بسم الله الرحمن الرحيم

Sudan University of Science and Technology

The College of Graduate Studies

Synthesis and Biological Activity of some New Ketonic and Phenolic Mannich Bases

التصنيع و الفعالية الأحيائية لبعض قواعد مانيخ الفينولية و الكيتونية الجديدة

A Thesis Submitted In Fulfillment for the Requirements of the Master Degree in Chemistry

By

Samual Alhadi Jar Alnabi Ahmed

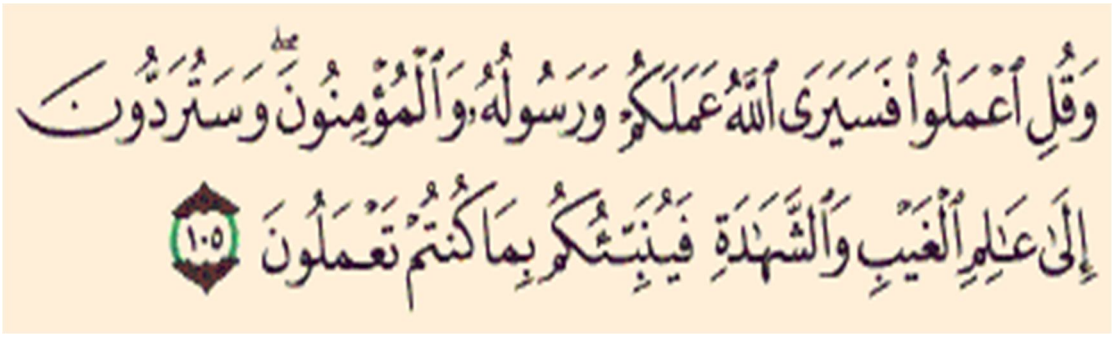
(B.Sc. Education, Chemistry - Higher Diploma in Chemistry)

(SUST)

Supervisor:

Prof. Mohamed Abdel Karim Mohamed

December, 2014



صدق الله العظيم

(التوبة ١٠٥)

Dedication

Dedicated to:

My Parents

Sisters and Brothers

Acknowledgement

I would like to thank Allah Almighty for giving me strength and will to accomplish this study.

I would like to Thank my supervisor Prof. Mohamed Abdel Karim for advice and valuable comments.

I would also like to thank the University of Holy Quran for offering me a scholarship.

Thanks are extended to the staff of the Central Lab. , University of Khartoum for the spectral measurements.

I would also like to thank the Department of Chemistry, Sudan University of Science and Technology for all the facilities.

Thanks are also extended to my family for their infinite support.

Abstract

This study was aimed to the synthesis of some ketonic and phenolic Mannich bases . The biological activity of the targeted molecules are be evaluated.

A General synthesis protocol was adopted, The active hydrogen component, formalin and a secondary amine were refluxed in ethanol for one hour to afford the Mannich base .In this way the following Mannich bases were synthesized:

i) 1-hydroxymethyl-1-piperidinomethyl-2-naphthylacetate

ii) 1,1-dimorpholinomethyl-2-naphthylactate

iii) 1,1-dimethylaminomethyl-2-naphthylactate

iv) 1,1-dimethylaminomethyl(2-aminophenyl)acetate

v) 1,3-dibenzylidine-3-hydroxymethyl-1-morpholinomethylpropanone

vi) 2-hydroxy-3,6-bis-dimethylaminomethylbenzoic acid

vii) 2-hydroxy-bis-3,5-piperidinomethylbenzoic acid

viii) 1-piperidinomethyl-3-phenylpropanone

ix) 3,3-bis-piperidinomethylpentan-2,4-dione

The targeted molecules were evaluated for their antimicrobial activity against six standard human pathogens and significant results were obtained. The biological activity of synthesized Mannich bases was adopted against four types of bacteria (+ve and –ve Gram stain) and two types of fungi. There micro organisms are:

i) *Bacillus subtilis* (G^{+ve})

ii) *Escherichia coli* (G^{-ve})

iii) *Staphylococus aureus* (G^{+ve})

iv) *Pseudomonas aeruginosa* (G^{-ve})

v) *Aspergillus niger* (fungi)

vi) *Candida albicans* (fungi)

The synthesized Mannich bases which prepared from Salicylic acid and Acetophenone were showed higher biological activity against tested micro organisms by comparison with other synthesized Mannich bases.

الخلاصة

تهدف هذه الدراسة الى تصنيع عدد من قواعد مانيخ الكيتونية والفينولية ، ثم دراسة اثرها البيولوجى. استخدمت طريقه عامه لتصنيع هذه القواعد حيث سخن مركب الهيدروجين النشط ، الفورمالين والأمين لمده ساعة تحت التقطير الانعكاسي فى الايثانول ليعطى النواتج. بهذه الطرقه تم تصنيع :

i) 1-hydroxymethyl-1-piperidinomethyl-2-naphthylacetate

ii) 1,1-dimorpholinomethyl-2-naphthylactate

iii) 1,1-dimethylaminomethyl-2-naphthylactate

iv) 1,1-dimethylaminomethyl(2-aminophenyl)acetate

v) 1,3-dibenzylidine-3-hydroxymethyl-1-morpholinomethylpropanone

vi) 2-hydroxy-3,6-bis-dimethylaminomethylbenzoic acid

vii) 2-hydroxy-bis-3,5-piperidinomethylbenzoic acid

viii) 1-piperidinomethyl-3-phenylpropanone

ix) 3,3-bis-piperidinomethylpentan-2,4-dione

أخضعت القواعد المصنعه لاختبارات الفعالية ضد الميكروبات وتم الحصول على نتائج جيده ، حيث اختبرت الفاعلية البيولوجية لقواعد مانيخ ضد أربعة أنواع من البكتريا موجبة و سالبة الجرام و نوعين من الفطريات و هي:

i) *Bacillus subtilis* (G^{+ve})

ii) *Escherichia coli* (G^{-ve})

iii) *Staphylococus aureus* (G^{+ve})

iv) *Pseudomonas aeruginosa* (G^{-ve})

v) *Aspergillus niger* (fungi)

vi) *Candida albicans* (fungi)

أظهرت قواعد مانيخ التي تم تحضيرها من حمض السالسيلك و الأسيتوفينون نشاطية بيولوجية عالية ضد كل من البكتريا و الفطريات التي تم اختبارها مقارنة بقواعد مانيخ التي تم تحضيرها من بقية المتفاعلات.

List of Contents

Chapter One

1-Introduction

Chapter Tow

2-Material and Methods

Chapter Three

3- Result and Discussion

References

Chapter One
Introduction

1. Introduction

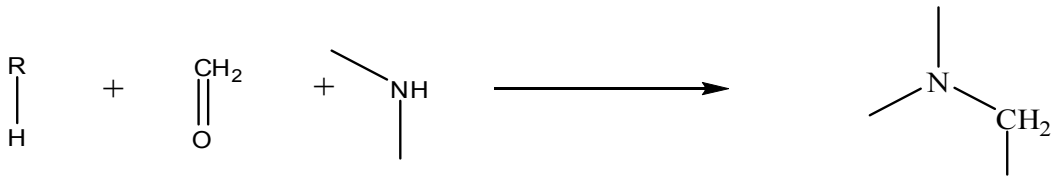
1.1. general approach

The Mannich reaction involves the condensation of formaldehyde with ammonia or a primary or secondary amine with a third compound containing active hydrogen , these compounds are most frequently those in which a methylene group is activated by a neighboring keto group[1,2,3], the Mannich reaction undergo a number of conversions useful in synthesis[4], and the applications of this reaction in synthesis are numerous including: the synthesis of ethylenic compounds, pyrazolines, etc[5,6,7,8].

The compounds which are capable of forming an enol react with imines from formaldehyde and a primary or secondary amine to yield β-amino alkyl carbonyl compounds called Mannich bases[10]

The chemistry of Mannich bases, first studied by Mannich, has been the subject of investigations by an ever increasing number of researchers, several studies which appeared before 1960 together with books by Reichert and by Hellman and Opitz, provide excellent coverage on practically the entire chemistry of Mannich bases up to 1960[1].

The general structure of Mannich reaction can be written as the following:



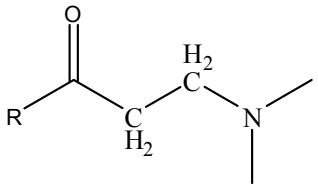
Active Hydrogen Compound | Formaline | Amine | Mannich base

In this equation the product is representing the general form of the Mannich bases[1].

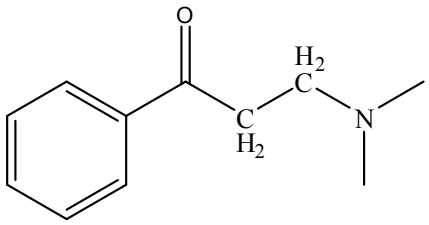
Several Mannich bases possess considerable biological activity, they have several prominent effects such as: anti microbial, anti-mycobacterial, anti-fungal, anti-amoebic, anti-inflammatory, analgesic, anti-depressant, and anti-cancer activities[7,8,9].

The general structure of Mannich bases could be written as the following[1]:

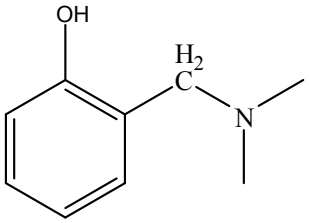
1. C - Mannich bases:



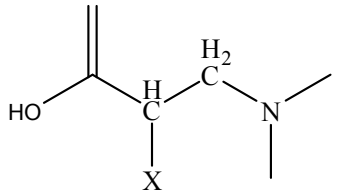
C - Mannich base of aliphatic ketone



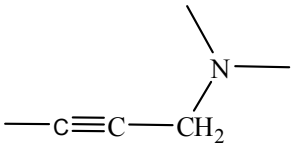
C - Mannich base of aliphatic aromatic ketone



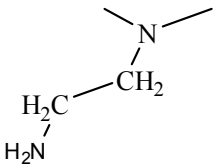
C - Mannich bases of phenols



C - Mannich bases of halides carboxilic acids



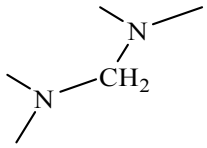
C - Mannich bases of alkynes



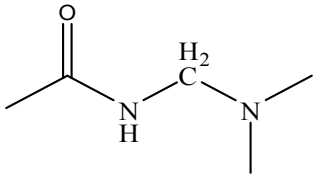
C - Mannich bases of alkyl amines

Heterocyclic compounds which are attached by C atom afford N-Mannich bases:

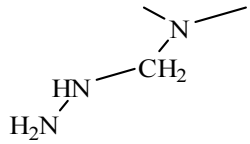
2. N - Mannich bases:



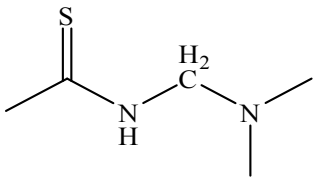
N - Mannich bases of ammonia



N - Mannich B. of amides



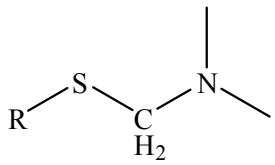
N - Mannich B. of hydrazine



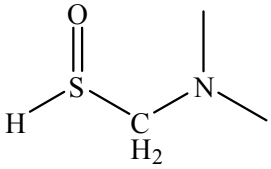
N - Mannich bases of amino sulphide

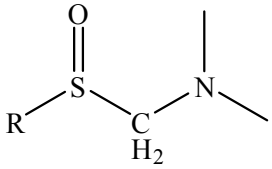
Heterocyclic compounds which are attached by S atom afford:

3. S - Mannich bases:

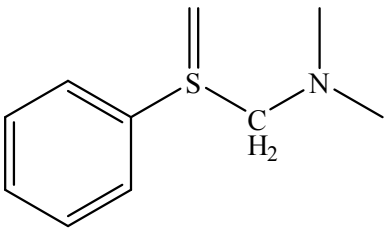


S - Mannich bases of sulphide

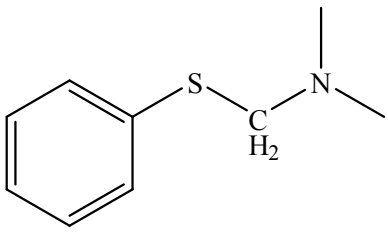




S - Mannich bases of sulphoxy compounds



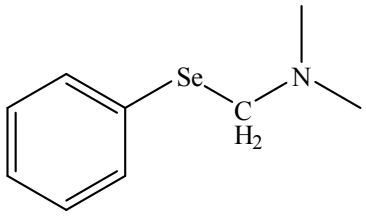
S - Mannich bases of benzo sulphoxy compounds



S- Mannich bases of benzo sulphide

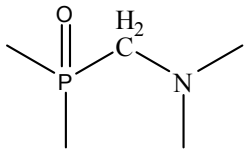
When the heteroatom is selenium or phosphorus , Mannich bases could also be generated:

4. Se - Mannich bases:

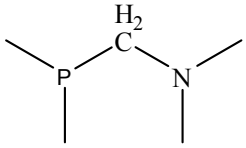


Se - Mannich bases.

