratrum groups are present as glycosides of sugar like glucose, rhamnose and galaclose. Piperine is present as amide whereas atropine, cocoaine are present as esters of organic acids.

A3. Extraction of Alkaloids:

They are found in the root, bark, leaves and seeds of plants. The following procedure is commonly used in the isolation of alkaloids.

The dried powdered plant is extracted with boiling methanol. The solvent is distilled off and the residue is treated with inorganic acids. The alkaloids are then extracted as their soluble salts. The free bases are liberated by the addition of sodium carbonate. It is then extracted with solvents like ether, chloroform etc., the mixture of bases is subjected to various methods of separation including chromatography. Finally they are purified through fractional crystallization / distillation.

A4. General Properties:

Generally they are colourless crystalline solids insoluble in water, but are soluble in organic solvents like ether, chloroform, etc., some are liquids, example, coniine and nicotine. Some are coloured, example berberine is yellow. Alkaloids have a bitter taste and are optically active. The optically active alkaloids are useful in the resolution of racemic mixtures.

They form characteristic precipitates with definite melting points with certain reagents. These reagents are referred to as alkaloidal reagents. Some of them are: **Dragendorff's reagent** (Potassium bismuth iodide) **Mayer's reagent** (Potassium mercuri lodide), **Wegner's reagent** (iodine dissolved in potassium iodide) **Hager's reagent** (saturated solution of picric acid in water) etc., Chloroplatinic (H_2PtC_{16}) Hager's reagent ($HAuCl_4$) are also used as precipitating reagents. These reagents are very useful in identifying alkaloids present in small amounts.

A.5 General methods for determining structure:

The first step toward the structure elucidation of any unknown compound is elemental analysis.

Being an alkaloid and by a definition of them are likely to have carbon, hydrogen and nitrogen. Some may contain oxygen also.

From elemental analysis and molecular weight determination of the pure specimen, the molecular formula may be arrived at. If the alkaloid is optically active, its specific rotation is also measured.

If element oxygen is present in the alkaloid, what are the possibilities that one can think of? If is has just one oxygen atom, the possibilities are, hydroxyl, methoxy, carbonyl, ether. If it has two oxygen atoms apart from the above functional groups, we can consider methylene dioxy, carboxylic acids, esters, lactones etc.

Element nitrogen may be present along or along with oxygen, then what are the possibilities?

When element nitrogen alone is there, it may be present as primary, secondary or tertiary amines. If may be present as an N-methyl group.

With oxygen it may be present as amides, lactams etc.

Let us have a bird's eye view of the identification of the above functional groups, if present in the alkaloid.

(i) Hydroxyl group: The presence of this group may be ascertained by the action of acetic anhydride or acetyl chloride. This must of course be considered in conjunction with the nature of nitrogen. If the presence of hydroxyl is ascertained, then their number can be found out from acetylation

Next we have to identify the hydroxyl as alcoholic or phenolic. If the substance is soluble in cold dilute sodium hydroxide and can be regenerated upon acidification then it must be phenolic. If the compound does not behave as a phenol then the hydroxyl may be asxsumed to be verified by the use of dehydrating agents like sulphuric acid, phosphoric acid etc., alternately the alkaloid may be subjected to treatment with oxidizing agents, to find the nature of the alcoholic group.

Carboxyl Group: The solubility of a compound in aqueous sodium bicarbonate with brisk effervescence of carbondioxide is an indication of the presence of carboxyl group.

OXo group: Formation of oxime, semicarbazone with hydroxiylamine, semicarbaszide hydrochlorides respectively may indicate the presence of OXO group in alkaloids.

Methoxy group: The presence and their number in an alkaloid may be determined thro' Zeisel method. (The alkaloid may be heated with con. Hydroiodic acid its b-pt 126°C). The methoxyl groups are converted into methyl iodide. The methyl iodide vapous are absorbed in an ethanolic solution of silver nitrate. The precipitated silver iodide is filtered, dried and weighed. One mole of Silver iodide = One methoxy group).

Methylene dioxy group: If an alkaloid on heating with con. hydorchloric or sulphuric acid gives formaldedhyde, then the presence of methylene dioxy group can be confired.

Zerewittinoff's active hydrogen determination: An active hydrogen is one which is joined to oxygen, nitrogen or sulphur atoms. When compounds with active hydrogen are treated with Grignard reagent, the alkyl group of the reagent is converted to the alkane.usually methyl magnesium bromide is used as the Grignard reagent.

$$CH_4\uparrow + Mg(OH)Br \xleftarrow{H_2O} CH_3MgBr \xrightarrow{ROH} CH_4\uparrow + Mg(OR)Br$$

This procedure is known as the Zerewittinoff active hydrogen determination. The methane liberated in this retain is measured (by volume), one molecule of methane being equivalent to one active hydrogen atom.

Hydrolysis: The hydrolytic products of an alkaloid can give us an idea as to the nature of alkaloid as esters, lactones etc.,

The functional nature of nitrogen: The functional nature of nitrogen in an alkaloid can often be found by their reactions with acetic anhydride, methyl iodide and or nitrous acid. If these reactions are negative it may be inferred that the nitrogen is most probably tertiary.

The alkyl groups attached to the nitrogen can be inferred by the distillation of an alkaloid with aqueous potassium hydroxide. The products may be methylamine, dimethylamine or trimethylamine depending on the number of methyl group attached to the nitrogen. (Usually the alkaloids contain methyl as the N – alkyl group. However there is one exception viz. aconitone, which contains an N – ethyl group).

The presence of N – methyl groups and their number can be determined by means of Herzing – Meyer method. In this method the alkaloid is heated with, con.hydroiodic acid at 150-1300o under pressure in a sealed tube. The N – methyl groups are converted into methyl iodide which is absorbed in alcoholic silver nitrate. The preciated silver iodide is filtered and weighted.

One molecule of silver iodide = one N – methyl group.

Hofmann's exhaustive methylation method: This method is very useful in the structure elucidation of alkaloids. By the application of this method, we can predict is present in cyclic rings only), monocyclic or bi-cyclic.

In this method first the heterocyclic ring is saturated (if it is unsaturated). A quaternary salt of the alkaloid is prepared and is heated with aqueous sodium hydroxide. This results in the elimination of β - hydrogen with the formation of an olefinic bond. This sequence of reactions is called the HEM procedure. Let us see below how this method operatres

Example : I

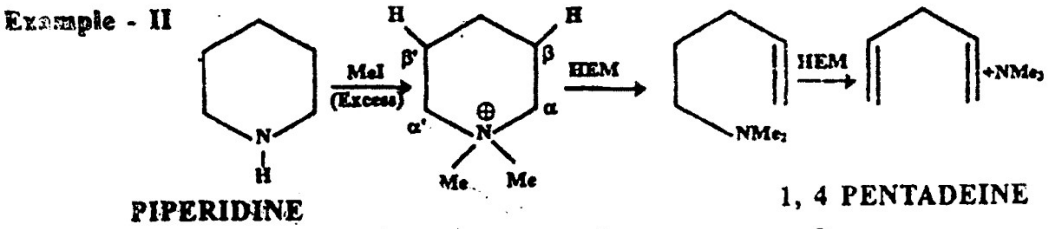
$CH_3 - CH_2 - CH_2 - NH_2 \xrightarrow{MeI\ (Excess)} CH_3 - CH_2 - CH_2 - NMe_3I^{\ominus}$

Propylamine

$\xrightarrow[\Delta]{aq.NaOH} CH_3 - CH = CH_2 + NMe_3$

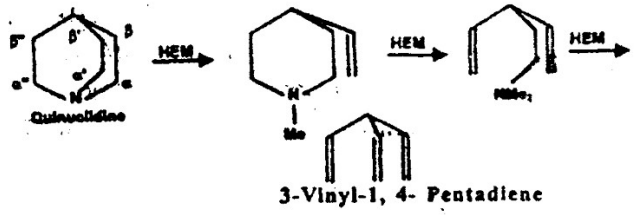
PROPENE

Example - II



PIPERIDINE **1, 4 PENTADEINE**

Example - III



3-Vinyl-1, 4- Pentadiene

In example I the nitrogen is lost by the application of HEM procedure, since the molecule has only β - H (so if an alkaloid looses nitrogen by the application of one HEM procedure, then it should have the nitrogen in an acyclic chain).

In example II, the nitrogen is retained after the first HEM procedure and an scyelic compound with nitrogen is obtained (a tertiary amine). In the second operation, the nitrogen is removed as trimethylamine and a diene is obtained. (So if in an alkaloid, the nitrogen is lost after two HEM procedures only, then we can conclude that the nitrogen is present in a monocyclic ring).

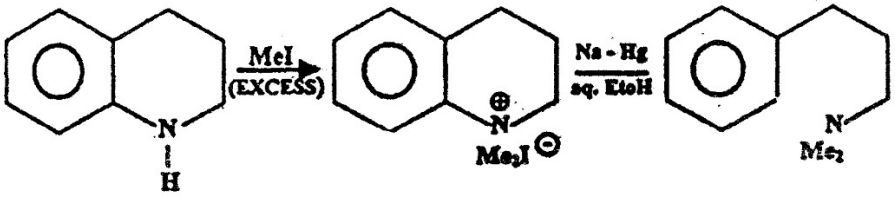
In example III, as we observe the successive application of one, two HEM procedure make the compound, monocylic and then acyclic respectively. The nitrogen could be removed only after the third HEM (so if an alkaloid looses nitrogen only after the application of 3 HEM procedures, then the nitrogen must be present in a bi-cyclic ring).

Thus the Hofmann's exhaustive methylation procedure offers a means of identifying the structure of alkaloids.

