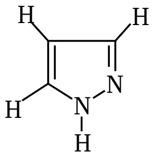
Introduction

1.1. Pyrazoles

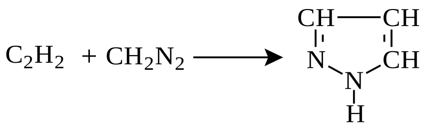


The simplest member of the pyrazole family is pyrazole compound with molecular formula $C_3H_4N_2$, molecular weight 68.6, melting point 69.5-70°C. The pyrazole compounds are not known to occur in nature. (Fowden *et al.*, 1959) but α–amino-β-1-pyrazolyl propionic acid was isolated from water melon seed, and this acid has been synthesized in good yield (Finar., 1980).

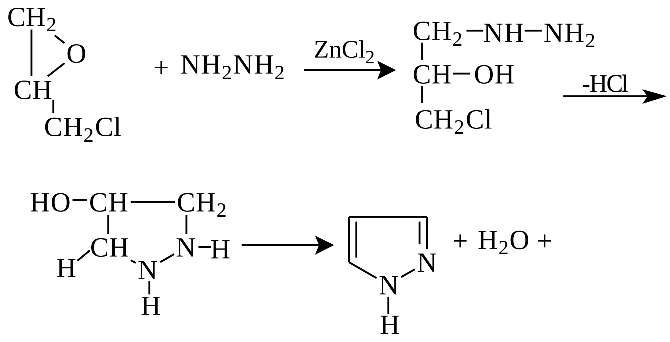
1.1.1. Preperation of pyrazole:

Pyrazole can be synthesized in a number of ways, some of the more convenient methods being the following.

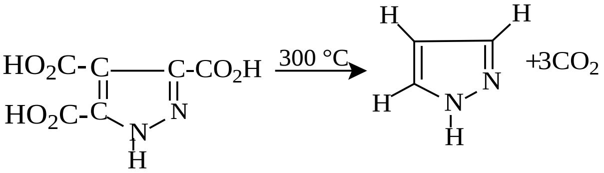
A- By passing acetylene into a cold ethereal solution of diazo methane (Tedder and Nerchvatal .1967)



B- By heating epichlorohydrin with hydrazine in presence of zinc chloride (Balbiano, 1890).



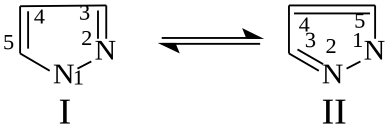
C- By the decarboxylation of various pyrazole carboxylic acids. e.g. by heating pyrazole-3,4,5-tri carboxylic acid



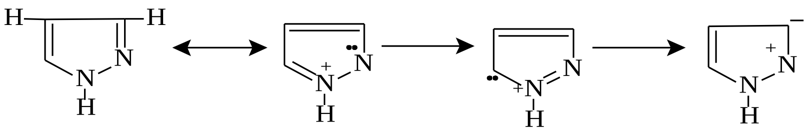
D- Pyrazole may be prepared by condensation of 1,1,3,3-tetra-ethoxy propane $(C_2H_5O)_2CH-CH_2-CH(C_2H_5O)_2$ with hydrazine dihydrochloride (Jones, 1949).

1.1.2. Properties of pyrazole:

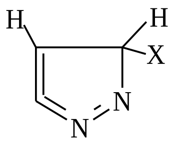
Pyrazole is a colorless solid, it is a tautomeric substance, the existence of tautomerism can not be demonstrated in pyrazole itself, but can be inferred by condensation of pyrazole derivatives. If pyrazole is tautomeric then the positions 3 and 5 will be identical, if pyrazole is not tautomeric then these positions are different. On oxidation, both 3-methyl-1-phenyl-pyrazole and 5-methyl-1-phenyl pyrazole gave the same products, thus position 3 and 5 must be equivalent in pyrazole and this can only be explained by assuming that pyrazole is tautomeric I and II. (Knorr *et al.*, 1893)



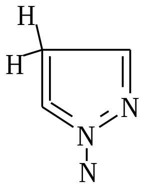
Therefore it follows that in pyrazole there can only be two carbon alkyl derivative 3-(or 5) and-4 if however the imino hydrogen is replaced by an alkyl or aryl group then three carbon-alkyl derivatives are possible 3,4 and 5 since tautomerism is now impossible and so position 3 and 5 are no longer equivalent. Pyrazole exhibits aromatic properties. e.g. it is readily halogenated, nitrated and sulphonated. The groups enter at position 4, the following resonating structures are possible for pyrazole (Finar, 1975; Tschabold *et al.*, 1988).