5. P - Mannich bases:



P - Mannich bases of phosphoxy compounds

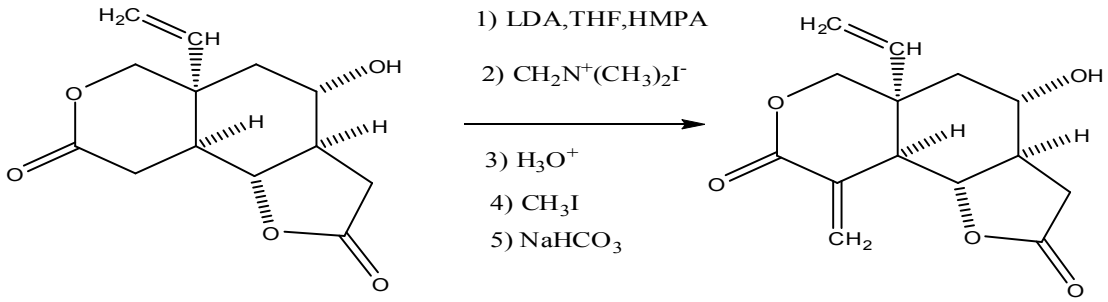


P - Mannich bases of phosphide compounds

Mannich reaction could occur by many routes; three component Mannich reaction (asymmetric Mannich reaction; direct Mannich reaction) represent the type of intermolecular reactions , while intramolecular reactions represent a non classical Mannich reaction. [4,11 ,12]

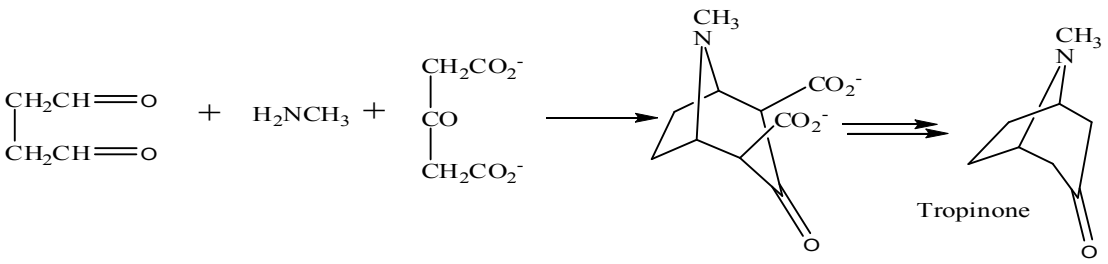
Mannich bases from a ketone , formaldehyde , and dialkyl amine follow the classical procedure[4], alternatively formaldehyde equivalents may be used ; such as bis-(dimethyl amino) methane. On treatment with trifiuoroacetic acid , this amine generates the imnium trifluoroacetate as a reactive electrophile . N,N-(dimethyl) methylene ammonium iodide is commercially available and is known as Eschenmoser's salt[4, 13] , this compound is sufficiently electrophilic to react directly with silyl enol ethers in neutral solution[4, 14] .The reagent can be added to a solution of an enolate or enolate precursor , which permits the reaction to be carried out under non acidic conditions; the reaction of ester enolates with N,N-(dimethyl) methylene ammonium trifluoroacetate or Eschenmoser's salt

has been used for introduction of the α-methylene group in the synthesis of vernolepin ; a compound with anti-leukemic activity.[4]



Vernolepin

Mannich reactions , or a mechanistic analog , are important in the biosynthesis of many nitrogen – containing natural products , as a result , the Mannich reaction has played an important role in the synthesis of such compounds ; especially in synthesis patterned after the biosynthesis , i.e. , biomimetic synthesis[4, 15] , the earliest example of the use of Mannich reaction in this way was Robinson's successful synthesis of tropinone ; a derivative of the alkaloid tropine in 1917.[4, 16]

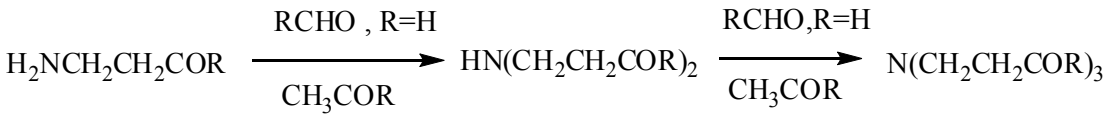


Tropinone

Others types of Mannich reaction such as di alkylation and thermal decomposition are useful in construction of synthetic intermediates products ; di alkylation reaction can be used to advantage in ring closures; and thermal decomposition to produce α,β-unsaturated ketones and

aldehydes which are used as reactants in conjugate addition ; Robinson annulations ; and in a number of other reactions.[4, 15]

The Mannich bases can react further in three ways[10, 17, 18]; if it's a primary or secondary amine , it may condense with one or two additional molecules of aldehydes and active compound , e.g.:

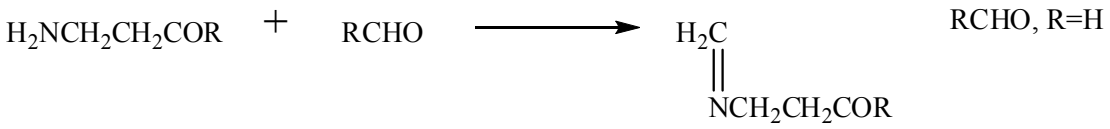


$$H_2NCH_2CH_2COR \xrightarrow[CH_3COR]{RCHO,\ R=H} HN(CH_2CH_2COR)_2 \xrightarrow[CH_3COR]{RCHO,R=H} N(CH_2CH_2COR)_3$$

If the active hydrogen compound has two or three active hydrogen , the Mannich base may be condense with one or two additional molecules of aldehydes or amine , e.g.:

$$H_2NCH_2CH_2COR \xrightarrow[NH_3]{RCHO,\ R=H} (H_2NCH_2)CHCOR \xrightarrow[NH_3]{RCHO,\ R=H} (H_2NCH_2)CCOR$$

Another further reaction consists of the condensation of the Mannich base with excess formaldehyde , e.g.



Some side reactions often occurring in Mannich synthesis are the formation of methylene - bis - derivatives , deamination and decarboxylation [1, 17] by- products have been identified in some instances. They may be formed by some change of the reaction product itself , or they may be produced by condensation of the formaldehyde with the amine or ketone[17]. Thus, di ethylamine may be converted to N,N`-tetraethyl methylene diamine[17, 19], and piperidine to methylene di-piperidine[19, 20] . From a reaction involving cyclohexanone ; there have been isolated 2- methylene cyclohexanone and di (2- cyclohexanonyl

methyl) ether[17, 21]. Similarly, methylene di -β-naphthol [17, 22]and methylene diantipyrine[19,23] have been produced in reactions involving β-naphthol and antipyrine , respectively .

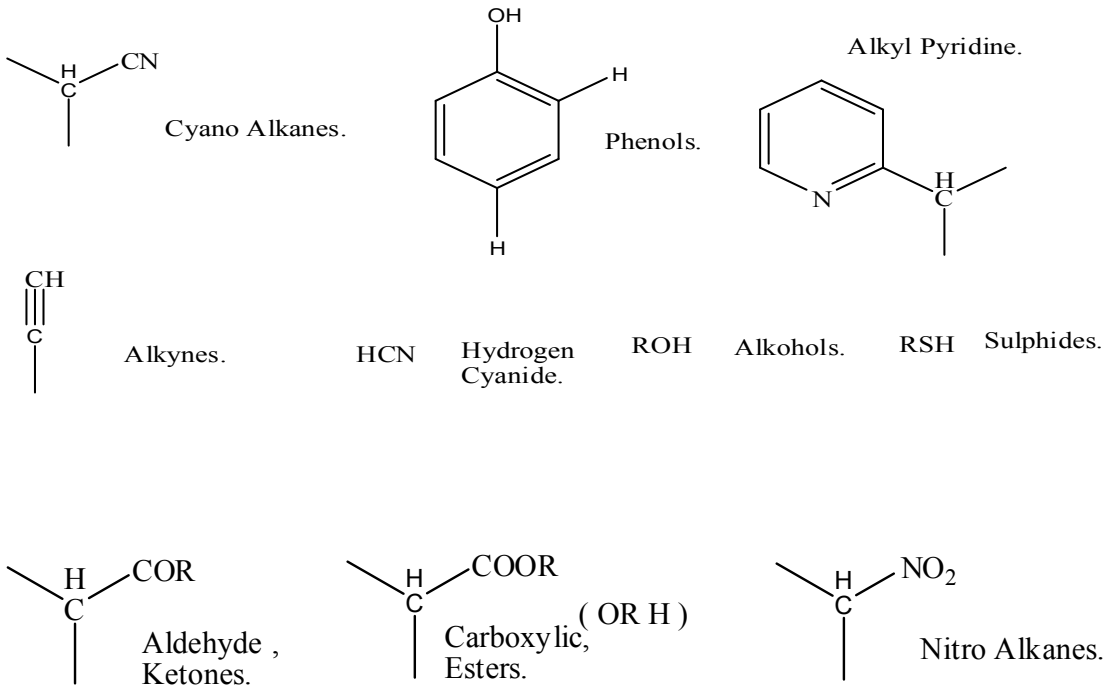
The using of catalysts in Mannich reaction have been established , especially ; asymmetric Mannich reactions .This recent progress have been called (Organocatalystic) ; the research about this progress have been developed and utilized to overcome accomplishment in Mannich synthesis[24].

1.2. The Scope of the Mannich reaction

Scope of the Mannich reaction involve the details about reactants, reagents , conditions , mechanism and related reactions ; all of this terms were studied and reported intensively.