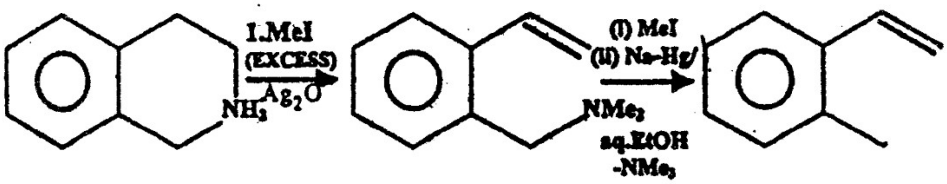
Suppose if the compound doesn't have a β- hydrogen, we cannot apply the HEM procedures (or sometimes the HEM may fail with certain compounds like the tetrahydroisoquinoline. In such cases we can apply Emde degradation).

Emde degradation:

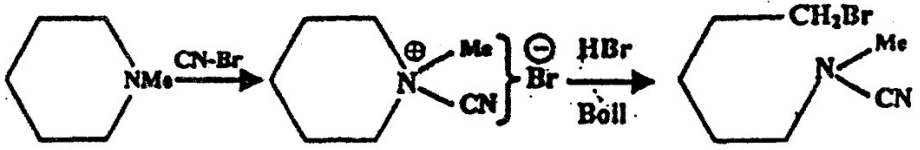
Example I:



Example II :

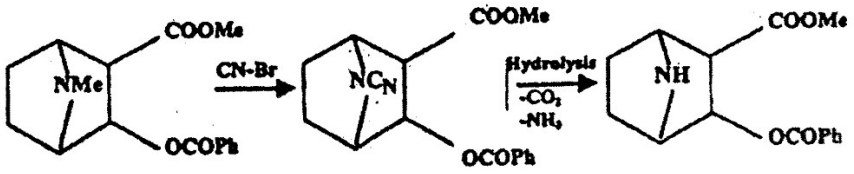


Von Braun degradation method is useful is opening cyclic tertiary amines. Von Braun degradation.

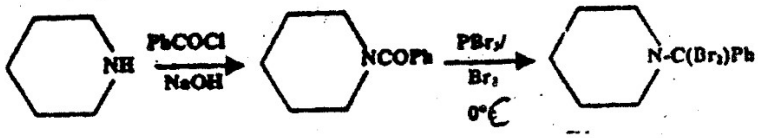


$\longrightarrow$ Br CH_2-$(CH_2)_4$- NHMe

In some cases (ex. Cocaine) the N-cyanoderivative is obtained. This on hydrolysis gives the secondary amine. Thus a tertiary amine is converted into a secondary amine, without opening the ring.



This method can be used to open cyclic secondary amines too.



Distilled under reduced Pressure

$(CH_2)_5\ Br_2$
1, 5 Dibromopentane

+ PhCN
Phenyl cyanide

Unsaturation:

The presence and number of centers of unsaturation can be determined by the addition of bromine.

Oxidation: In general this is an useful means of structure elucidation of any natural product. By varying the concentration of the oxidizing agents and temperature, it is possible to get a variety of oxidation products. By analyzing these products, one can obtain useful information about the structure of an alkaloid.

Zinc dust distillation: Of an alkaloid may result in the formation of polynuclear hydrocarbons. By analyzing the polynuclear hydrocarbons, one can classify the compound to particular class of alkaloids.

Physical methods: This is one of the valuable tools in the hands of an organic chemist. Many a structural problems can be resolved with the help of spectroscopic techniques like UV, IR, NMR ^{13}C NMR, X – ray diffraction methods can also provide with useful information about the structure of an alkaloid.

Synthesis: This is the final proof for the structure of an alkaloid. The intended compound must be synthesized in the laboratory and matched with that obtainable from nature. Various techniques like mixed m.pt mixed b.pt., measurement of optical rotation (for optically active alkaloids) may have to be employed to confirm the structure with authenticity.

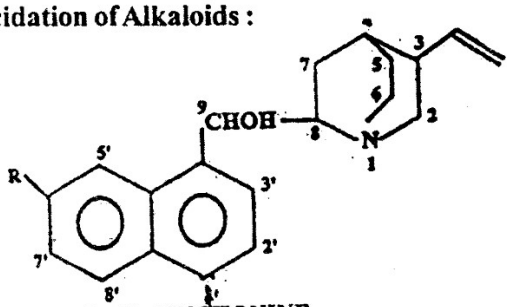
A6. Classification of alkaloids:

Initially alkaloids were classified on the basis of the natural source from which they were obtained eg. Ephedra, cinchona etc. Or as the pharmacological activities of the alkaloids. (analgesic alkaloids, carboactive alkaloids etc). as these methods of classification have been found to be imperfect, a most rationable method of classification based on the type of ring system (usually heterocyclic ring) present in them is adopted. Thus we have,

(a) Quinoline group
(b) Isoquinoline group
(c) Phenanthrene group
(d) Indole group
(e) Isoquinoline group etc.

A7. Structure Elucidation of Alkaloids :

A7.1 (-) Quinine



This is one of the cinchona alkaloids and is used as a febrifuge and as an antimalarial. From elemental analysis and molecular weight determination, the molecular formula of the compound was found to be $C_{20} H_{24} O_2 N_2$.

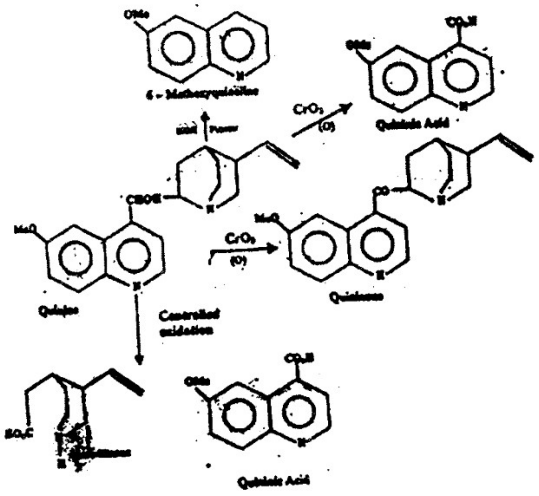
Quinine adds on two molecules of methyl iodide to form a di – quaternary salt, so it must be a di – tertiary base. When heated with con. Hydrochloric acid, quinine forms on molecule of methyl chloride. Hence it must contain one methoxy group.

On mild chromium trioxide oxidation it gives a ketone, quinine. Thus quinine is found to have a secondary hydroxyl group.

Quinine adds one mole of bromine or on catalytic hydrogenation it takes up one mole of hydrogen. This shows the presence of one olefinic bond. It is found to be a methylenic double bond, since ozonolysis or oxidation with permanganate give a molecule of formic acid. On potassium hydroxine fusion quinine gives methoxyquinonline, which shows the presence of a quinoline nucleus in the molecule.

Quinine on chromium trioxide oxidation gives quininic acid and on controlled oxidation gives quinine acid meroquinene. When the formulae for quininc acid and meroquinene put together, give the same number of carbon atoms as in quinine gives methoxyquinoline, which shows the presence of a guioline nucless in the molecule.

Quinine on chromium trioxide oxidation gives quininic acid and on controlled oxidation gives quinine acid and meroquinene. When the formulae for quinine acid and meroquinene put together, give the same number of carbon atoms as in quinine. Thus the alkaloid quinine may be made up of these two units. The structure elucidation of these two units, plus the piecing together of them may result in the actual structure of quinine. Before ahead with it, let us formulate the reactions, so far we have been.



Structure of Quinine acid:

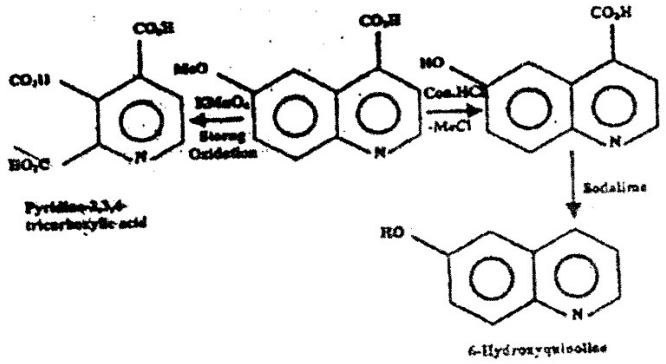
It gives brisk effervescence of carbon dioxide with sodium bicarbonate and form a monosodio derivative. So it must be a monocarboxylic acid.

Quininic acid on treatement with con. Hydrochloric acid give 6 –hydroxyquinoline 4 carboxylic acid. This shows the presence of a methoxy group at position -6.

Decarboxylation of it with sodalime yields 6 – hydroxquinoline.

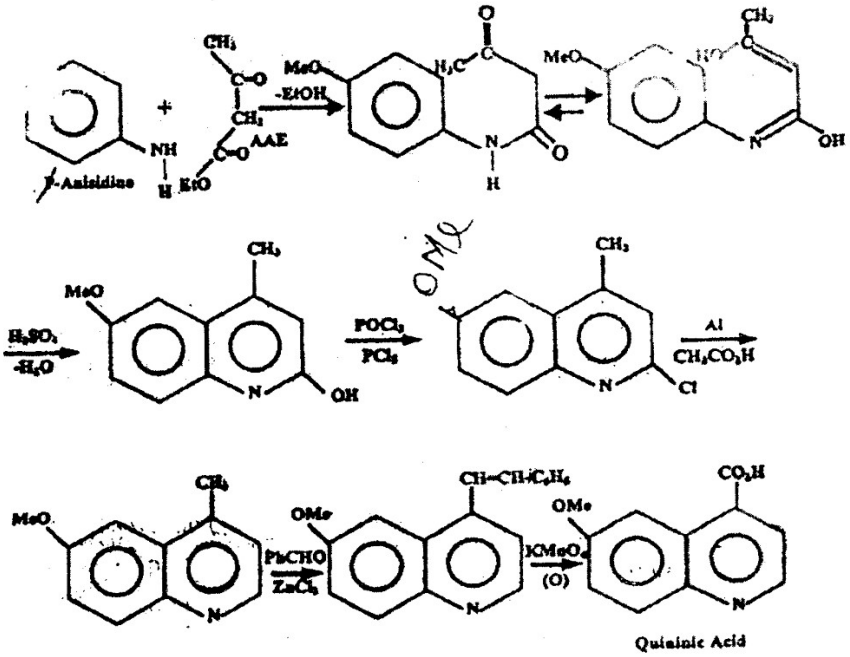
Strong oxidation of quinine acid results in pyridine -2,3,4- tricarboxylic acid. The carboxyl group at position 4 may be the original carboxylic acid group that is present in quinine acid itself. The other two carboxyl groups should have been produced during oxidation is indicative of the presence of a benzene ring at 2 & 3 positions. The disappearance of methoxy group in this oxidation product indicated that it should be present in the carbocyclic and not in the heterocyclic ring.