If these structures are contributed equally well at position 3,4 or 5 in pyrazole it self, position 3 and 5 are equivalent, electrophilic attack occurs exclusively at position 4, the reason for this is not certain, possibly the reasonating structures are not contributed equally. Dewar, (1949) has suggested that substitution on pyrazole occurs in the 4-position because the transition state for 4-substiution is more symmetrical.

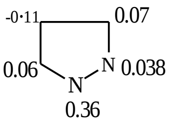


3-substitution

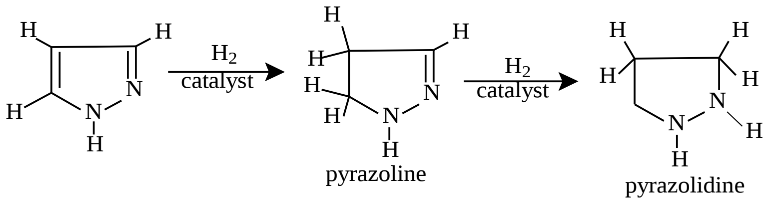


4-substitution

Consequently, it is more stable than the transition state for 3-(or 5-) substitution, however (Orgel *et al.*, 1951) calculated the electron distribution in pyrazole and it can be seen from their results that 4-substitution will be favoured by electrophilic reagents. Brown (1955) has also calculated the electron densities in pyrazole.

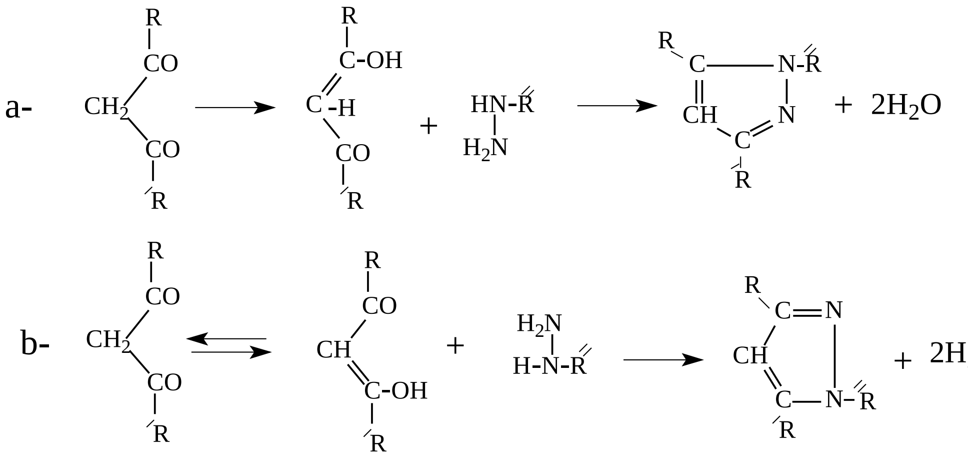


It is interesting to note that pyrazole 4-diazonium salts are stable to boiling water. Pyrazole is basic and forms salts with inorganic acids, the imino hydrogen may be replaced by an acyl group. Pyrazole is very resistant to oxidizing and reducing agents but may be hydrogenated catalytically first to pyrazoline and then to pyrazolidine- both of these compounds are stronger bases than pyrazole.(Faner 1955)

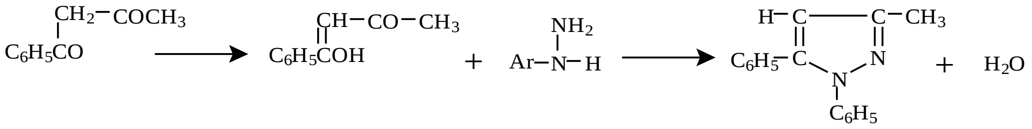


1.1.3. Syntheis of pyrazole derivatives:

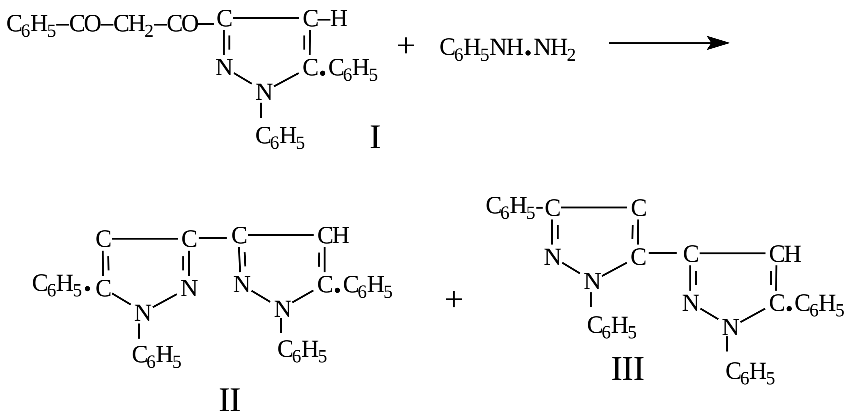
Avery important method for preparing pyrazole derivatives is by the reaction between β-keto aldehydes and hydrazines (Knorr *et al.*, 1883).