1.2.1. The reactants in the Mannich reaction

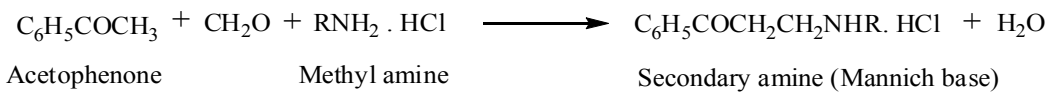
Mannich reaction represent some reactions which are called (three component or multi component reactions) , thus ; primary or secondary amines , ammonia or its salts , formaldehyde and compounds which involve one or more active hydrogen atoms are condensed to give products which are called (Mannich bases) .The following compounds are represent some active hydrogen components.[1, 4, 8, 10,17]

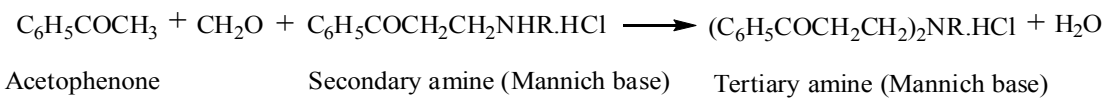


1.2.1.1. Ketones

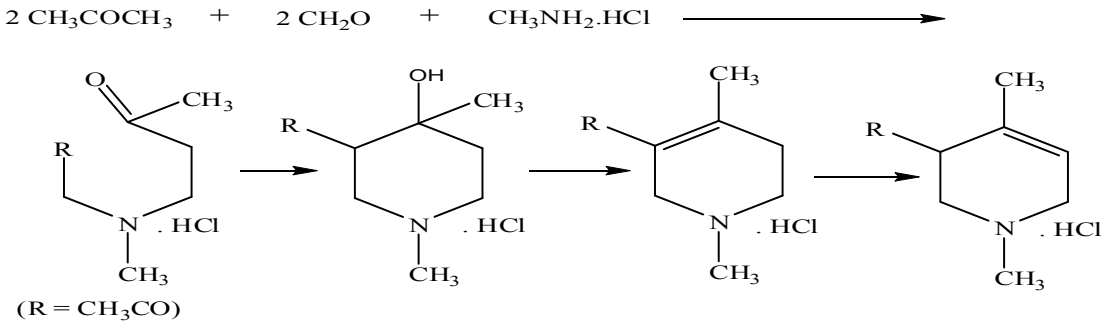
Many types of ketones can be condensed with amines and aldehydes (especially formaldehyde) to give corresponding Mannich bases ; such as saturated ketones ,aliphatic aromatic ketones , including those in which the aromatic ring is heterocyclic and certain heterocyclic ketones containing a carbonyl group in ring.[1, 17]

When a primary amine or its salt is used in a Mannich reaction the first product is a secondary amine , but this often react with more of the reagents to give a tertiary amine.[17]

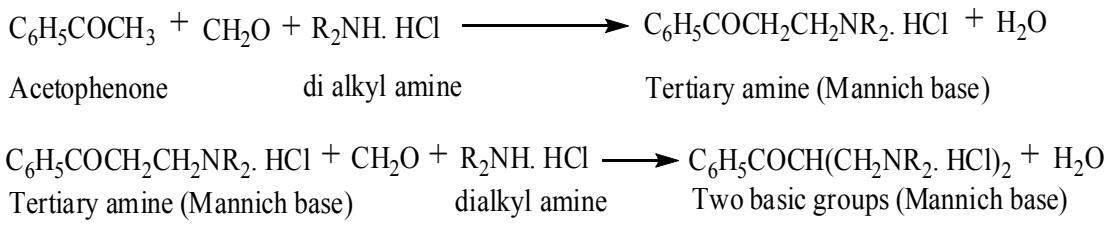




aliphatic ketones and primary amines give rise to a number of products ; products which are derived from two molecules of ketone , two molecules of formaldehyde , and one molecule of primary amine are unstable and readily undergo cyclization. The compounds obtained from acetone ,formaldehyde and methyl amine are illusterated.[1,17,25]



When a secondary amine or its salt is used in Mannich reaction the first product is a tertiary amine , the product from a methyl ketone containing reactive hydrogen atoms , in some cases, may carry the reaction one step further , yielding a compound with two basic groups.[1,17]

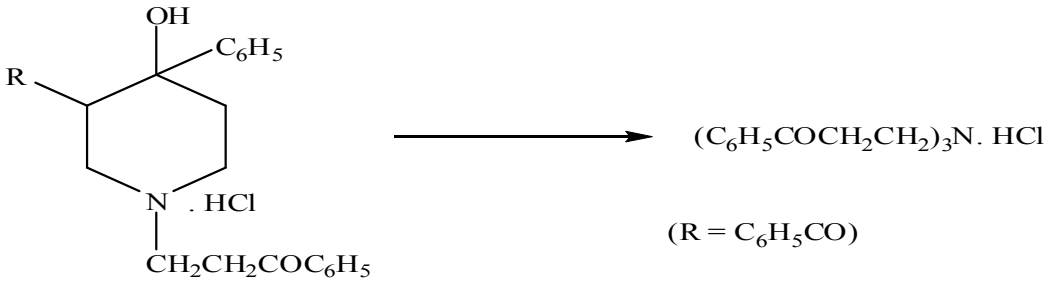


Also a primary amine is the first product to be expected from a Mannich reaction in which ammonia or an ammonium salt and formaldehyde react with a compound containing an active hydrogen atom, with the simple ketones subsequent reaction of the primary amine so formed usually leads to the production of tertiary amines, salts of certain of these primary and secondary amines have been isolated and found to be stable , but the free bases change to the tertiary amines, the dis proportionation of the primary and secondary amines obtained from acetophenone, formaldehyde and ammonia is an example.[17, 26]

$$3\,C_6H_5COCH_2CH_2NH_2 \longrightarrow (C_6H_5COCH_2CH_2)_3N + 2\,NH_3$$

$$3(C_6H_5COCH_2CH_2)NH \longrightarrow 2(C_6H_5COCH_2CH_2)_3N + NH3$$

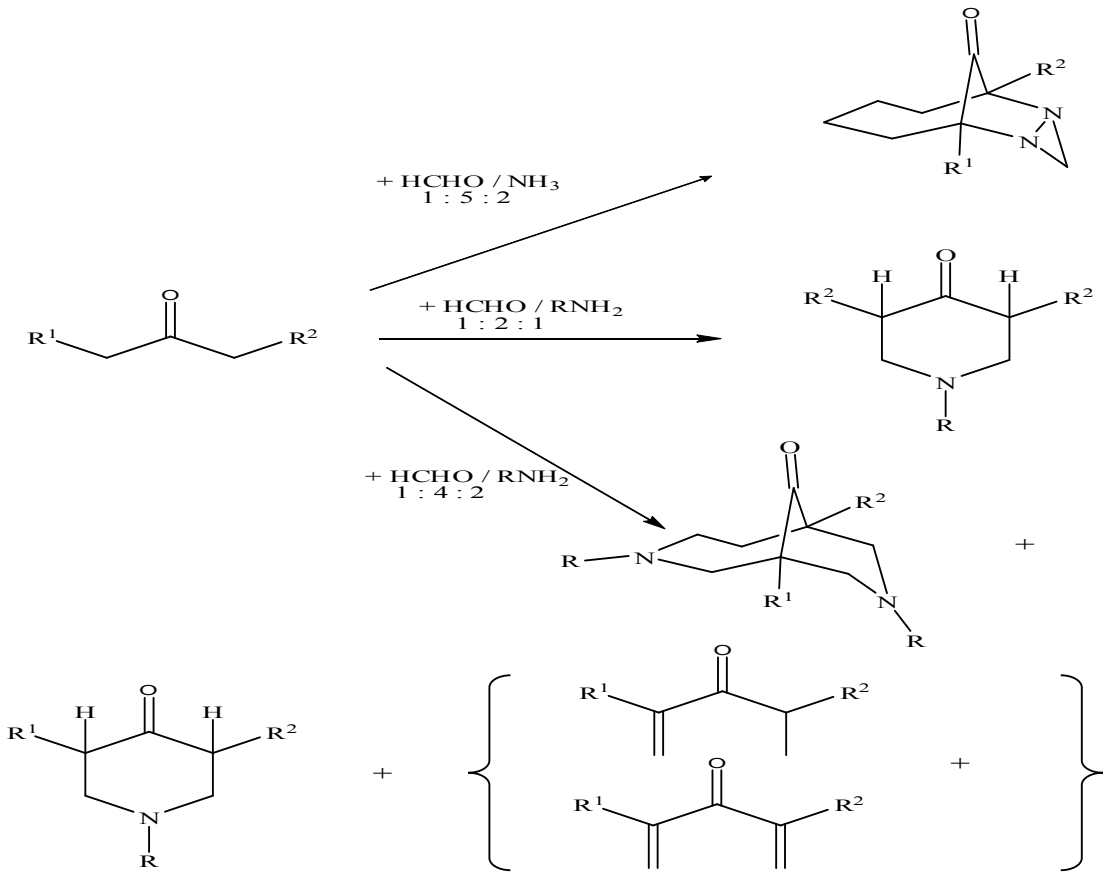
In some instances cyclic products are obtained from ketones, ammonia and formaldehyde ; from acetophenone , ammonium chloride , and formaldehyde there has been isolated a substance which is believed to be a substituted piperidine,[17,26] It readily changes to the salt of Tri-(β-Benzoyl ethyl)-amine.[17, 27]



With cyclohexanone the tertiary amine is obtained directly[17, 28], in analogy with the reaction of anti pyrine[17, 28, 21], the formation of cyclic products derived from methylamine , by reaction of acetone, formaldehyde, and ammonium chloride has been mentioned . The

reaction with diethyl ketone takes a similar course, producing a tri methyl piperidone[17].

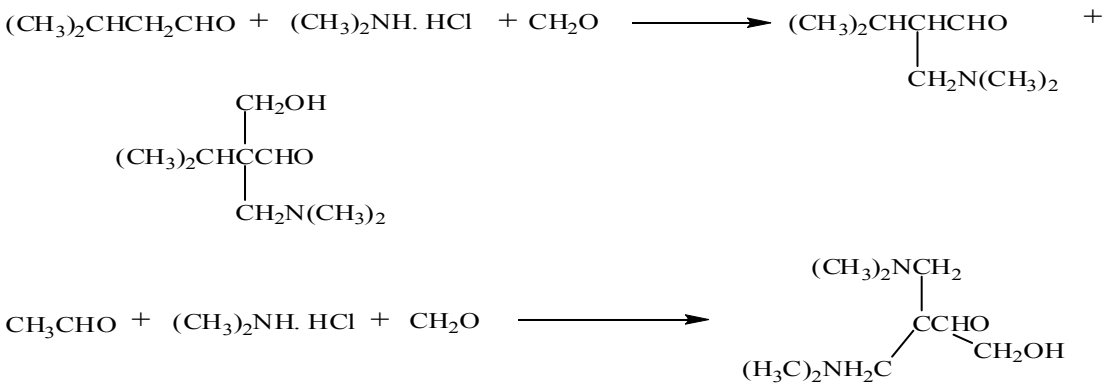
Dialkyl ketones could produce cyclic and bicyclic compounds when condensed with ammonia and primary amine and formaldehyde by use of different molar ratios of each ; here the bulky o-substituted alkyl groups can orient the Mannich condensation.[1]