All the above reactions can be formulated as follows:



Quininic acid otherwise known as 6-methoxycinchoninic acid.

Finally the structure has been confirmed by a synthesis of it starting from p-anisidine.



This reveals that quinine is built up of 6 – methoxyquinoline with a side chain at the 4th position, which ultimately appears as meroquinene.

Structure of meroquinene:

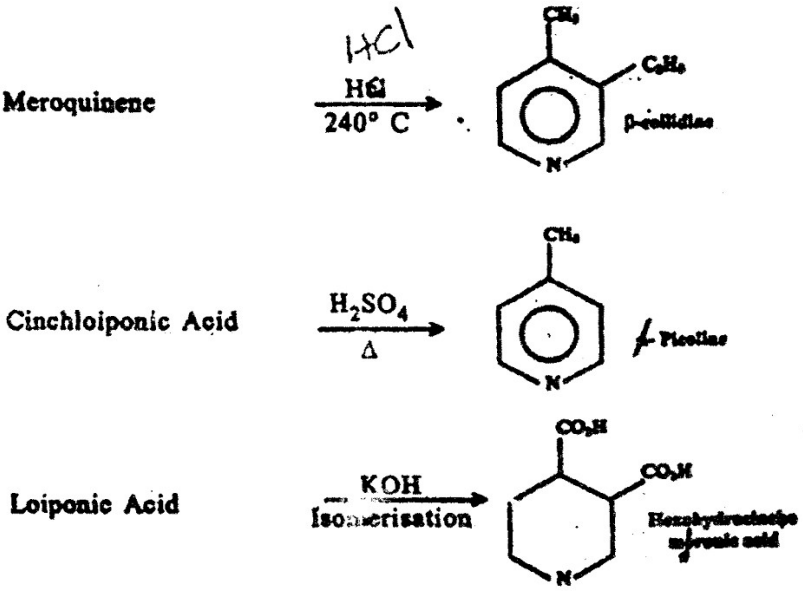
Usually reactions indicate it to be a monocarboxylic acid. It absorbs one mole of hydrogen during catalytic hydrogenation indicating the presence of one olefinic bond.

Meroquinene on oxidation with acidified permanganate (cold) gives formic acid and cineholoiponic acid. Thus the olefinic bond is methylenic in nature.

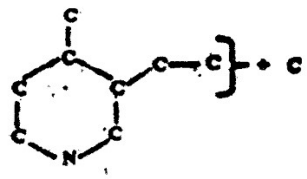
The latter acid on further oxidation gives loiponic acid, a diearboxylic acid.

Loiponic acid has one – CH_2 group less than its precursor, i.e., cincholoponic acid. This suggests that the latter should contain atleast the following side chain, - $CH_2 - CO_2H$.

All these acids were found to be secondary bases by the following reactions.



The structure of hexahydrocinchomeronic acid is established by synthesis. Thus, a possible skeleton for meroquinene may be written as.

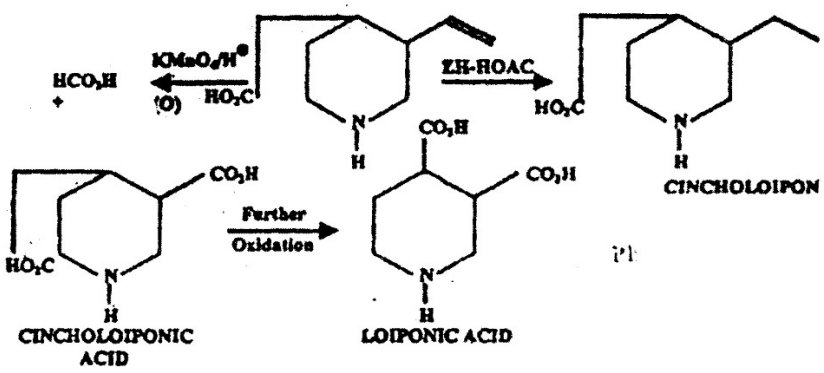


Now the problem is to fix the position of the remaining since all the three acids are secondary bases, this cannot be an group.

Considering the presence of - $CH = CH_2$ group in order to account for the extra carbon atom considered to contain an allegal group.

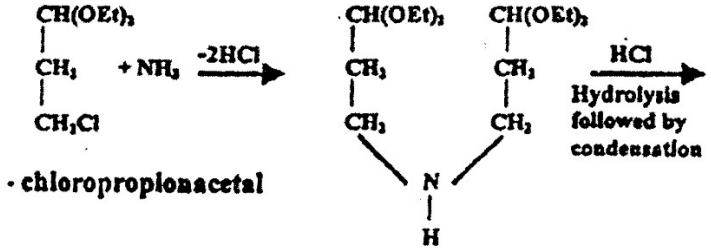
But this assumption cannot withstand the fact that the reduction of meroquinene gives cincholoipon, which contains one carboxy group and one ethyl group.

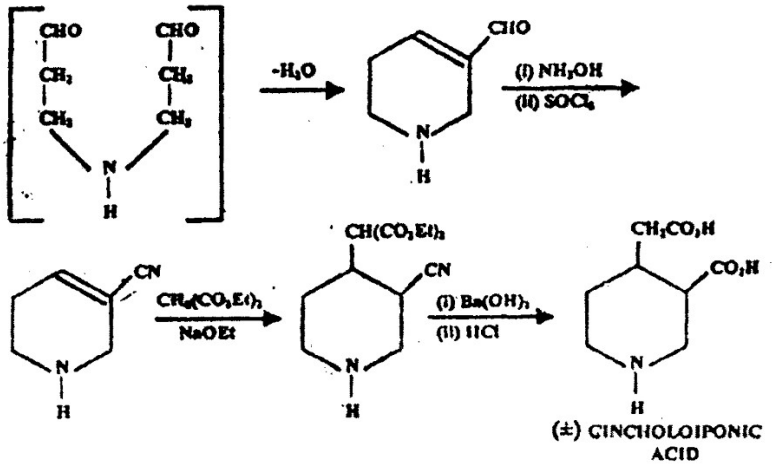
Thus the side chain cannot be an ally group, the reduction of which might have given a propyl group. The side chain is therefore vinyl. This leaves only one possible position for the extra carbon atom. viz 4. This would give a - CH_2 - CO_2H group at this position. All the reactions of meroquinene may thus be explained as follows.



The structure given for meroquinene is confirmed by the synthsis of cincholoiponic acid.

Synthesis of Cincholoiponic Acid :-



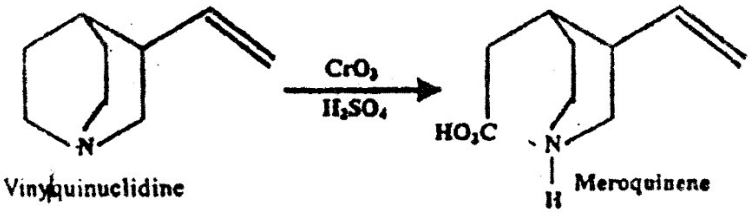


The racemic acid is resolved as its acyl derivative, using brucine, The (+) form is identical with that obtainable from meroquinene.

Meriquinene is one of the oxidation products of quinine. So the carbon atom of the carboxy group in meroquinene will be the point of linkage to the quinoline half at which fisson of the "Second half" occurs.

Since quinine is a ditertiary base, the 'Second - half' therefore contains a tertiary nitrogen atom. But meroquinene is a secondary base and it therefore follows that in its formation the teritiary nitrogen atom is converted into a secondary nitrogen atom, a carboxy group also being produced at the same time.

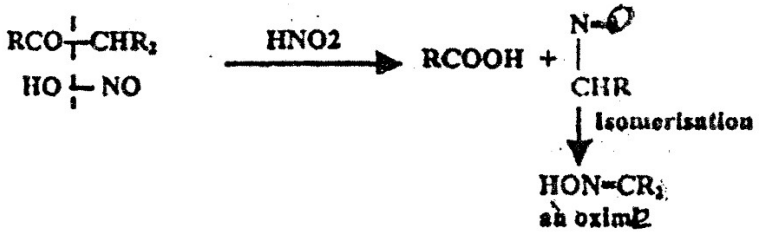
A possible explanation for this hebaviour is that the teritary nitrogen atom is part of a bridged ring, one C-N bond being broken when quinine is oxidized. Thus for example,



Thus, in quinine the "quinoline - half" must be joined via its side chain at position 4 to the 'quinoline - half' at position 8. The remaining problem is to ascertain the position of the secondary alcoholic group in the 'second - half'.

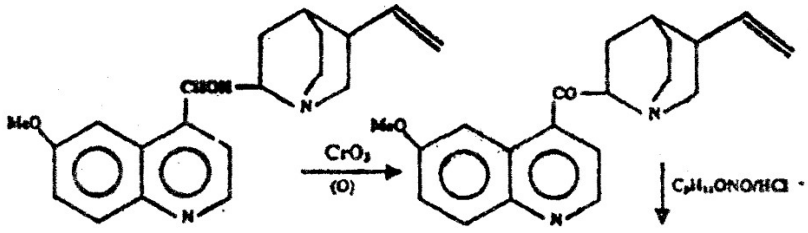
The position of hydroxy group was ascertained as follows. (Rabe etal).