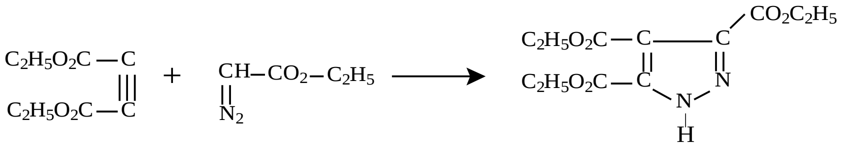
Benzoyl acetone and phenyl hydrazine form 3-methyl-1,5-diphenyl pyrazole (Drum, 1931).



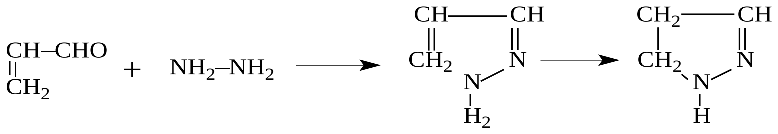
in a few cases, two isomers have been isolated e.g.3-α-benzoyl acetyl-1,5-dipheny pyrazole reacts with phenyl hydrazine to produce a mixture of 1,1,5,5-tetraphenyl-3,5-diphenylpyrazolyl (Finar, *et al.*, 1955).



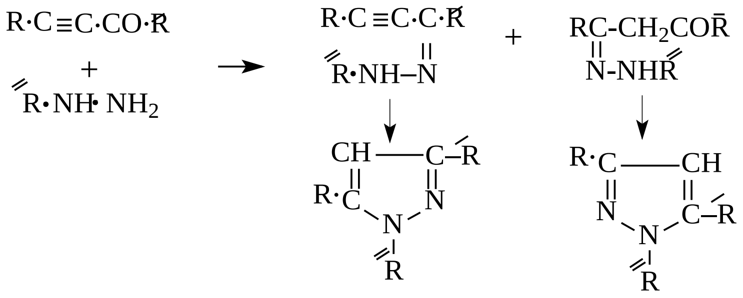
Pyrazole carboxylic acids are produced by the reaction between diazoacetic ester and acetylenic compounds. e.g. with ethyl acetylene dicarboxylate, ethyl pyrazole-3,4,5-tricarboxylate was formed.



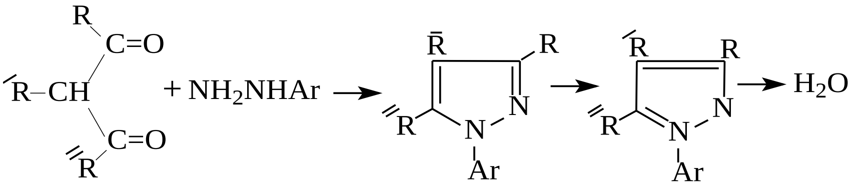
Pyrazolines are obtained by the condensation of β-unsaturated ketones or aldehydes with hydrazine e.g. arylaldehyde and hydrazine give pyrazoline.



Pyrazolines can be oxidized to pyrazoles by bromine or mercuric oxide. Pyrazoles are produced by the reaction between acetylenic carbonyl compounds and hydrazines and a mixture of isomers is obtained.



Formation of pyrazole derivatives from hydrazines or hydrazides, semi carbazides and aminoguanidines by condensation with 1,3-dicarbonyl compounds yields two structurally isomeric pyrazoles.

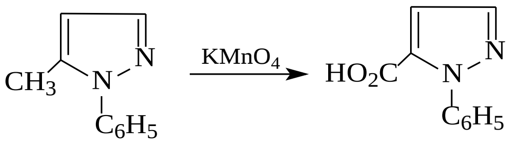


1-(2,4-dinitrophenyl)-3,5-dimethyl-4-arylazopyrazoles were prepared by coupling 2,3,4-pentane trione and 3-arylhydrazone-2,4-dinitro phenylhydrazine in presence of EtOH, 2-naphthyl sufonyl hydrazine was reacted with aromatic aldehydes and aldehydo sugars to give the corresponding hydrazones which undergo Michael addition reactions with malononitrile or ethylcyanoacetate to form pyrazole derivatives (Hamid *et al.*, 2002).