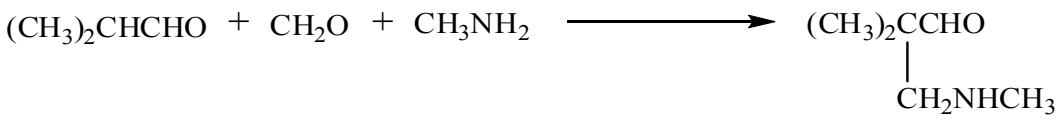
1.2.1.2. Aldehydes

The behavior of aldehydes in the Mannich reaction is similar to that of ketones , the α-hydrogen atom of the aldehydes is substituted by a dialkyl amino methyl group .A secondary reaction which sometimes occurs

involves the simultaneous introduction of a methylol group on the α-carbon atom.[1, 17, 29]

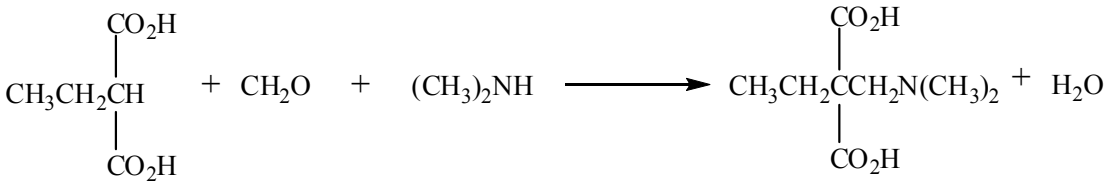


For the condensation of aldehydes with primary amines ; apparently the only known reaction involving an aldehyde , a primary amine , and formaldehyde is that of iso butyraldehyde and methyl amine.[17, 30]

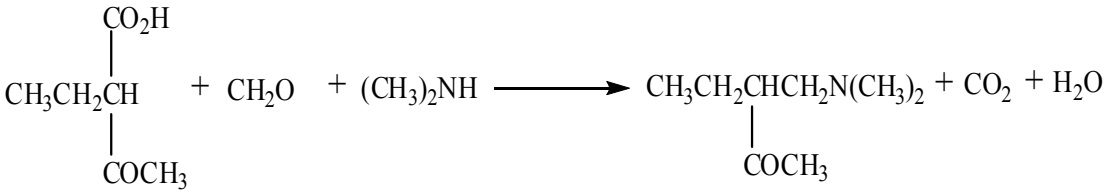


1.2.1.3. Acids and esters

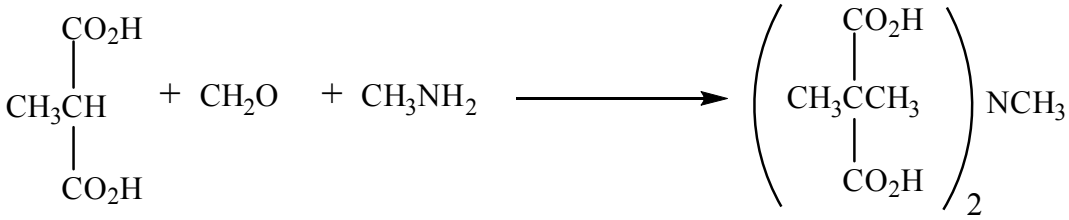
A number of acids containing highly active hydrogen atoms in the α-position can be used instead of aldehydes or ketones , the replacement of a lone active hydrogen atom is illustrated.[17, 31]



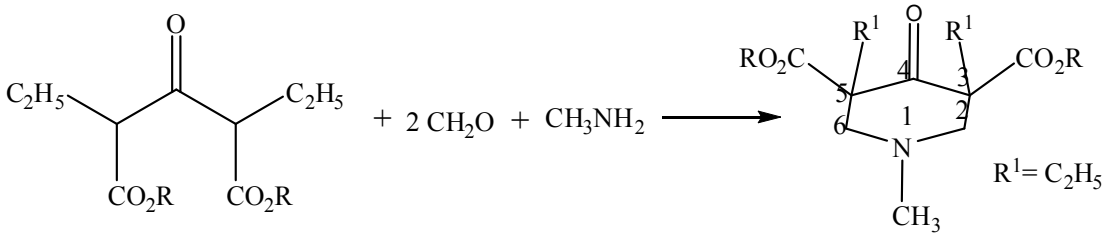
A side reaction which often occurs involves the decarboxylation of the acid.[17, 32]



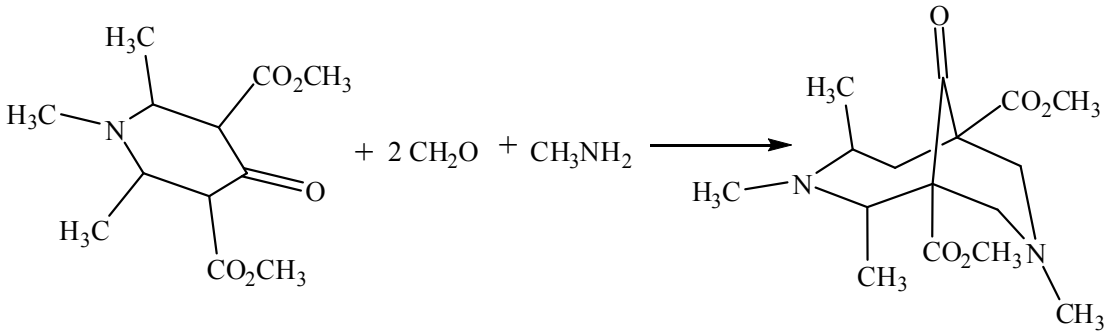
The Mannich reaction of primary amines with acids containing active hydrogen atoms leads to the same types of compounds as described above in connection with secondary amines, as might be expected ; the first product often undergoes further condensation to form a tertiary amine, the reaction of methyl malonic acid, formaldehyde, and methyl amine is an example.[17, 33]



When a primary amine is used with a poly carbonyl compounds which contains reactive hydrogen atoms located in 1,3- positions with respect to each other, the cyclic products may be expected , thus; esters of α,α-diethylacetone di- carboxylic acid react with formaldehyde and methyl amine to give pyridones.[17, 34]

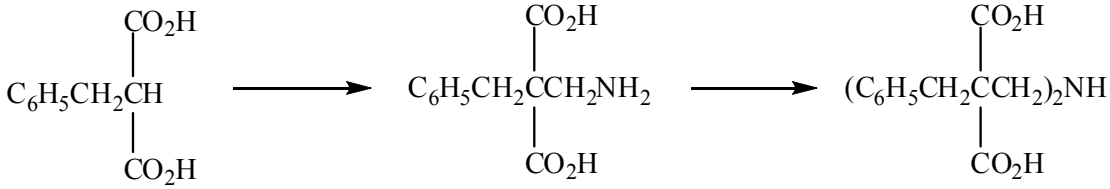


If the pyridone contains hydrogen atoms on 3- and 5- carbon atoms , the condensation may be carried one step further and a bicyclic system may be produced, for example ; the pyridone obtained by a reaction of the Mannich type from methyl acetone di carboxylate , aldehyde , and methyl amine can be condensed with formaldehyde and methyl amine.[17, 35]

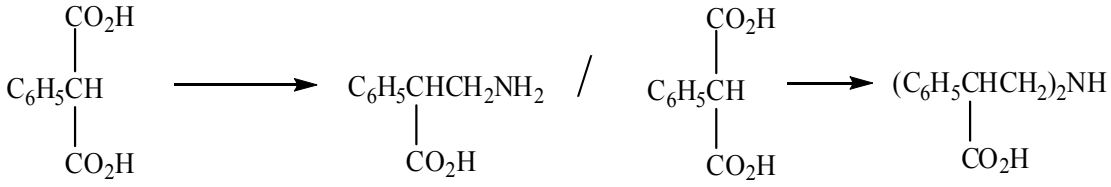


The name (bispidin) has been suggested for the bicyclic ring system produced in such reactions.[17, 35, 36], also this reaction can be used to build up tricyclic systems.[19]

From the reaction of benzyl malonic acid, ammonia, and formaldehyde both a primary amine and a secondary amine have been isolated.[17, 31]



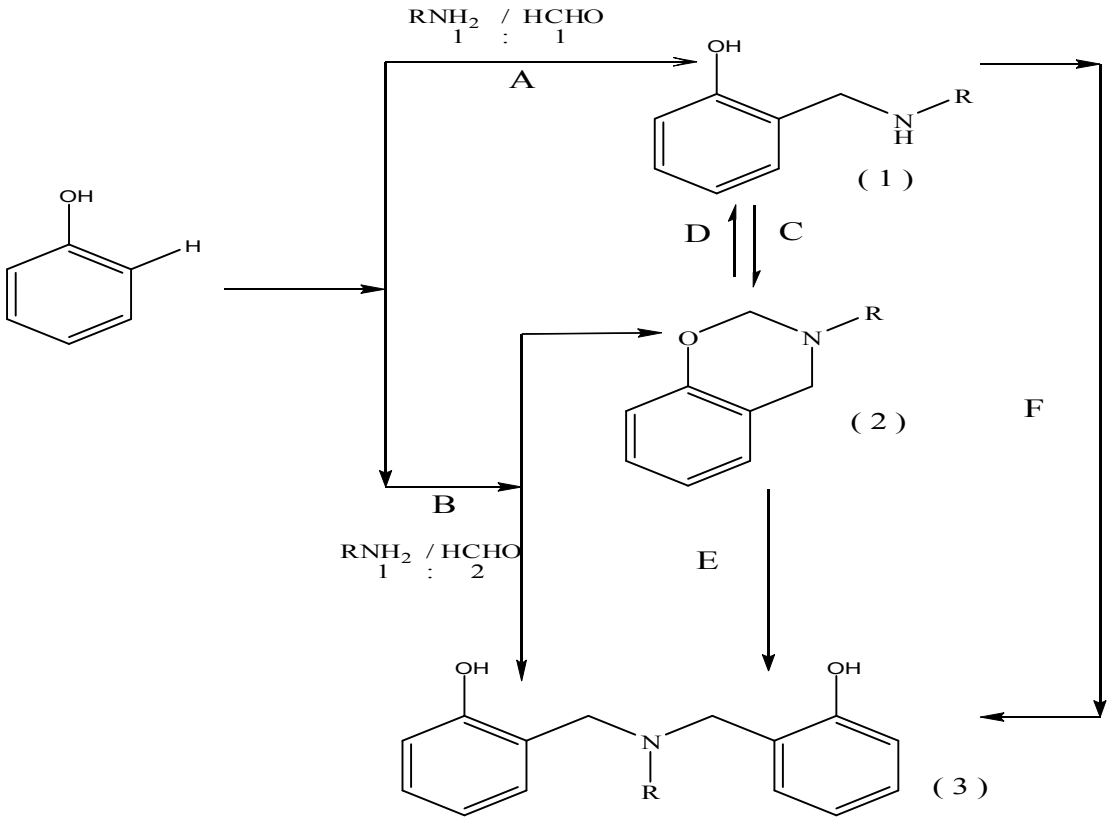
In the case of phenyl malonic acid a primary amine is produced and decarboxylation occurs when ammonia is used. When ammonium chloride is employed the decarboxylated secondary amine is obtained[17,31]



1.2.1.4. Phenols

The o- and p- hydrogens in phenols are sufficiently active to enter into the Mannich reaction, thus; products from phenol[17, 37, 38, 39], 4-acetaminophenol[17, 37], o- and p- cresol[17, 38], m- cresol[17, 39], 3,5- dimethyl phenol[17, 40], 2- methyl-4-ethylphenol[17, 38], 2- and 4- methoxy phenol, β-naphthol[17, 41], and 8- hydroxyquinoline[17, 37]with formaldehyde and dimethyl amine or piperidine or morpholine have been reported. From p-cresol a mono- and a di substitution product are obtained, and from phenol and m- cresol tri substitution products.[17]