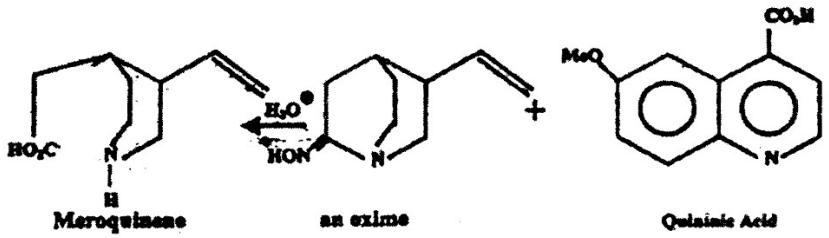
Quinine on gentle oxidation with chromium trioxide gives quininone. Both the nitrogen atoms in the products are teritary in nature. Quininone on treatment with amy nitrite and hydrochloric acid gives quininic acid and an oxime. The formation of an acid and an oxime indicates the presence of the group CO - CH_3 a methine group adjacent to a carbonyl group.



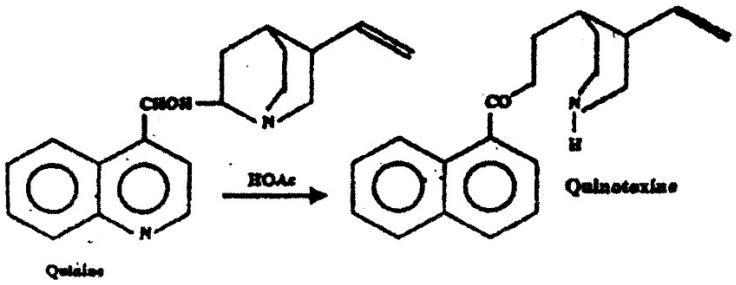
The structure of the oxime obtained from quinine was shown to be 8-oximino -3 - vinyl - quinuclidine by its hydrolysis to hydroxylamine - and meroquinene.

If we assume that the secondary alcoholic group connects the quinoline - half, to the quinuclidine nucleus, then the foregoing reactions may be explained as follows, on the assumption that the structures of quinine is as given below.



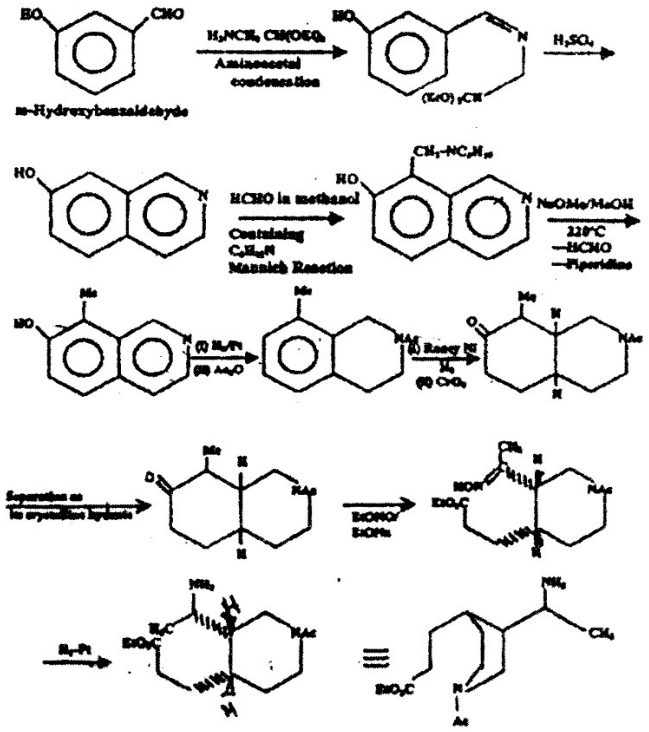


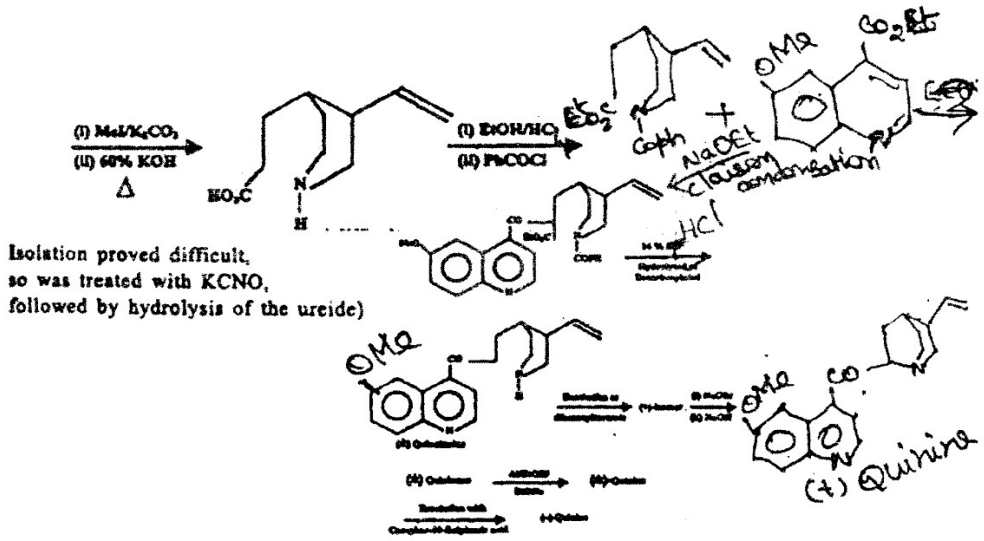
Quinine on heating with acetic acid gives "quoinotoxine". This isomerisation is known as "Hydramine fission".



Finally its structure has been confirmed by its synthesis.

SYNTHESIS OF QUININE :





Sterochemistry

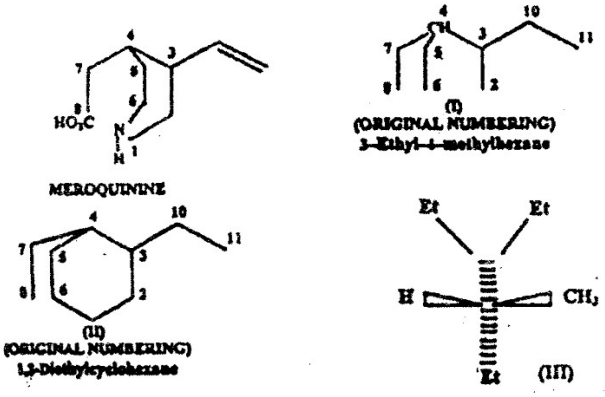
There are 4 asymmetric in the alkaloid, quinine, So, 16 stereoisomers are theoretically possible.

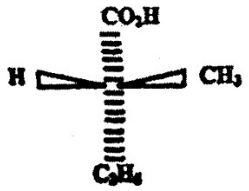
Configuration at C_3 & C_4 All the cinchona alkaloids (Cinchonine, Cinchonidine, quinine, and quinidine) give the same meroquinene on systematic degradation. In meroquinene, the obtained from these alkaloids also give the same dihydrobase. Thus all the cinchona alkaloids have the same configuration at C_3 & C_4.

Cinchonine was systematically degraded through a series of reactions to 3 – ethyl – 4 methyl hexane (I) Compound (I) on a 6 step sequence of operation gave 1,2 – diethylcyclohexane (II). Compound (I) was found to be laevorotatory and its configuration was correlated with that of the known (-) 2 – methylbutyric acid.

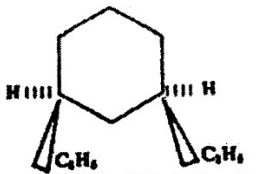
Compound (I) is represented by the Fischer projection formula (III). In formula (III), the sole center of dissymmetry is the cinchon a (c_3, and cinchonine has at that atom the configuration of (-) 2 methylbutyric acid.

The hydrocarbon (II), viz -1,2 dimethylcyclohexane, is optically inactive. It is therefore represented as the internally compensated meso (or cis-) form (IV). In this molecule, not only the cinchona C-$_3$ but also C_4 retain their asymmetry. They differ from their original condition in the alkaloid in that they have become similar, like the two asymmetric centers in tartaric acid. From these results, the configurations at C_3 and C_4, may be represented by the space diagram (V). In this the configuration of C_8 and C_9 are uncertain.

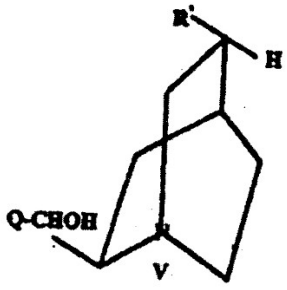




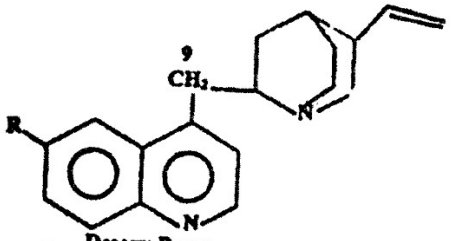
(-) -2- Methylbutyric acid



Meso - 1,2 - Diethylcyclo hexane (IV)



Q = Quinoline – half
R' = Vinyl group



Desoxy Bases
(C8 - Asymmetric)

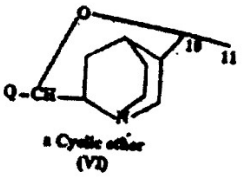
Configuration at C_8

Although cinchonine and cinchonidine furnish one and the same cinchotoxine, the alkaloids give rise to two different desoxy bases. Cinchonine gives dextrorotatory desoxy base while cinchonidine gives the laevorotatary desoxy base. Here C_9 is symmetrical. The only difference between them is the opposing configurations at C_8

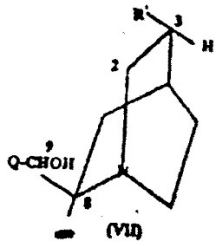
The means the parent alkaloids, cinchonine and cinchonidine have opposing configurations at C_8.