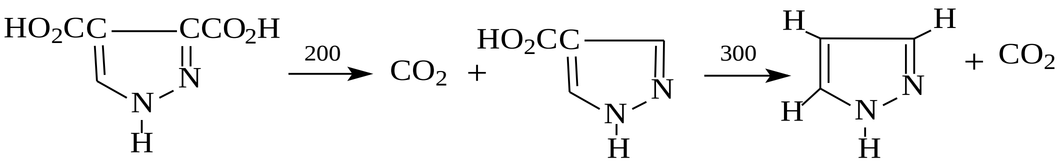
1-H-pyrazole-1-carboxamidies were prepared as potential inhibitors of the three isozymes of nitric oxide synthase. All of the compounds were found to be competitive inhibitors of all three isoforms. The most selective compound prepared was 1H-pyrazole-n-(3-aminomethyl anilino)-1-carboxamidine (Lee *et al.*, 2000).

1.1.4. Properties of pyrazole derivatives:

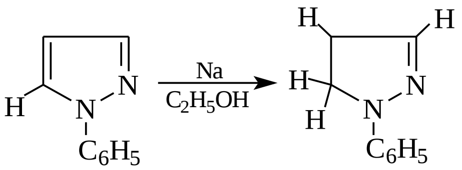
Pyrazole with a substituent methyl group may be oxidized by potassium permanganate to the corresponding pyrazole carboxylic acids.



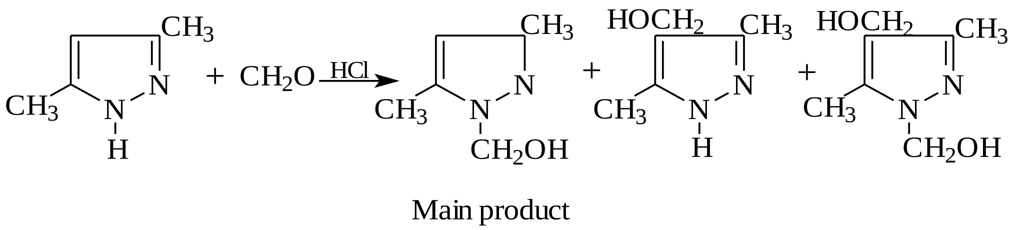
Pyrazole-3-and 5 carboxylic acids are readily decarboxylated by heating above their melting points, pyrazole-4-carboxylic acids are more stable but can neverless be decarboxylated at elevated temperature.



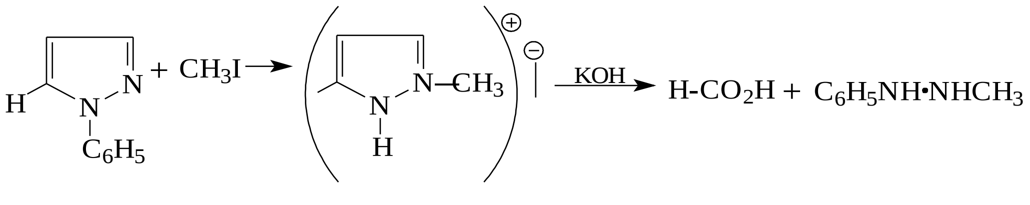
Pyrazole itself is not reduced by sodium and ethanol, N-phenyl substituted pyrazoles are readily reduced e.g.



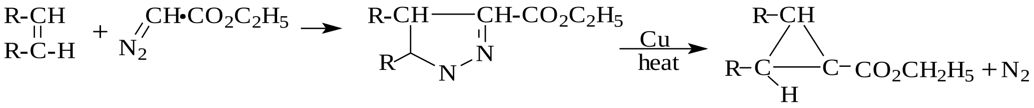
unsubstituted pyrazole apparently can not be chloromethylated, instead carboinols are produced (Droetzky. 1950, Finar 1954).



When boiled with concentrated aqueous postassium hydroxide, quaternary pyrazole are converted into hydrazine (Knorr *et al.*, 1906).



Knorr used this reaction to prepare sym-disubstituted hydrazine at the same time, this reaction proves the structure of pyrazole- quaternary salts. Esters of pyrazoline carboxylic acid eliminate nitrogen on heating to give cyclopropane derivatives if the compound is heated with copper powder



4-chloromethyl-1-phenyl pyrazole can be converted into 1-phenyl pyrazole-4-aldehyde by means of the Sommelet reaction. The 4-aldehyde is more conveniently prepared by the direct formulation of 1-phenyl pyrazole with dimethyl formamide and phosphoryl chloride (Finar *and Lord.*, 1957). 1-phenyl pyrazole can also be mercurated in the 4-position (Finar., 1954).