Variously substituted phenols and naphthols, as well as phenols condensed with cycloalkanes or heterocyclic rings which are commonly used in the Mannich reaction, with a few exception, aminomethylation always occurs at the position ortho- to the hydroxy group, even if the para- position is unoccupied, primary amines can react to give various products, as shown by the following scheme[1]:



One or both of the amine H- atoms (pathways A and B respectively) can be substituted by use of the appropriate reaction conditions, path (A) gives secondary bases (1) directly, but the reaction involving acid hydrolysis of dihydrobenzoxazine (2) (path D) is often preferred, pathway (B) usually gives compounds (2) rather than bis-[2-hydroxybenzyl]-amines(3), for this reason; the latter products are best obtained via path (F) leading to bis-[2-hydroxybenzyl]-amine (3) and using compounds (1) as starting materials, is only practicable if (R) represents a linear or singly branched alkyl group, when (R) is a bulky group (e.g., t-butyl or t-octyl), the reaction follows path (C) and the oxazine derivatives (2) is obtained together with considerable amounts of the corresponding o,o- di hydroxy di aryl methane (e.g., bis-[2-hydroxy-1-naphthyl] methane) from 2-naphthol. [42]. In the following the conditions of these pathways are shown:

pathway (A): phenol, amine, and aqueous formaldehyde were refluxed in ethanol for 24hr. , the mixture was then allowed to stand at room temperature for another 24hr.[1, 43]

pathway (B): amine and formaldehyde were refluxed in di oxane for 24hr., the phenol was then added and the mixture refluxed for another 12 hr.[1, 43]

pathway (C): amino methyl phenol and aqueous formaldehyde were refluxed in iso propanol for 1hr.[1, 43]

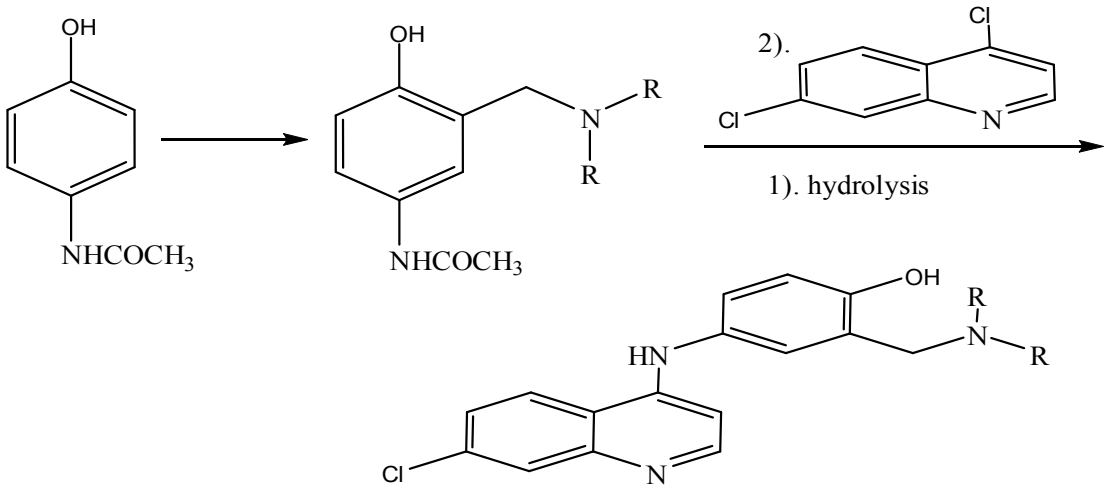
pathway (D): dihydrobenzoxazine was heated in ethanol/conc. hydrochloric acid (2 : 1)[1, 44], or with half conc. hydrochloric acid.[1, 49]

pathway (E):dihydrobenzoxazine and a suitable phenol were mixed without solvent or with a little ethanol and the mixture was allowed to stand at room temperature for 1-2 days.[1, 45]

pathway (F): the hydrochloride of the secondary amine was suspended in water and an ethereal solution of ethanol amine was added with stirring, the free base was isolated and warmed at 60ºC in 95% ethanol for 5 min, the product was crystallized on cooling.[1,42]

The influence of functional substitution of the Mannich reaction in the case of phenols is complex; in addition, the reaction conditions play an important role, thus; 2-(2-hydroxy phenyl)- benzamidazole is amino methylated at the phenolic benzene nucleus rather than at the heterocyclic NH group; on the other hand, salicylamides first react at the amide group and only subsequently at the position ortho- to the phenolic hydroxy group[1, 46]. 4-Acetamidophenol is only amino- methylated at the position ortho- to the hydroxy group. The products were used as starting materials

for the synthesis of certain quinoline derivatives possessing anti malarial activity.[1,47]



In the case of binuclear phenols having the hydroxy group in a position (α) to ring fusion, the reaction always proceeds to afford the product of ortho- attack, even if the para- position is free. When the ortho- position (β- to ring fusion) is occupied, the product of para- substitution is obtained, often in good yield.[1, 48, 49]. When the o- substitution (β- to ring fusion) is a hydroxy group, aminomethylation occurs at the position o- to this substituent rather than position p- to the first hydroxy group.[1, 49]

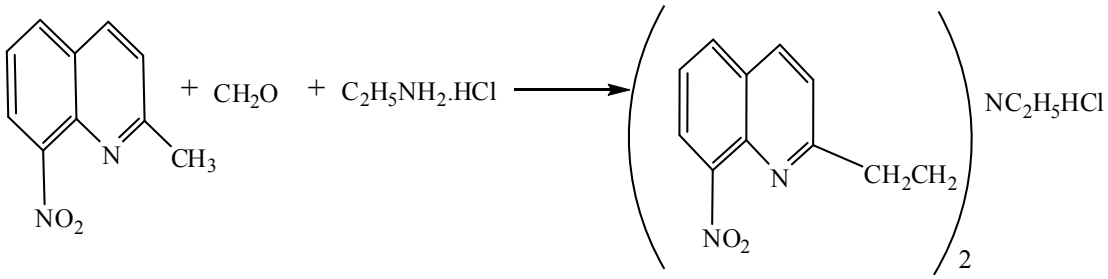
In the case of binuclear phenols having the hydroxy group in a position (β) to ring fusion, the reaction always proceeds in the o- position α- to ring fusion, even if the o,β- position is unoccupied; when the o-α-position is occupied, the reaction occurs at the free o-β- position. However; amino- methylation of β- naphthol with bulky amines (e.g. dicyclohexyl amine) takes place at the o-β- position.[1, 50]

1.2.1.5. Quinaldines and α- picolines

Since an α- methyl group in a pyridine or quinoline nucleus has hydrogens of about the same activity as those in the methyl group of a methyl ketone, the Mannich reaction might be expected to take place with

such molecules. α- Picoline[17, 51], 2- methyl quinoline[17, 51, 52](quinaldine), 2-methyl-4-hydroxy quinoline[17, 52], 2-methyl-8-nitro quinoline and 2-ethoxy-4- methyl quinoline have been condensed with various secondary amines, either as the free amine or as the amine hydrochloride.[17,52]

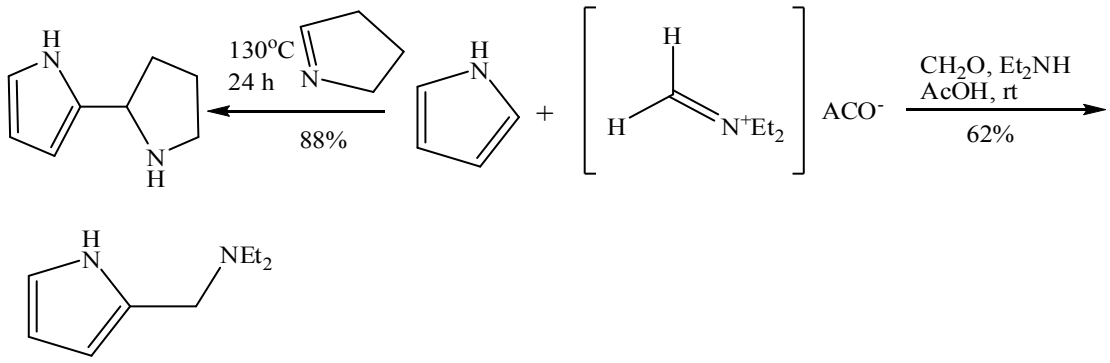
Of the compounds containing a methyl group in the 2- position of a pyridine nucleus only 2- methyl-8- nitro quinoline has been treated with a primary amine and formaldehyde the amine used was ethyl amine and the product was a tertiary amine.[17, 52]



1.2.1.6. Heterocyclic compounds

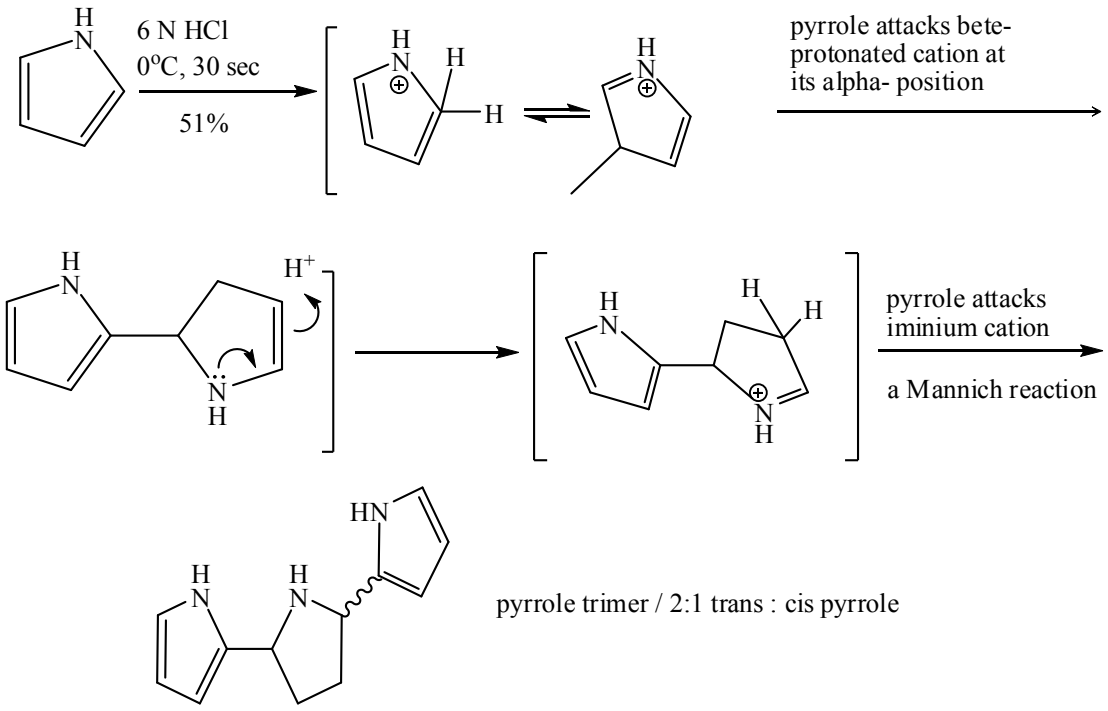
Various heterocyclic compounds were condensed with amines and aldehydes to produce corresponding Mannich bases which were used as a bioactive molecule , the ability of heterocyclic compounds to enter in Mannich reaction is demonstrated below:

The Mannich reaction of pyrrole produces dialkyl amino- methyl derivatives, the iminium electrophile being generated *in situ* from formaldehyde, dialkyl amine and acetic acid[53, 54]. There are only a few examples of the reactions of imines themselves with pyrroles; the condensation of 1- pyrroline with pyrrole as reactant and solvent is one such example[53, 55]. N- Tosyl- imines react with pyrrole with $Cu(otf)_2$ as catalyst.[53, 56]

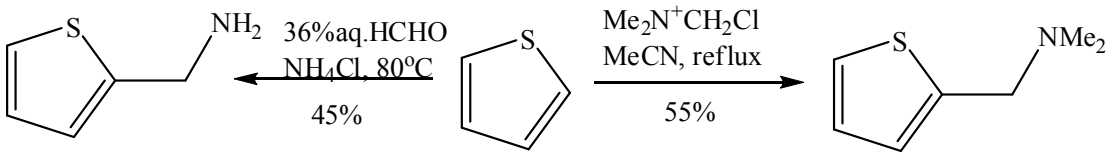


The mineral – acid catalyzed polymerization of pyrrole involves a series of Mannich reactions, but under controlled conditions pyrrole can be converted into an isolable trimer, which is probably an intermediate in the polymerization. The key to understanding the formation of the observed trimer is that the less stable, therefore more reactive, β-protonated pyrrolium cation is the electrophile that initiates the sequence, attacking a second mole equivalent of the heterocycle. The (dimer) an enamine, is too reactive to be isolable, however (pyrrole trimer), relatively protected as its salt, reacts further only slowly.[53, 57]

Aminomethylation of thiophene[53, 58], was reported long before the more common Mannich reaction . Dimethyl amino- methylation – which although it can be achieved under routine conditions with methoxy thiophenes[53, 59], requires the use of ($Me_2N^+CH_2Cl^-$: Eschenmoser's salt) for thiophene and alkyl thiophenes.[53, 60]

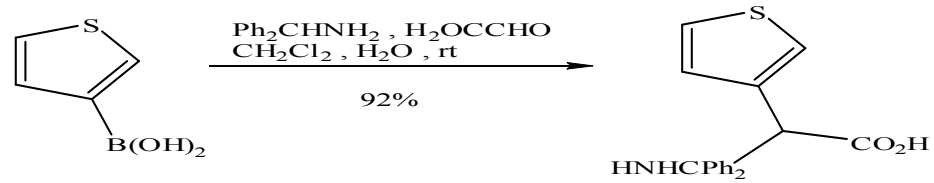


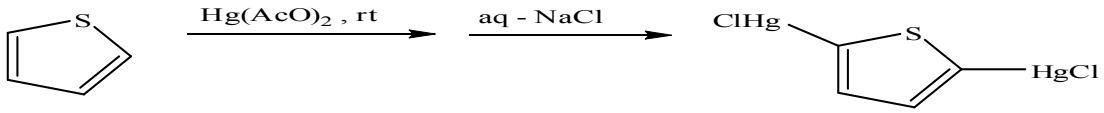
The mineral – acid catalyzed Mannich reaction of pyrrole



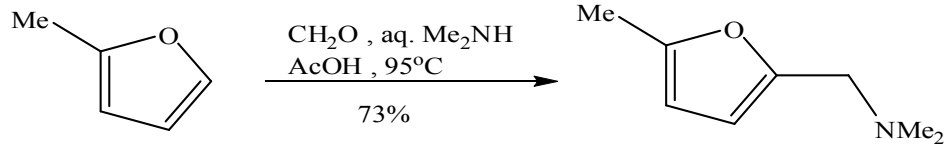
The amino alkylation of thiophene

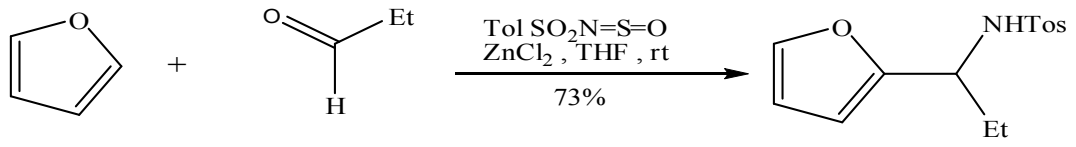
Another device for bringing thiophenes into reaction with Mannich intermediates is to utilize thiophene boronic acids ; primary aromatic amines can also be used as the amine component.[53, 61]

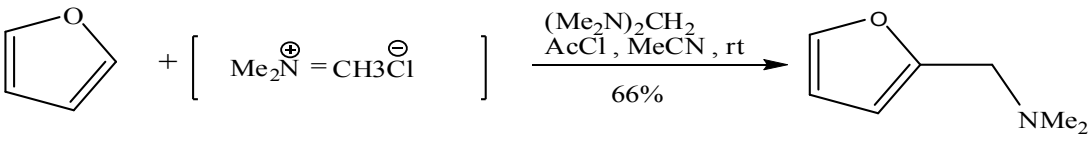


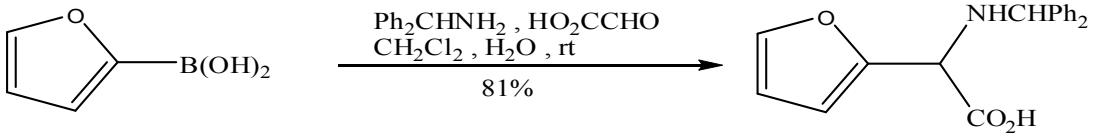


Mono alkyl – furans undergo Mannich substitution under normal conditions[53, 62], but furan itself requires a preformed iminium salt for 2-substitution[53, 63]. N-Tosyl-imines, generated *in situ* from N-sulfinyl-p-toluene sulfonamide and aldehyde, bring about Tosyl amino alkylation at C-2[53, 64]. The use of furan boronic acids allows Mannich substitutions at both α- and β- positions, with primary or secondary amine components.[53,61]

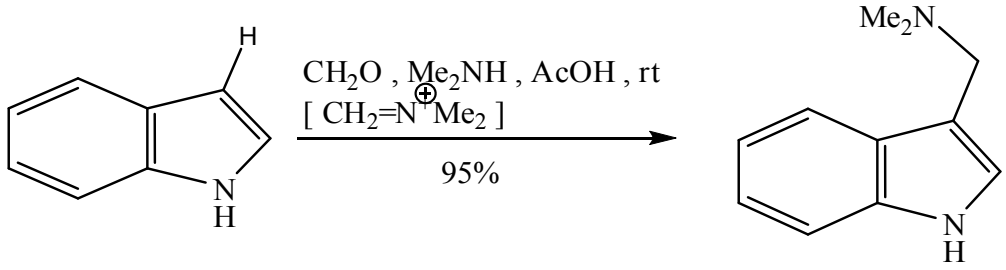




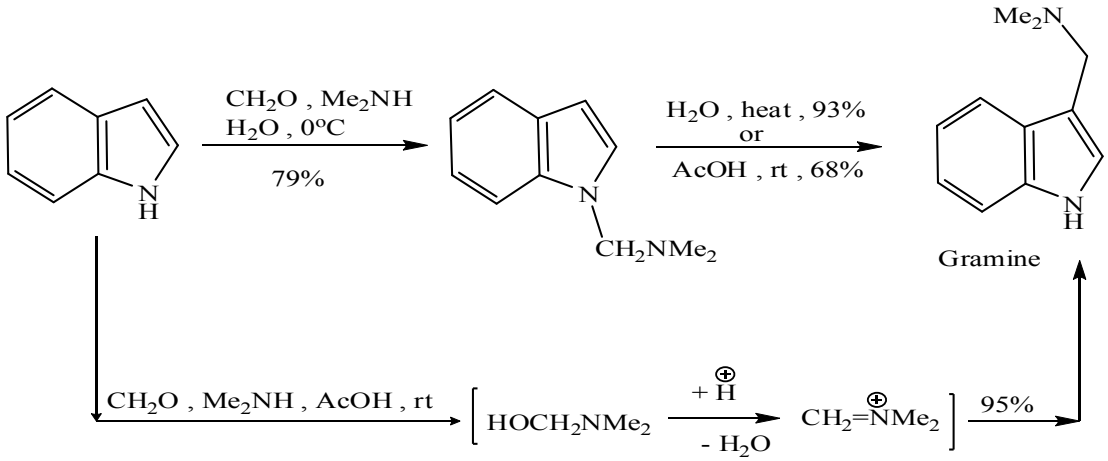




The facility with which indoles undergo substitution can be illustrated using the Mannich reaction. The electrophilic species in such reactions ($C=N^{+}R_2$) is generally considered to be a weak electrophile, yet substitution occurs easily under mild conditions.

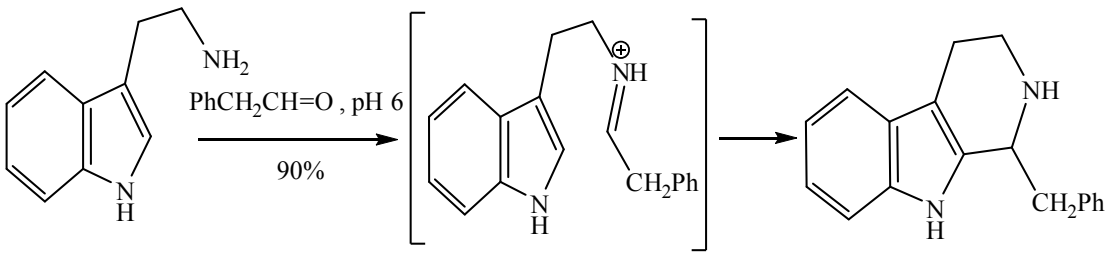


Under neutral conditions and at 0ºC, indole reacts with a mixture of formaldehyde and dimethylamine by substitution at the indole nitrogen[53, 65]. This N-substitution may involve a low equilibrium concentration of the indolyl anion or may result of reversible kinetic attack followed by loss of proton. In neutral solution at higher temperature or in acetic acid, conversion into the thermodynamically more stable 3-dimethylamino-methyl indole gramine; takes place. Gramine is formed directly, smoothly and in high yield, by reaction in acetic acid[53, 66]. The Mannich reaction is useful in synthesis because not only can the electrophilic iminium ion be varied widely, but also the produced gramines are themselves intermediates for further manipulation



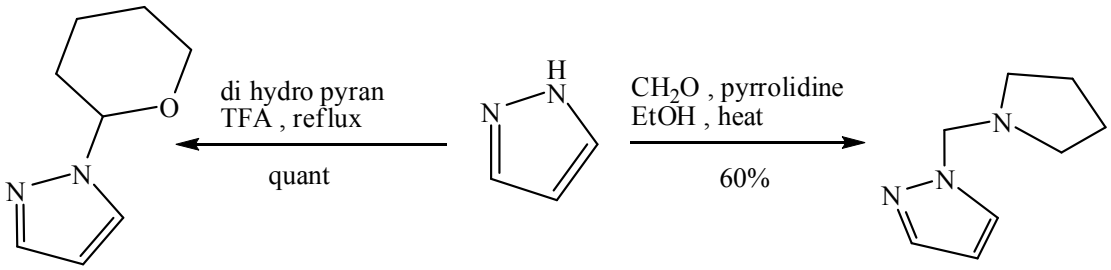
The iminium ion electrophile can also be prepared separately, as a crystalline solid known as (Eschenmoser's salt : $Me_2N^+=CH_2I^-$)[53, 67]and with this, the reaction is normally carried out in a non-polar solvent; examples that illustrate the variation in iminium ion structure that can be tolerated include the reaction of indole with quinolines, catalyzed by indium(ш) chloride[53, 68], benzylidene derivatives of aryl amines, lanthanide triflates[53, 69], ethyl glyoxylate imines[53] and with di hydro-1,4-oxazine-2-ones.[53, 70]