The configurations of these alkaloids were determined by their ability to form cyclic ethers (VI). The d-isomer (cinchonine) formed the said ethers while the l-iosmer (cinchonidine) did not.

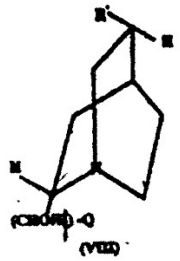
Hence the dextrorotatory cinchonine must have cis-configuration w.r.to $C_{(3)}$ and $C_{(8)}$ the laevorotatory cinchonidine should be trans w.r. to the above two centers. This results in the space diagrms (VII) & (VIII) respectively.



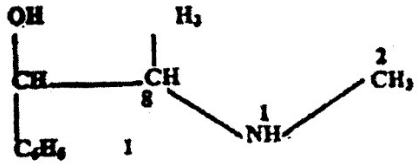
a Cyclic ether
(VI)



(VII)



(VIII)



(Numbering based on that of Quinine)

THE EPHEDRINES AND SPEUDOEPHEDRINE

Configuration at C_9:

There has been a general agreement among the scientists that cinchonidine and cinchonidine are $C_{(8)} - C_{(9)}$ antipodes. Cinchonidine and cinchonidine are opposed at $C_{(8)}$. Cinchonine and epicinchonine have the same configuration at C_8 but opposing configuration at C_9. the same is the case with cinchonidine – epicinchonidine pair. Based on this the configuration of these four isomerides can be written as follows.

	Cinchonine	epicinchonine	cinchonidine	epicinchonidine
C(8)	+	+	-	-
$C_{(9)}$	+	+	-	-

The cinchona alkaloids are, at $C_{(8)} - C_{(9)}$ 1,2 alkanolamines closely analygous to the four ephedrines. (The design and numbering are based on the cinchona pattern).

One of the pairs of $C_{(8)}$ $C_{(9)}$ antipodes in the cinchona series must therefore have the erythro configuration of (+) and (-) ephedrine, while the other diastereoisomeric pair will have the thereo configuration of the two enantiomeric pseudoephedrines. The point is, of course to decide which is which.

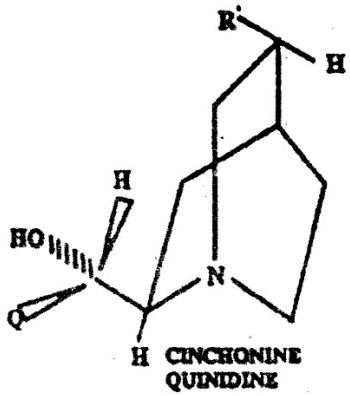
It now presumed that the $C_{(8)}$ $C_{(9)}$ antipodes are cinchonine – cinchonidine and epicinchonine - epicinchonidine respectively. The former have the erythro configuration of the ephedrines and the latter the throe configuration of the pseudoephedrines.

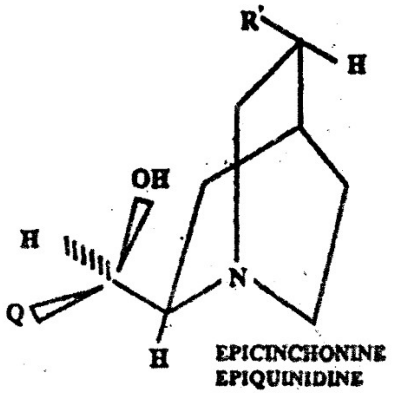
This is referred to as the prelog configuration and the configuration based on the R, S – nomenclature is depicted below for the $C_{(8)} - C_{(9)}$ antipodes.

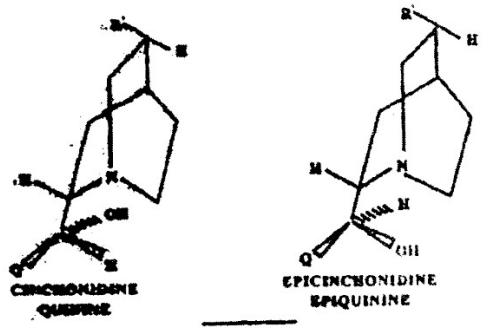
Stereoisomeride	Configuration	
	C(8)	C(9)
Cinchonine	R	S
Epicinchonine	R	R
Cinchonidine	S	R
Epicinchonidine	S	S

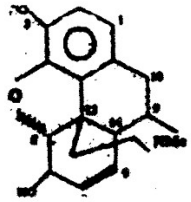
The space diagrams for the cinchona alkaloids are as follows:

Note: Cinchonidine belongs to the (-) ephedrine series, quinine too belongs to the same, hence grouped here.





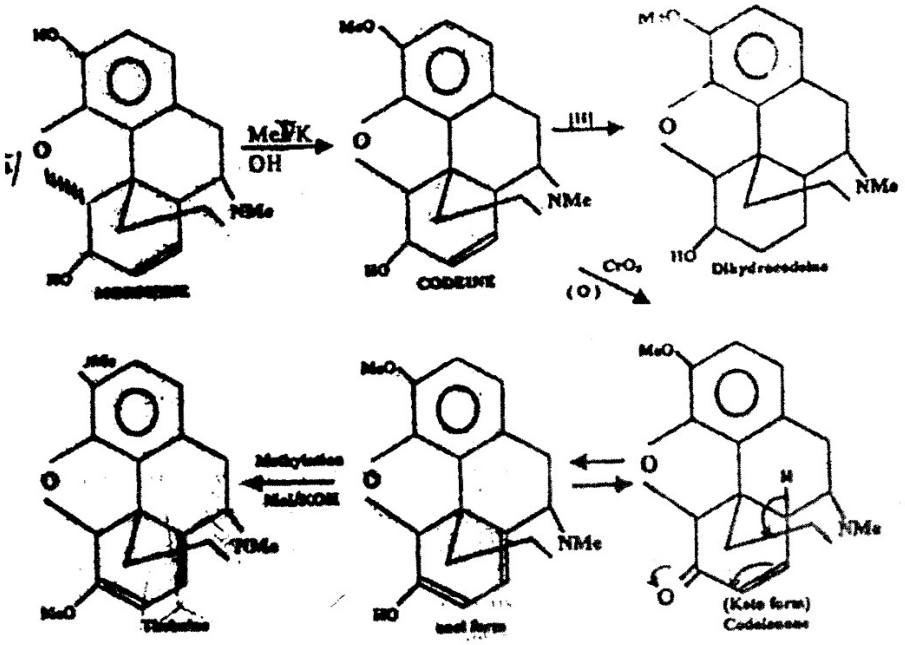




I. M.F.$C_{17}H_{19}NO_3$. II. It forms a diacetate with acetic anhydride. so must contain two hydroxyl groups.

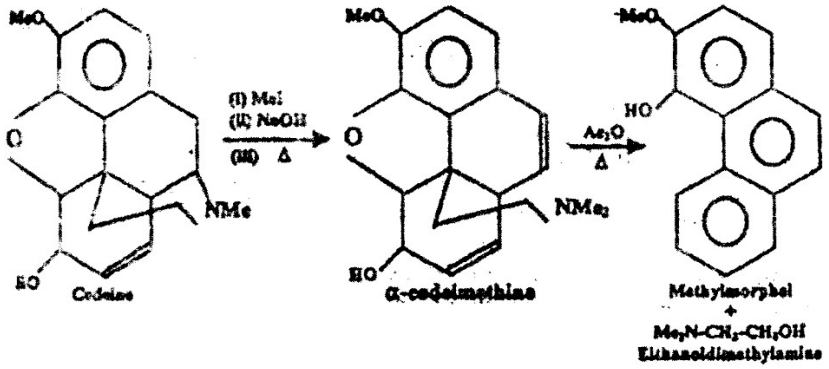
iii. It gives colour reaction with neutral $FeCl_3$, indicating the presence of a phenolic group. Morphine forms a monosodium derivative only with NaOH. Hence one of the hydroxyl group is phenolic & the other is alcoholic. Iv. On chromiumtrioxide oxidation it gives a ketone, the hydroxyl must be then a secondary one. V. On treatment with methyliodide and aqueous potassium hydroxide, morphine forms codeine. The latter on catalytic hydrogenation gives dihydrocodeine. This shows that presence of a double bond in codeine, in turn in morphine.

Relationship between Morphine, Codeine and Thebaine is indicated as follows.



This third oxygen atom is inert and is present as an ether linkage. Zn dust distillation of morphine give phenanthrene as one of the products along with other products. Thus morphine should contain a phenanthrene skeleton.

The structural skeletion of morphine and been deduced from the following reactions of codeine.