The sugars of pyrazoline derivatives were sensitive to oxidation, but high yields were achieved with 2,2,2-trifluoroethyl acetoacetate in midly acidic solution. Azo coupling of the pyrazolones produced highly coloured azopyrazolone derivatives that prevented further degradation, and this may prove useful labels for chlromatographic analysis of carbohydrates (Kett *et al.*, 2000).

1.1.5 The biological activities of pyrazole derivaties:

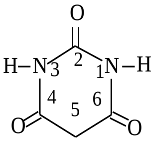
Compounds having pyrazole structure have been known to posses tranqualizing muscle relaxant, anticonvulsant and monoamine oxidase inhibitor and antidepressant activities. Pyrazole derivatives are able to activate central nervous system and posses antidiuretic properties. 3,5-dimethyl pyrazole was found to be potent in lowering blood sugars.

5-Aryl-3-pyridin-2-yl(4,5-dihydro-pyrazol-2-imidazol) derivatives were synthesized and tested for their *in vitro* antifungal activity. These compounds showed a moderate activity against strains of *Candida parapsilosis* and *Candida glabratar* (Mamolo- *et al.*, 2003). Twenty-five

2-phenyl-5,6-dihydro-2H Thieno(3,2-c)-pyrazol-3-ol derivatives were synthesized for evaluation as new inhibitors of bacterial cell wall biosynthesis; many of them demonstrated good inhibitory activity against gram-positive bacteria (Huww *et al.*, 2003).

Novel coupling products 4-arylhydrazono-2-pyrazoline-5-ones were synthesized and evaluated for antimycobacterial activity against mycobacterium tuberculosis and mycobacterium avium (Kucukguzel and Rollas, 2003). Some pyrazolo (3,4-d)-pyrimidin-4-thione derivatives were synthesized and screened for antifungal activity against the caused agent of rice blast disease (Vicentini *et al.*, 2002).

1.2 Barbiturates



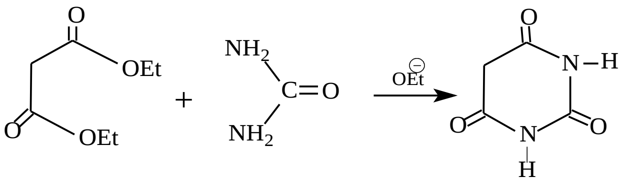
1.2.1 Chemical and physical properties

Barbituric acid is a six membred heterocycle compound, with formula $C_4H_4N_2O_3$, molecular weight of 128.099, melting point of 248 °C, boiling point 260 °C, and it contains two nitrogen atoms..

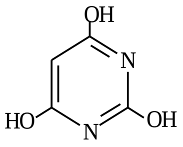
A conformation study on barbituric acid and thiobarbituric acid was performed at level on the neutral protonated, mono and di-anionic forms. Acid base equilibria were studied by comparing the electronic transitions evaluated for the most stable conformations and the experimental spectra at different pH values (Zuccarello *et al.*, 2003).

1.2.2 Preparation of Barbituric acid:

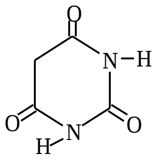
By condensation of diethyl malonate with urea in the presence of sodium ethoxide, or of urea with malonic acid in the presence of phosphoryl chloride (Grimaux, 1879).



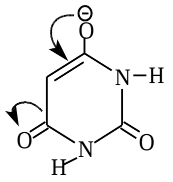
Barbituiric acid may be regarded as 2,4,6-trihydroxy pyrimidine, but in the crystalline state it exists as the triketo form. In aqueous solution the compound is remakedly acidic as a result of ionization of the mono enolic form with the formation of resonance stabilized anion.



2,4,6-trihydroxypyrimidine

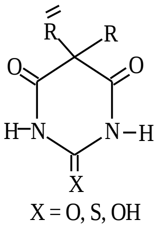


triketo form



1.2.3 Barbiturates:

Barbiturate derivatives of babituric acid were first introduced for medical use in early 1900,s more than 2500 barbiturates have been synthesized, in the height of their popularity about 50 were marked for human use, one of them called barbital under the name of vernoal which was of the first sleeping inducing barbiturates (Fischer *et al.*, 1903).



Thousands of barbiturates have been synthesized on a trial and error basis although many structural features required for hypotontic activity were recorded, no clear correlation between structure and activity emerged (Doran, 1959). In 1951 barbituric acid derivatives were divided into classes of hypotontics and inactive compounds (Sundberg, 1951).