Mannich reactions have been much used for the construction of tetrahydro-β-carbolines[53, 71], tryptamines carrying a 2-carboxylic acid group, which can be conveniently prepared, but are not easily decarboxylated as such but under cyclising Mannich condensation with aldehydes and ketones, with loss of the carbon dioxide in final step.[53, 72]



These cyclization may proceed by direct electrophilic attack at the α-position, or by way of β-attack.[53]

Exposure of pyrazole to Mannich condensation produces an N-protected pyrazole, presumable via attack at the imine nitrogen, followed by loss of proton from the other nitrogen[53, 124], and an N-tetra hydro pyranal pyrazole can be similarly prepared.[53, 74]

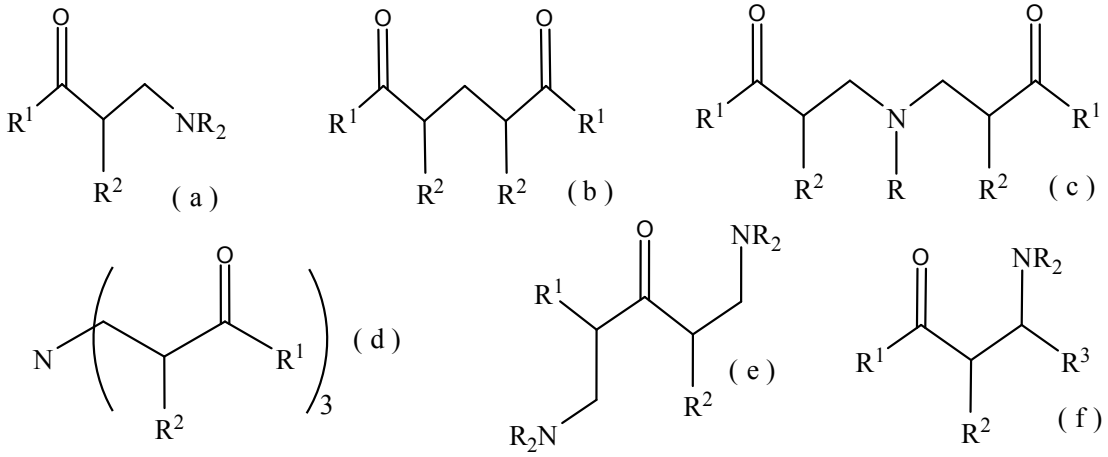


1.2.2. The intermolecular and intramolecular routes in Mannich reaction:

Two routes of reaction strategy could occur in Mannich synthesis by the classical procedure which involves direct reaction between the three components of Mannich reaction; and this is called: (direct Mannich reaction or three component Mannich reaction), and reaction here is an intermolecular reaction. On the other hand some of the modern methods were developed to overcome the limitations of classical methods, this modern methods occur by intramolecular reactions for the reactants which have ability to this mode of reactions; their reaction methods were called: (indirect Mannich reactions).[1, 11]

1.2.2.1. Intermolecular Mannich reactions

The classical intermolecular Mannich reaction is however, plagued by a number of serious disadvantages[11, 75], due to the drastic reaction conditions and long reaction times, unwanted side reactions often take place, major problems here are de-amination and the formation of methylene bis ketones (b). Single products (a) are generally only obtained when secondary amines are used, if one uses a primary amine or ammonia as the amine component reaction can continue until all the H-atoms on the nitrogen are replaced, as a consequence, one obtains, in addition to the desired product (a), the other Mannich bases (c) and (d) as major components. Ketones with two reactive α-position must be used in large excess, in order to avoid the production of bis Mannich bases (e).[11]



In the case of the unsymmetrical ketones a further problems is encountered, the regioselectivity cannot be controlled to any significant extent and is often strongly dependent on reaction conditions. Additionally and with very few exception; one can only use formaldehyde[11, 76], therefore, Mannich bases such as (f) which would very probably also be extremely attractive intermediates are not accessible by this method. A further limitation is that some other carbonyl compounds such as carboxylic acids and their derivatives cannot be amino-

methylated, in addition the classical Mannich reaction is not suited to the enantioselective synthesis of β-amino ketones and amino aldehydes. Thus, the majority of pharmaceutical products, which are derived from Mannich reaction are used in the form of racemates, the application of enantiomerically pure Mannich bases is only possible when this are available by separation of the racemate[11, 75, 77]. This problem becomes more severe when one takes into consideration the increasing importance of stereo chemically pure pharmaceuticals (the avoidance of isomer ballast and of undesirable side effects[11, 77]). Due to the very attractive nature of Mannich bases, there have been many attempts to find alternative synthetic routes to this compounds, which do not suffer the sever drawbacks of the classical procedure.[11]

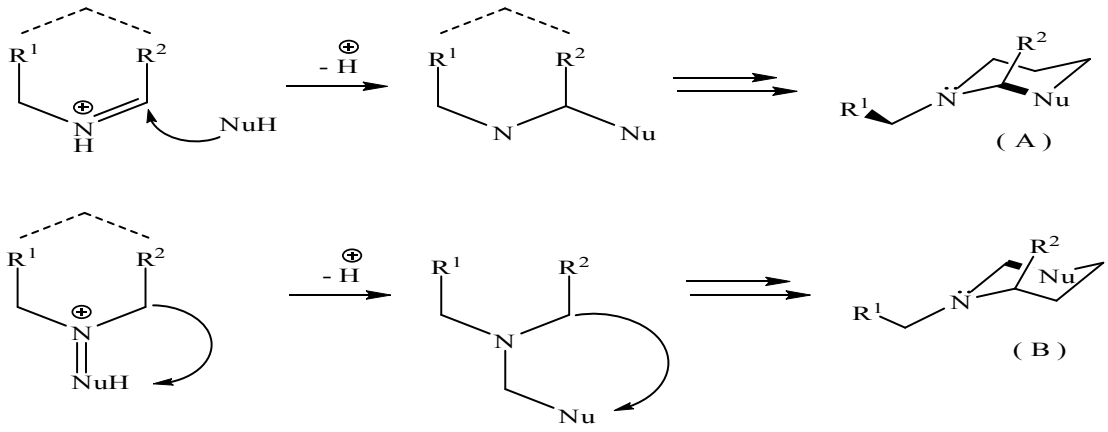
The problems in intermolecular Mannich reaction would be overcomed by using of (Organocatalystic progress), which can play important role in the orientation of one – pot three component Mannich reaction to give enantiochemically products and regioselectivity would take place in this type of reactions.[78]

1.2.2.2. Intramolecular Mannich reaction

Intramolecular Mannich reactions possess a significantly wider range of applications than their intermolecular counter- parts. Their extremely high value – particularly as the key step in reaction sequences – has long been recognized and used amongst other applications, in biomimetic natural product synthesis. Since the first ground – breaking work, such as Robinson synthesis of tropinone[11, 16], modern methods such as the combination of [3,3] sigma tropic rearrangements with intramolecular amino alkylation, or powerful new methods for the generation of iminium salts under mild reaction conditions have allowed simple highly region –

and stereo selective access to a large number of complex target molecules.[11, 16]

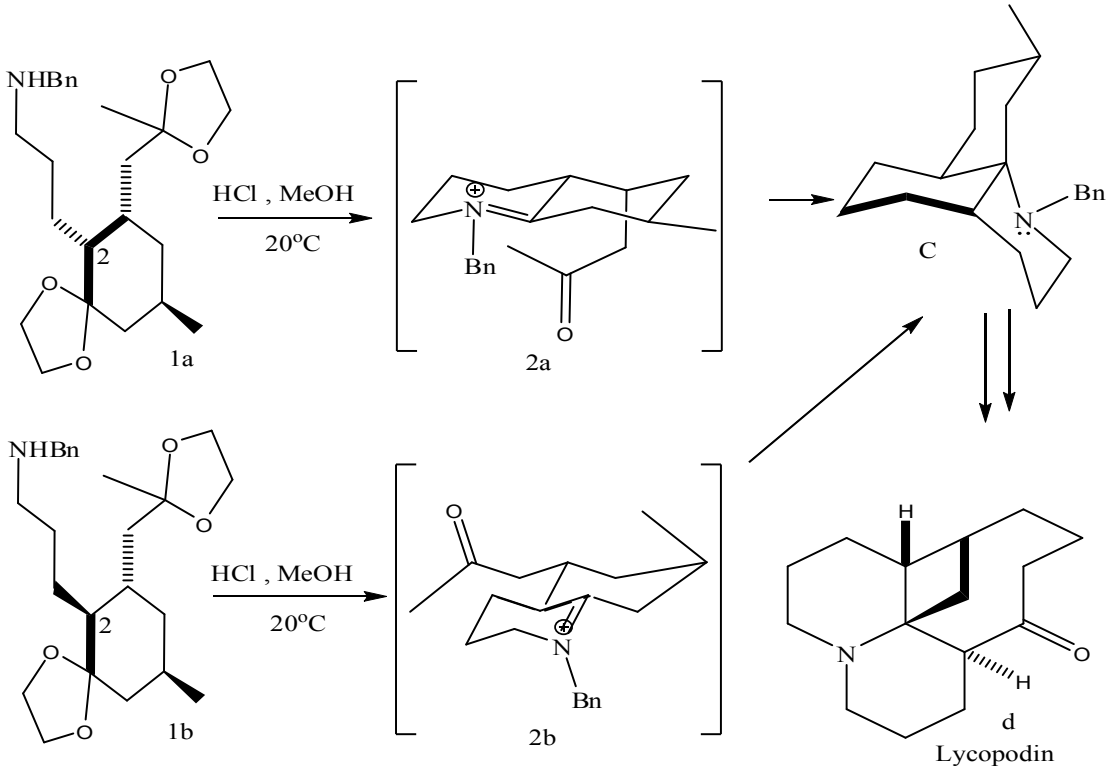
The intramolecular variant is not restricted to amino- methylation but can be applied in its widest sense to amino- alkylation, its chemoselectivity also offers a much wider range of potential applications. The carbonyl compound, as is the case with the intermolecular variant, can be used in the form of an acetal or a (silyl) enol as in the intramolecular reaction, whereas, in the presence of aqueous mineral acid the protecting group is cleaved and the enol is the reactive species. The stereo- chemical pathway of a nucleophilic attack on an iminium ion is often controlled by stereo electronic factors[11, 79]. Because of the anti perplaner conformation of the developing electron pair and the incoming electrophile in the product, reliable predictions can therefore be made about the stereo-selectivity of the cyclization.[11]



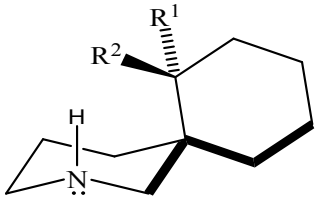
Scheme shown the stereo electronic control in the cyclization initaited by iminium ions form exo-trig (A) and endo-trig (B) products.