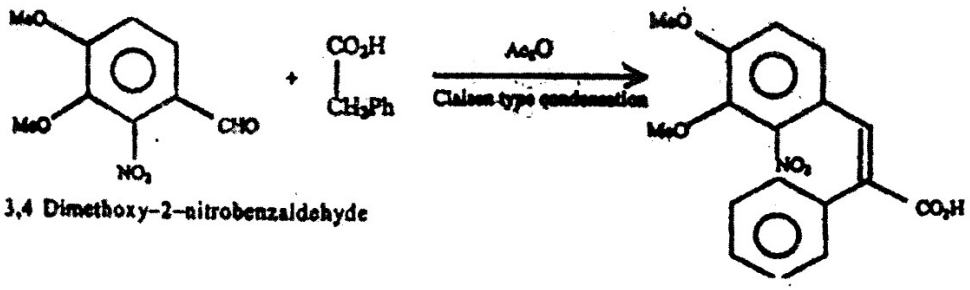


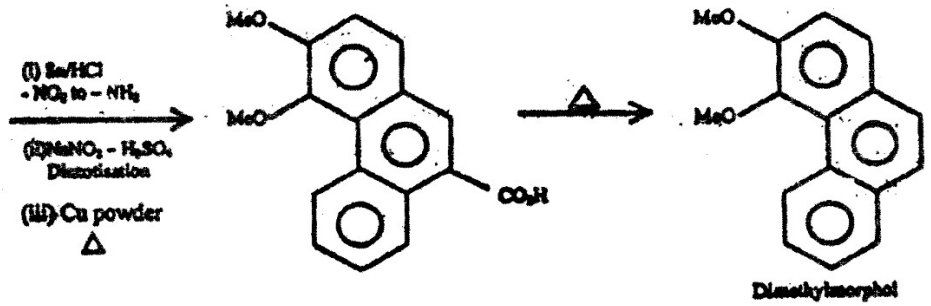
Structure of Methylmorphol:

Methylmorphol on heating with hydrochloric acid at 180°C gives methyl chloride and a dihydroxyphenanthrene, morphol.

Discetylmorphol on oxidation gives diacetylphenanthroquinone, indicating that the 9, 10 – positions are free morphol. The quinine on further oxidation gives phthalic acid. There fore the two acetoxyl groups should be present in one and the same ring, and in trun the hydroxyl groups. Morphine on fusionin with alkali gives protocatechuric acid, (3, 4 – dihydroxybenzoic acid). The structure of methylmorphol is confirmed by a synthesis of dimethylmorphol.

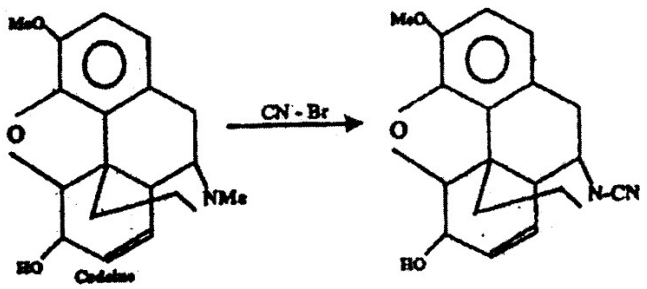
Synthesis of dimethyl morphol :-



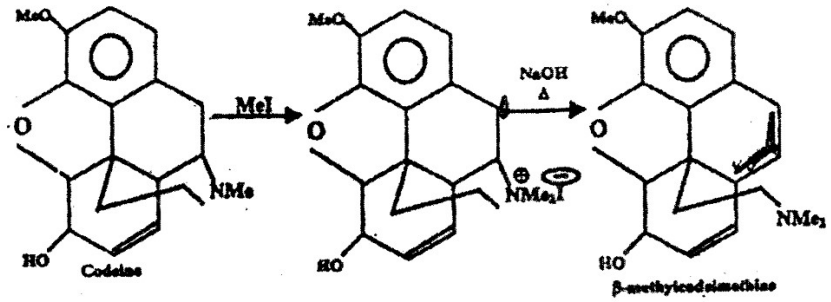


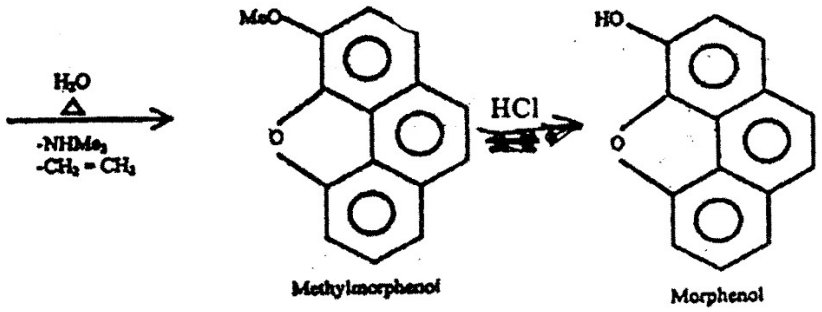
The formation of ethanoldimethylamine from alphamethylcodeimethine indicates that there is a *-N-Me-group in codeine, which is confirmed as follows :

Codeine on vonBraun degradation looses three hydrogen atoms and adds one nitrogen atom.



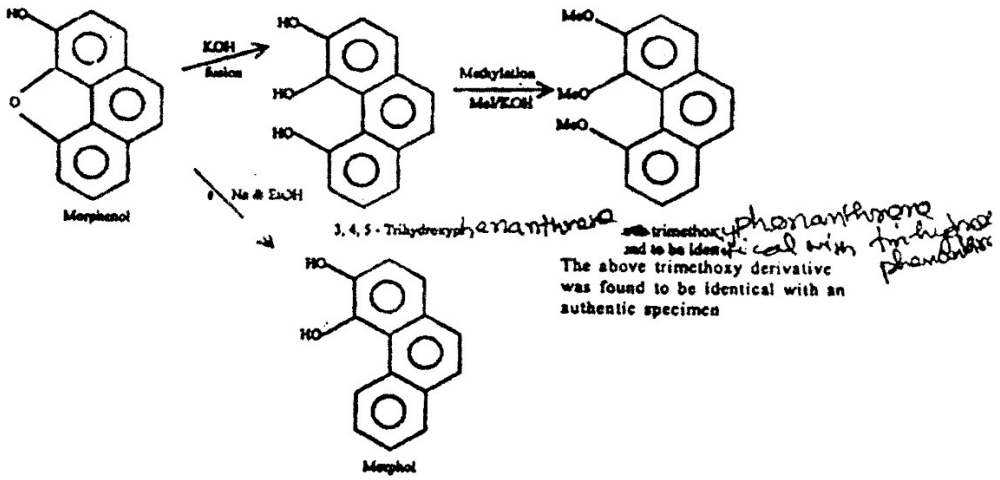
Morphine contains an ether linkage at 4, 5 - positions corresponding to phenanthrene is proved by the following sequence of reactions.



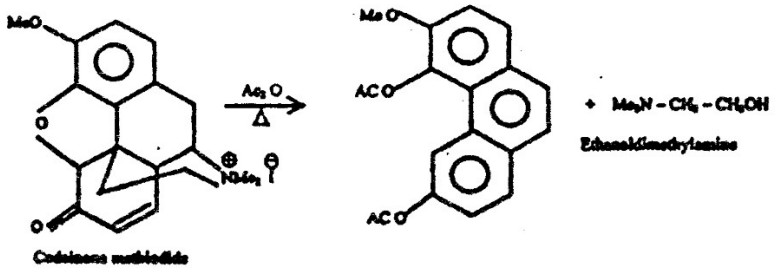


Morphenol contains one phenolic group and an inert oxygen atom. On fusion with KOH morphenol gives 3, 4, 5-trihydroxyphenoanthrene. The structure of this compound was shown by synthesis of 3, 4, 5-trimethoxyphenanthrene which was found to be identical with the product obtained by methylating the trihydroxyphenanthrene obtained from morphenol.

Na & EtOH reduction of morphenol gives morphol. These results can be explained by assuming that morphenol has a structure containing an ether linkage in position, 4, 5 - of the phenanthrene nucleus.



Alholic group was determined by the acetic anhydride degradation of the methiodide of codeione which gives 3-methoxy -4, 6- diacetoxyphenantherene and is confirmed by its conversion into 3, 4, 6-trimethoxyphenantherene, identical with an authentic specimen.



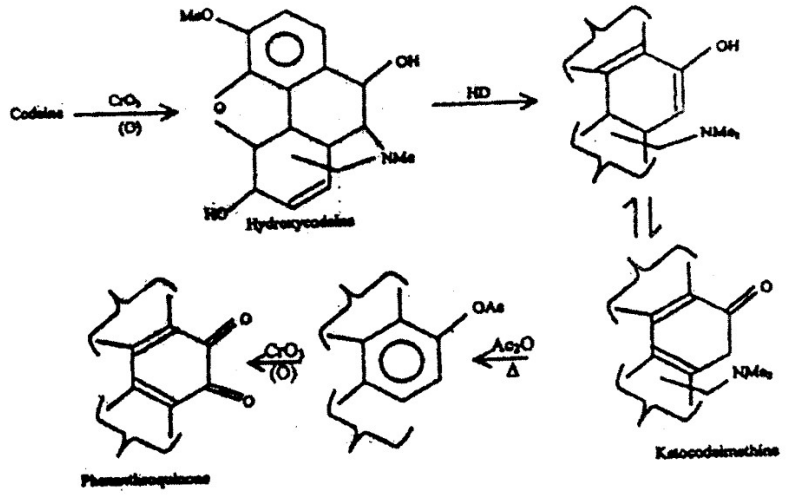
The position of methoxy group and position 4, of the – OH group have already been established. The hydroxyl group in position 6, must therefore be formed from the oxygen of the keto group in codeinone.

The presence of a cyclic tertiary base system is evidenced by the exhaustive methylation of codeine, which produces alpha – codeimethine, containing one more – CH_2 than codeine itselt, and the nitrogen atom is not lost. (if codeine contained and acyclic tertiary amine system, in trun morphine then the product would have contained fewer C atom and loss of N atom would have occurred).

The nitrogen atom was shown to be attached at position 9 or 10 as follows.

Oxidation of codeine with chromium trioxide affords some hydroxycodeine and Hofmann degradation of this gives a ketocodeimethine in which the oxygen appears as a carbonyl group. When ketocodeimethine is heated with acetic anhydride a methoxydiacetoxyphenantherene is obtained. The latter on oxidation looses an acetoxy group to afford a quinine.