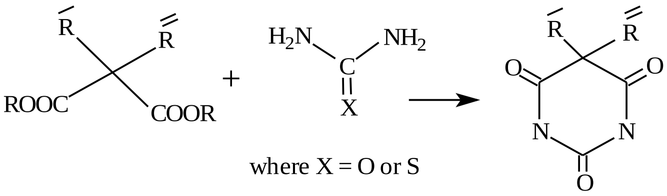
Barbiturates are sedative drugs comprising a vast class of synthetic substances with closely related chemical structure and similar pharmacological activities. They are odourless white crystalline solids which are only slightly water soluble and hence administrated mainly by the oral route.

1.2.4 Properties of Barbiturates

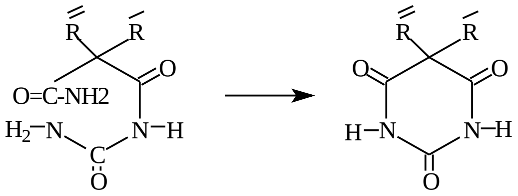
Barbiturates dissolve easily in fat, and they have ready access to the brain because they can easily cross the blood brain barrier . Barbiturates may also increase the flow of chloride ions across the neuronal membrane. Barbiturates are “donors” they work by reducing the amount of activity in the brain and central nervous system, and are widely used as sedatives, hypontics and antiepilpetics (Peter *et al.*, 2001). Aliquid chromatographic procedure for the determination of six barbiturates in urine samples is described (Martin *et al.,* 1999).

1.2.5 Preparation of Barbiturates

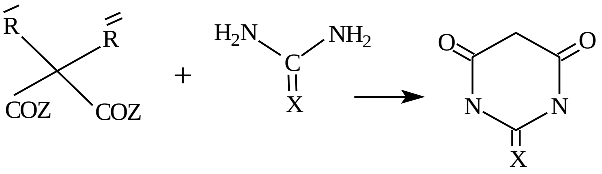
1- Condensation reaction in an alkaline medium involve malonic esters, cyano acetic esters and malonic amides on one hand, and urea or thiourea on the other hand.



2- Cyclization of N-substituted urea in an alkaline medium also produced barbiturates.



Condensation reaction in neutral or acidic medium takes place readily between malonyl chlorides or malonic acids and urea or thiourea.



where Z = OH or Cl and X = O or S

1.2.6 Structure Activity Relationships:

Extensive synthesis and testing of the barbiturates over a long time has produced well defined structure activity relationships (Daniels, *et al*, 1982). Both hydrogen atoms at the 5-postion of barbituric acid must be replaced. If one hydrogen is available at postion 5, tautomerization to a highly acidic trihydroxy pyrimidine can occur.

The duration of action depends mainly on the substituents at position –5 which confer lipophilicty. Hypnotic activity increases with lipid solubility, optimal activity is exhibited by compounds in which the sum of carbon atoms of both substituents is between 6 and 10 Further increase in lipid solubility as a consequence of the increase in the sum of the carbon atoms, decreases hypnotic activity and results in convalsunt or inactive compounds. With the same series, branched chain isomer has greater activity and shorter duration of action. Replacement of one hydrogen by a phenyl group at the 5 carbon imparts anticonvulsant properties, and the resulting compounds are used in epilepsy.

Substitution of one imide hydrogen at positions 1 or 3 by alkyl groups increases lipophilicity, leading to compounds with quicker on set and shorter duration of action, by which they are seldom employed as sedative hypnotics. Replacement of oxygen by sulfur on the 2 carbon increases lipid solubility and thus shorten the onset of the action, owing to very fast uptake into the central nervous system and decreases duration of action as a consequence of rapid redistribution into fatty tissuesThese compounds are called thiobarbiturates and are used as intravenous anesthetics (Watanabe *et al.*, 1999).

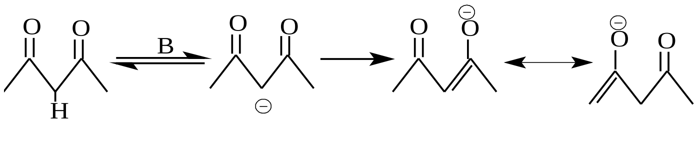
1.2.7 Biological effect of the barbiturates:

Barbiturates have been shown to be neuroprotective in several animal models but the underlying mechanisms are unknown. (Almeas *et al.*, 2000, Dereeper *et al.*, 2002)

Screen drugs used in obstetrical practice for effect on steroid hormone synthesis revealed that Phenobarbital inhibited progesterone synthesis in leyding tumor cells. The inhibition was apparently a drug class effect since it could be reproduced by other barbiturates. Barbiturates block steroidogenesis by inhibiting cholesterol transport to the cholesterol side chain cleavage enzymes (Gocze *et al.*, 1999)

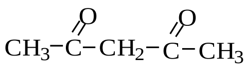
1.3 Active methylene compounds:

For the acidity of the C-H bond in some substances like nitro, carbonyl, cyano, sulfone or phenyl (groups) they are often called active methylene compounds. In some molecules there are H atoms that adjacent to 2 carbonyl groups, extra resonance stabilization of the enolate anions makes these H atoms more acidic than hydrogens adjacent to a single carbonyl group. These compounds are some times called active methylenes (Smith and Gristal, 1966).