The new acetoxy group in phenanthene, and hence the new hydroxyl group, in hydroxycodeine, must therefore be at position 9 or 10. since this group is converted into a carbonyl group during Hofmann degradation, a double bond must be introduced at position 9, 10 - during scission of the nitrogen atom must accordingly be linked at $C_{(9)}$ or C_{10}.



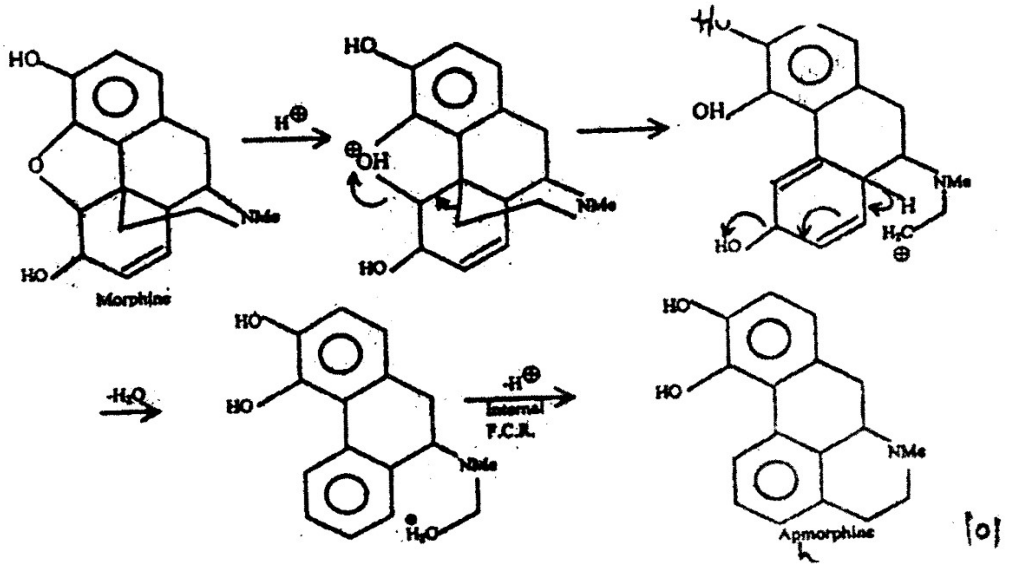
Positive evidence for the attachement of nitrogen at C_9 was given by a synthesis of morphine.

The morphine alkaloids have a unique property i.e., a tendency to loose the nitrogen containing side chain degradation giving phenanthrene derivatives.

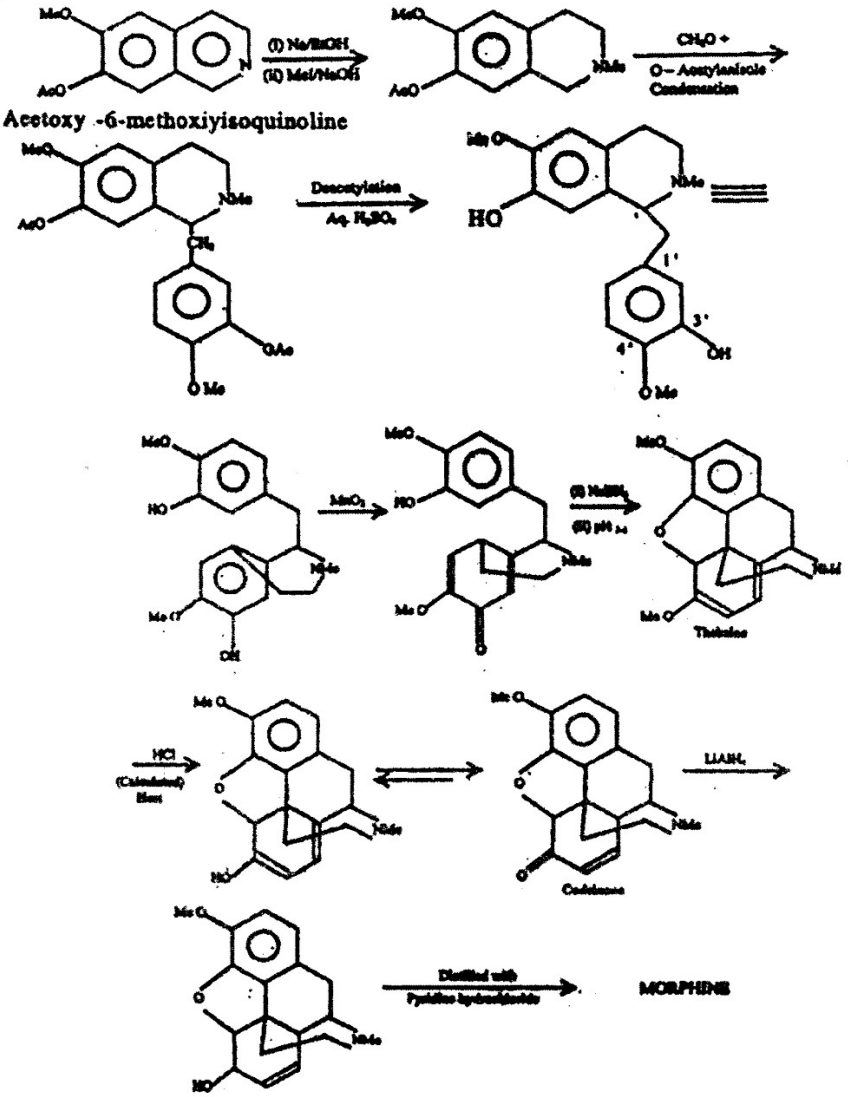
On these grounds the attachement of the side chain at an angular position was proposed, so that its elimination is a necessary part of aromatisation. Out of the two possible positions, C_{13} was considered as the correct position. Since on this basis it is easy to explain some of the rearrangements undergone by this group of alkaloids.

Morphine to Apomorphine Rearrangement :

Morphine when heated with con.hydrochloric acid gives apomorphine.



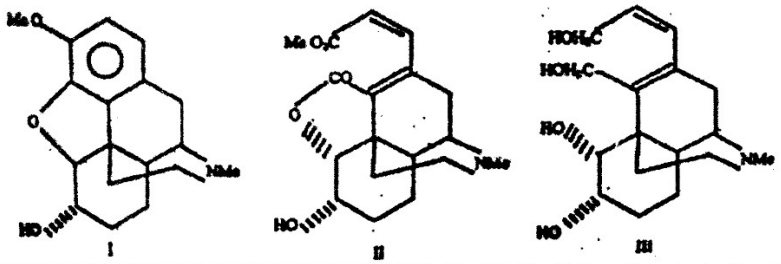
Synthesis ··



Stereochemistry of Morphine

The stereochemistry of morphine as reported by Rapport etal is outlined below :

Ozonolysis of dihydrocodedeine (I) yields the ester lactone (II) $LiAlH_4$ reduction of which yields the tetrol (III). A similar sequence with dihydroisocodeine, differing only in stereochemistry at C_6, yielded an isomer of (III).



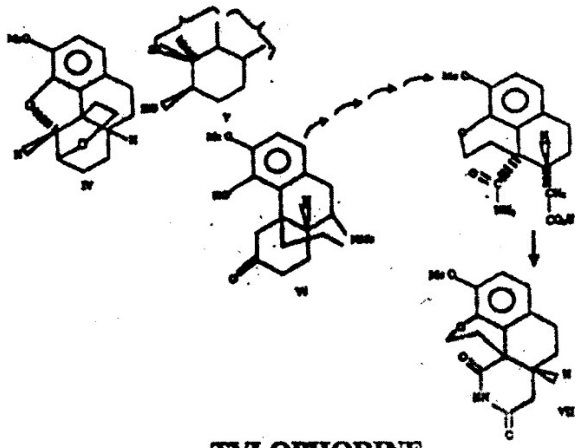
I II III

These isomeric tetrols were oxidized by lead tetra acetate at different rates. The one derived from codeine was oxidized three times more rapidly than its isomer. From which it was concluded that (III) is a cis - diol and therefore, that codeine has the oxygen functions at C_5 & C_6 in the cis relationship.

Relationship C_6 – OH and C_{13} side chain:

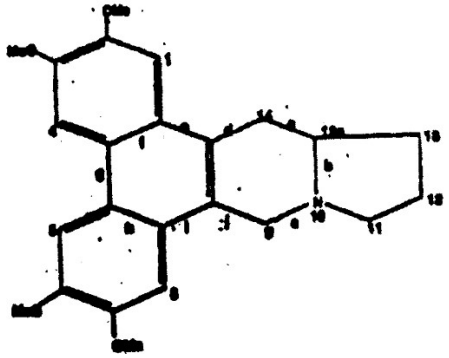
This was revealed from a study of the exhaustive methylation of dihydrocodeine and dihydroisocodeine with reduction after the first stage. Hofmann degradation of tetrahydrocodeimethine was founds to be accompanied by some methylation of the C_6 – hydroxyl at the expense of some quaternary salt and the degradation of tetrahydroisocodeimethine also furnished a cyclic ether 6 – codian. It was argued that since the cyclic ether system must be cis-used to the hydrophenanthrene system the product must have structure (IV) and dihydroisocodeien must be (V) in view of the previously determined relationship of oxygen functions, at C_5 & C_6.

Dihydrothebainone (VI) was converted to the cyclic imide (VII) through a series of reactions. By contrast the C_{14} epimer of the bainone i.e. beta – thebainone could be degraded only to a certain point and not to the cyclic imidle. Based on this it was argued that C_{13} & C_{14} must have a cis – geometry.



TYLOPHORINE

i. Form Zeisel estimation is was found to contain 4 - OMe groups.
ii. Negative Herzig - Meyer test indicates absence of - N - Me - group.
iii. UV indicates the presence of a phenanthrene chromophore in tylophorine.
iv. Hofmann degradation of tylophorine gives tylophorine methine (conjugated). This on further Hofmann degradation gives di-N-methyl-tylophorine methine. Thus the nitrogen atom must be present in a bicyclic ring.