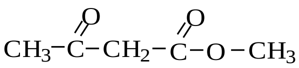
1,3-diketone

Some common active methylene compounds are shown bellow

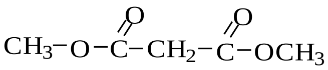


$$CH_3-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-CH_3$$

β-diketone



$$CH_3-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-O-CH_3$$



$$CH_3-O-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OCH_3$$

dimethyl malonate

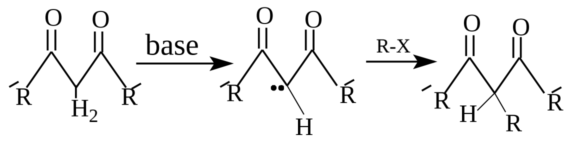
(Fuson *et al.*, 1950).

These compounds are useful synthetic intermediates, their enolates can be formed readily and can be alkylated. Active methylene compounds participate in conjugate addition reactions under basic conditions, this general process is called the Michael reaction. Active methylene compounds are easily deprotonated using alkoxide bases, when compounds with acidic hydrogens are placed in D_2O the acidic hydrogens exchange with deuterium. The net result of deuterium exchange is that the signal due to the acidic hydrogen disappears. From the spectrum this can be useful in assigning peaks in the NMR spectrum. The acidity of an active methylene compound is increased about 2 pK units by electron withdrawing chloro or bromo substituents and is decreased, about 1 to 2 pK units by an alkyl substituent.

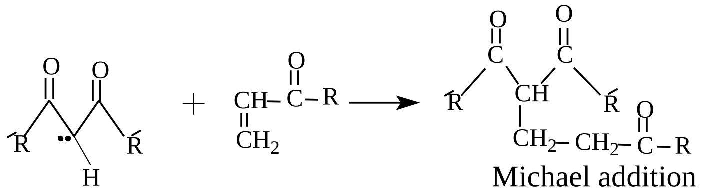
1.3.1 Reactions of active methylene compounds:

There are 3 potentially important reactions for active methylene compounds.

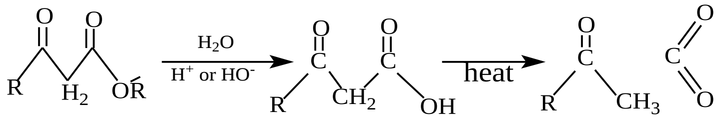
- Alkylation by alkyl halides.
- Conjugate addition : α, B unsaturated carbonyls.
- Loss of CO_2 : (decarboxylation).



alkylation



Michael addition

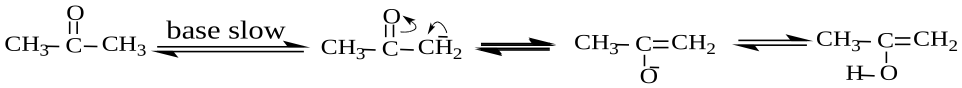


Decarboxylation

(Wheland .1949).

1.3.2. The formation of enoles and enolate anions:

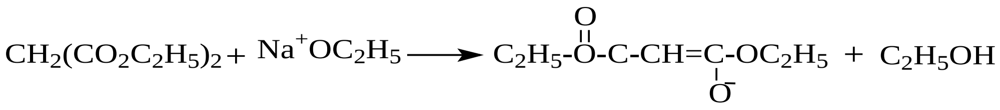
Reaction of anions derived from active methylene compounds constitutes avery important and synthetically useful class of organic compounds. The most common reactions of this class are those in which the anion has been derived by removal of a proton from the carbon atom alpha to the carbonyl groups. These anions, usually called enolate anions, are to be distinguished from enols which are present in equilibrium with the carbonyl compounds in the presence of either acidic or basic catalysts, (Bell, 1959).



$$CH_3-\overset{O}{\overset{\|}{C}}-CH_3 \xrightleftharpoons{\text{base slow}} CH_3-\overset{O}{\overset{\|}{C}}-\overset{-}{C}H_2 \rightleftharpoons CH_3-\underset{O^-}{C}=CH_2 \rightleftharpoons CH_3-\underset{H-O}{C}=CH_2$$

1.3.3 Alkylation of relatively acidic active methylene compounds:

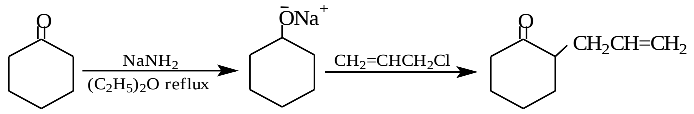
The methylene groups activated by a single nitro group or by two or more carbonyl ester or cyano groups are more acidic than the common aliphatic alcohols. As a result, compounds of these types may be converted in a large part to their enolate (or analogous) anions, by treatment either with relatively strong bases, in a protic solvent or with an anhydrous alchohol (Cope *et al.*, 1957).



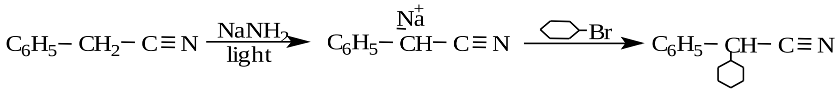
$$CH_2(CO_2C_2H_5)_2 + Na^+OC_2H_5 \longrightarrow C_2H_5\text{-}\overset{O}{\overset{\|}{C}}\text{-}C\text{-}CH{=}\underset{O^-}{\underset{|}{C}}\text{-}OC_2H_5 + C_2H_5OH$$

1.3.4 Alkylation of ketones and nitriles

A strong base like sodium ethoxide and a less acidic solvent than ethanol are be useful in order to obtain an appreciable concentration of an anion from a methylene group activated only by a nitrile or ketone function, alternatively, much stronger bases will convert either ketones or nitriles quantitutively to their corrrsponding anions



(Vander Werf *et al.*, 1955)

(2) 

(Hancock and Scope, 1955)

1.3.5 The Michael reaction

The nucleophilic addtion of enolate anions to the carbon-carbon double bonds of α-, β-unsaturated ketones, aldehydes, nitriles or carboxylic acid derivatives is a process known as the Michael reaction (Bergmann *et al.*, 1959), constitutes a method for the alkylation of active methylene compounds.

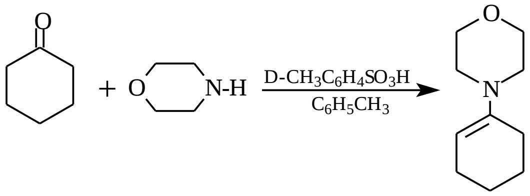
$$CH_2(CO_2C_2H_5)_2 + CH_2{=}CH\text{-}CN \xrightarrow[C_2H_5OH]{NaOC_2H_5} N{\equiv}C\text{-}\underset{\ominus}{C}H\text{-}CH_2\text{-}CH(CO_2C_2H_5)_2 \rightleftharpoons$$

$$N{\equiv}C\text{-}CH_2\text{-}CH_2\text{-}\overset{\ominus}{C}(CO_2C_2H_5)_2 \longrightarrow N{\equiv}C\text{-}CH_2\text{-}CH_2\text{-}CH(CO_2C_2H_5)_2$$

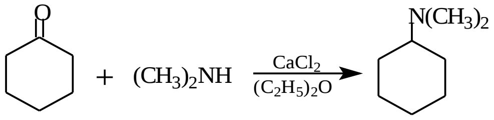
(Albeston and Fillman, 1949)

1.3.6 The formation and alkylation of enamines

An indirect, but widely used procedure for the selective alkylation of an aldehyde or a ketone involves the initial reaction of the carbonyl compound with a secondary amine to form an intermediate enamine (Strok *et al.*, 1963). Typical enamine preparations are outlined in the accompanying equations.It will be noted that the less highly substituted enamine is usually the predominant product, unless the enamine function is stabilized by conjugation with an adjacent function such as carbonyl group (Meyers *et al.*, 1969).



(Hunig *et al.*, 1961)



(Blan Chard, 1963)

1.4 Aim and Objectives

The current work aimed at synthesizing certain hetrocycles containing two nitrogens through the 1,3-dicarbonyl route. The essential purpose is that, the dicarbonyl compound is derivatized with a diazo functionality prepared from a group of sulphonamides or amines of known biological activity. The synthesis is then completed by the closing ring with certain hydrazine derivatives. These compounds are proposed to be worked from the suitable disconnection of the target pyrazoles and barbiturates

The main objective of this work is to test the different suitable routes for such a synthesis, and to identify the compounds prepared through different routes.

The identity of the prepared compounds can be elucidated by spectroscopic means , (UV ,IR ,NMR, MS).

Suitable reaction mechanisms and the disconnection protocols can be proposed for each reaction and composing one of the aims of this project.

One of the objectives of this work is to test for possible biological activities of the prepared compounds towards certain micro organsims