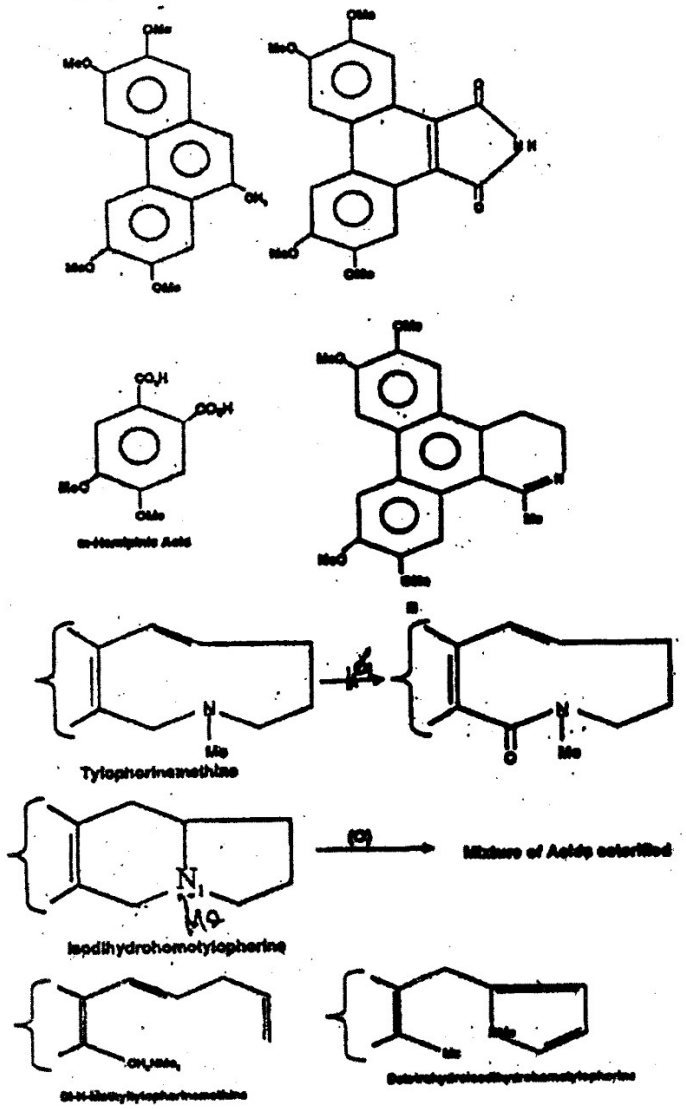


v. Tylphorine methochloride on Emde degradation gives isodihydrohomotylophorine. The latter on dehydrogenation with Pd/C gives detertrahydroisohydrohomotylo - phorine, a non - basic compound showing a positive Ehrlich test indicating the presence of a pyrrole ring.

vi. Oxidation of Hofmann degradation product from isodihydrohomotylophorine gives a mixture of acidic products. This on esterification followed by separation gives a monoester and a diester.

vii. The monoester on hydrolysis and decarboxylation yields 2,3,6,7 - tetramethoxy -9-methylphenanthrene (I), identical with an authentic specimen.

viii. The diester is hydrolysed to dicarboxylic acid. This may also be obtained by the oxidation of tylophorineisomethohydroxide with potassium permanganate along with a small amount of an imide. The latter was shown to be 2, 3, 6, 7 - tetramethoxyphenanthrene -9,10-dicarboxylimide (II) by comparison with a specimen obtained by the oxidation of the dihydroisoquinoline (III).

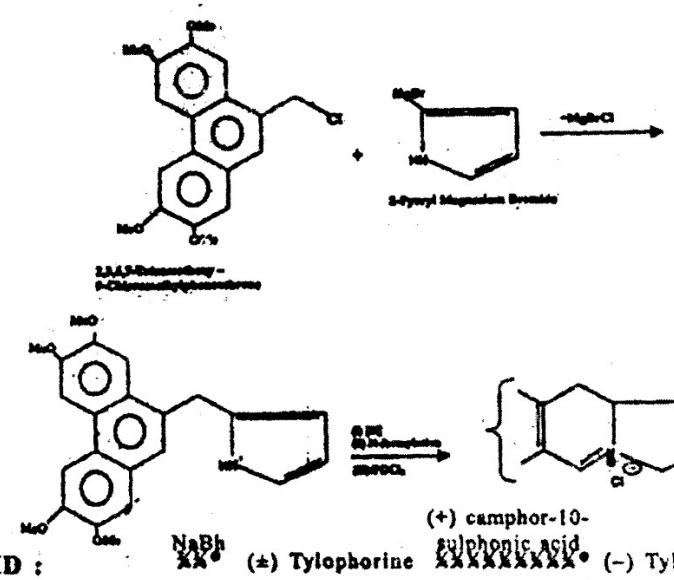


ix. Vigorous oxidation of tylophorinemethiodide with potassium permanganate yields m-hemipinic acid as the only isolable product.

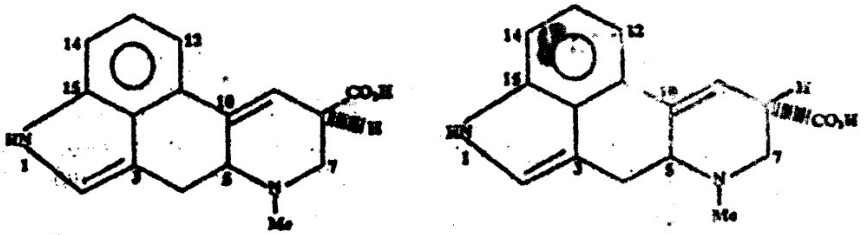
x. Oxidation of tylophorinemethine with potassium permanganate in pyridine yields a neutral nitrogenous substance, formed by the oxidation of a methylene group (adjacent to the N-atom) to a carbonyl group.

On the basis of these degradation studies tylophorine is f nulated as 9, 11, 12, 13, 13a-14-hexahydro -2, 3, 6, 7 tetramethoxy - dibenzo (f, h) pyrrolo [1, 2b] isoquinoline.

Synthesis :



LYSERGIC ACID :

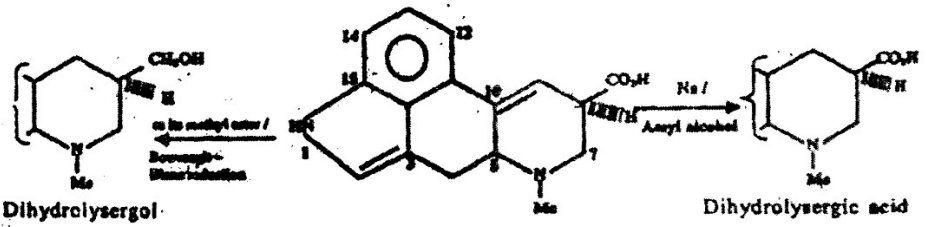


LYSERGIC ACID **ISOLYSERGIC ACID**

Both lysergic acid and isolysergic acid give blue colour with con.sulphuric acid and glacial acetic acid containing traces of iron chloride.

i. M.F.$C_{16}H_{16}O_2N_2$.

ii. Optically active monobasic acid.

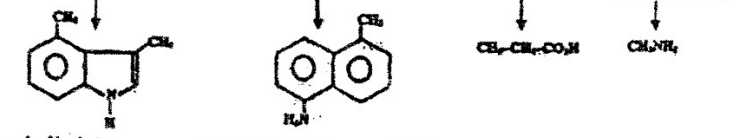


Dihydrolysergol Dihydrolysergic acid

LYSERGIC ACID

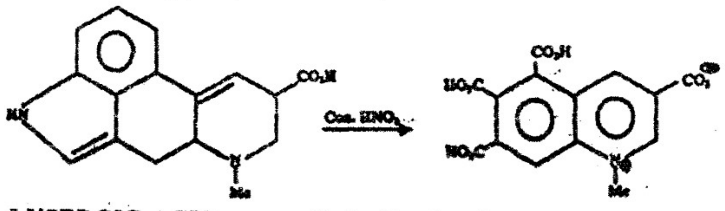
Dihydrolysergic acid

KOH fusion



3,4 Dimethylindole 1-Methyl-5-aminonaphthalene

The products obtained during potassium hydroxide cleavage indicated that lysergic acid contained a new tetracyclic system, which was named ERGOLINE. As methylamine is liberated in this reaction the –NH group of indole and the $-NH_2$ group of aminonaphthalene must be derived from an indole nucleus in lysergic acid.



LYSERGIC ACID Quinoline-betaine-tricarboxylic acid

Sodalime

⟶ Quinoline

The formation of quinoline in the above sequence suggests that lysergic acid may probably contain a reduced quinoline nucleus.

Comparison of the UV spectra lysergic and isolysergic acids with that of dihydrolysergic acid (which displayed a spectrum typical of an indole system) suggested that they contain an olefinic bond in conjugation with the indole nucleus.

The position of the carboxyl group was ascertained from P* measurements and the finding that the dihydrolysergic acid behaves like a beta-amino acid, giving of heating a neutral unsaturated substance that can be reduced to a tetrahydro derivatives.

(Betaine = trialkyle derivatives of aminoacids, existing as dipolar ions)

The lactam obtained by heating llysergic acid is optically active, and again the new double bond is in conjugation with that already present. These facts are sufficient to justify the placing of the double bond of lysergic acid at position 9, 10.

Removal of the asymmetry at C_8 at which the carboxyl group is situated, yielded identical products in the case of lysergic acid and isolysergic acid. This proved lysergic acid and isolysergic acid to be diastereoisomers at C_8.

Formation of Neutral Molecule :

Synthesis :