An excellent example of this stereo -controlled reaction is the synthesis of lycopodium alkaloid[11, 80], the starting material (1a), which is epimeric at C-2, cyclizes to give the single isomer (c) in 66% yield. This result can

only be explained by assuming an equilibration of the starting material after hydrolysis of the protecting group; a cyclization via the transition state (2b) is impossible on stereo electronic grounds.[11]

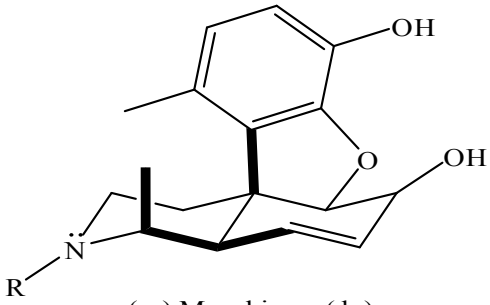


The above scheme represents the redundant synthesis of lycopodium alkaloid. In this synthetic sequence another major advantage of redundant or degenerate synthesis is exemplified. This is a feature of many Mannich cyclizations.[11]. Further examples of stereo electronically controlled synthesis of natural products are given by the synthesis of the structurally unusual 2-aza Spiro[5.5] undecane alkaloid nitramine (a1) and its region-isomer Iso nitramine (a2)[11, 81], and the analgesics (-) morphine (b) and (-) codeine (c).[11, 82]



Nitramine (a1)
R^1= H , R^2= OH

Iso Nitramine (a2)
R^1= OH , R^2= H



(-) Morphine (b)
R = H

(-) Codeine (c)
R = CH_3

Alkaliods synthesized by stereo electronically controlled Mannich reactions.

1.2.3. preformed Mannich reagents

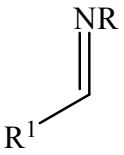
Modern versions of the Mannich reaction usually allow a distinctly simpler entry into β-amino carbonyl compounds through the use of preformed electrophiles (e.g. imnium salts or imines) or nucleophiles (e.g. enolates, enol ether and enamines). Such methods allow; at least in principle, all the limitations of the classical method to be overcome. The levels of performance and the versatility of these methods have already been powerfully demonstrated in the synthesis of β-amino acid derivatives and β-lactams.[11, 83, 84]

In comparison to the classical Mannich conditions, these preformed reagents guarantee a higher concentration of the electrophile leading to lower reaction temperatures and much shorter reaction times, as a consequence many undesired side reactions which so often cause problems in the Mannich reaction are avoided, even with sensitive substrates. Furthermore, one can avoid the use of protic solvents, in this way the carbonyl component can be replaced with much more reactive

synthetic equivalents such as enolates. This leads to a greatly extended spectrum of application for the reaction. One can therefore also successfully use reagents which are normally impossible under the classical conditions (e.g. sterically very demanding substrates or carboxylic acid derivatives). In addition; the reaction is not restricted to aminomethylation, but amino alkylation is also possible. It is also possible to carry out the reaction with high degree of regio – and stereoselectivity.[11]

1.2.3.1. Imines

The general form of the amine can be written as the following[11, 85]:

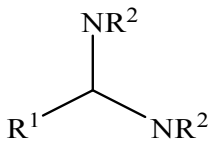


(R^1 = alkyl , Aryl)

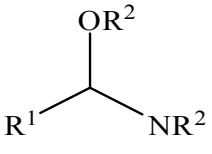
Amines are generally much less electrophilic than corresponding aldehyde amines . The use of enolizable imines should allow the reaction to proceed under very mild conditions with the avoidance of the aldol – types self condensation reactions[11. 86]. Formaldehyde amines (R^1 = H) are generally only stable at low temperatures, they are therefore best generate *in situ* or alternatively, a synthetic equivalent can be used.[11, 86, 87]

1.2.3.2. Aminals and N,O – Acetals

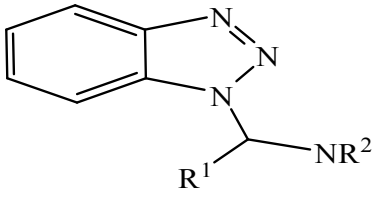
The general form of aminals and N,O-acetals can be written as the following:



(A)



(B)



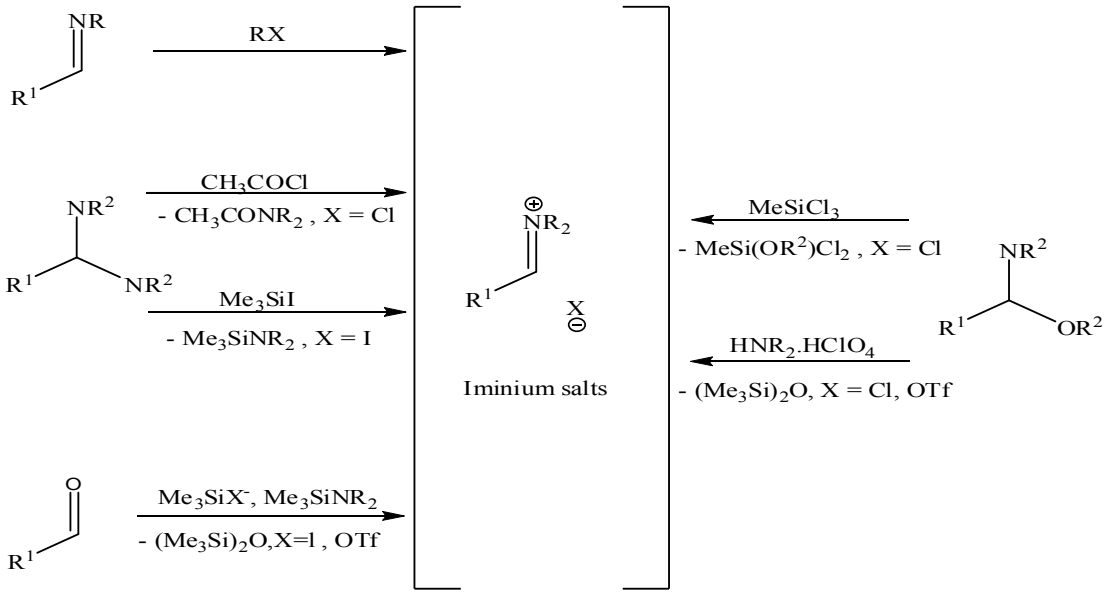
(C)

Aminals(A) and N,O-acetals(B) resemble imines in terms of their electrophilicity. They must therefore normally be activated by Lewis acids in order to react with nucleophiles. The benzo trizole aminals(C) represent a special case. These easily accessible compounds are very well suited for amino- alkylation, when derivatives of enolizable aldehydes or ketones are used or when derivatives of primary amines are involved[11, 87]. Benzo trizole aminals have been used in the synthesis amongst others β-amino carbonyl compounds.[11, 88]

1.2.3.3- Iminium salts

Iminium salts are generally readily accessible from basic Chemicals[11, 89]. The iminium salts are the most commonly applied Mannich reagents in the synthesis of β-amino ketones and aldehydes[11, 86, 90], this is because these are more powerfully electrophilic than imines, aminals and N,O-acetals. These are also suitable for the preparation of β-amino carboxylic acid derivatives[11, 91]. Basically, the preparative uses of these materials have been limited to three compounds: Eschenmoser's salt $[H_2C{=}NMe_2]^+I^-$[10, 92, 93], the corresponding chloride salt made popular by kinast and Tietze[11, 92], and the tri- fluoroacetate introduced by Potier et al.[11, 93]

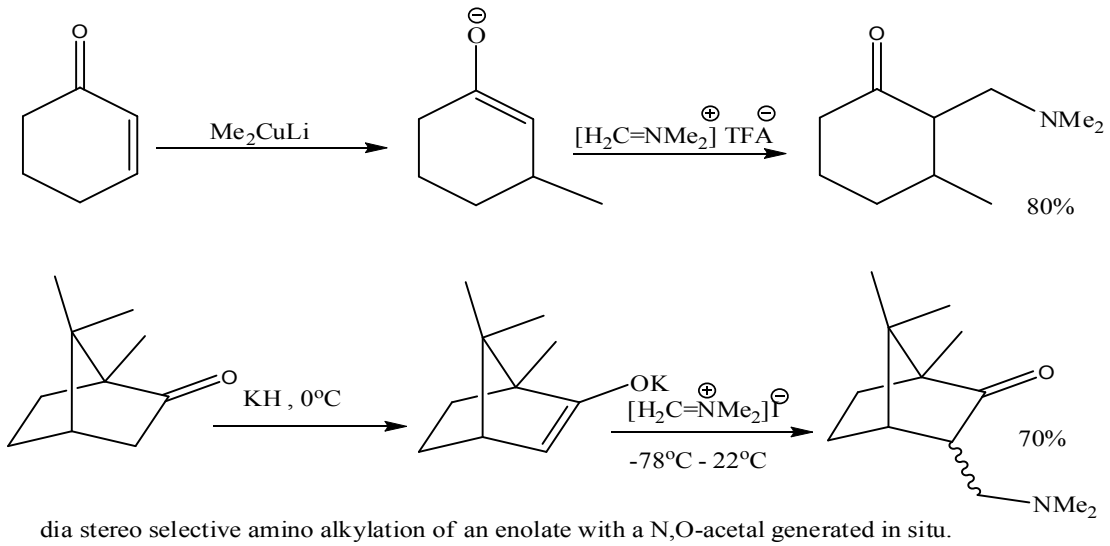
Iminium salts are normally hygroscopic and sensitive towards hydrolysis. Under exclusion of moisture, these can however be stored over long periods, nonetheless; salts with α-H atoms are often less stable.[11,89,92]



Synthesis of iminium salts

1.2.3.4. Enolates

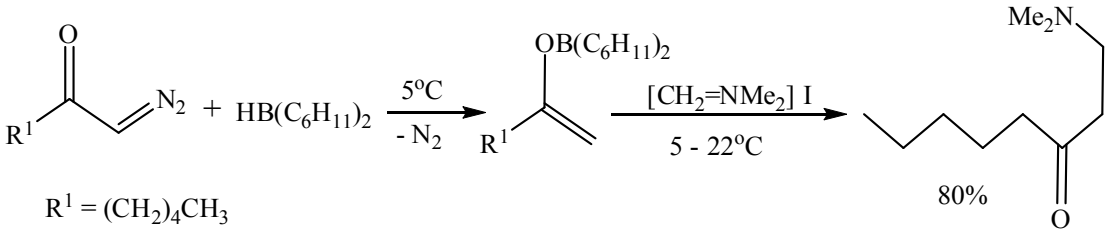
Ketone enolates react with Mannich reagents not derived from formaldehyde in a similar way to ester enolates[11, 86] .Their use allows the scope of the classical Mannich reaction to be extended from aminomethylation to amino alkylation. The reaction of lithium enolates (derivatives of cyclohexanone, acetone, or acetophenone) with *in situ* generated, N,O-acetals (derivatives of secondary amines and aromatic or aliphatic aldehyde)is the first generally applicable method for the amino-alkylation of ketones.[11, 94]



dia stereo selective amino alkylation of an enolate with a N,O-acetal generated in situ.

1.2.3.5. Boron Enol Ethers

The reaction of boron enol ethers with Eschenmoser's salt is a powerful method for the regioselective preparation of β-amino ketones



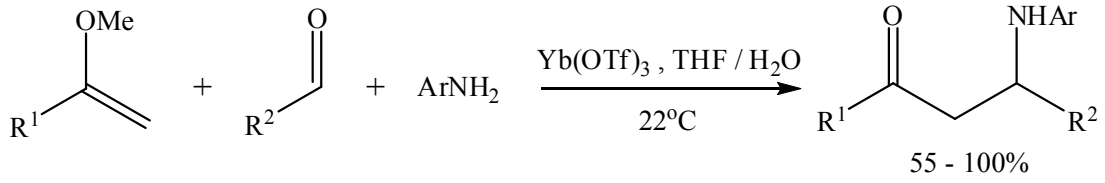
Regio selective synthesis of B-amino ketones by amino methylation of Boron enol ether with Eschenmosers salt.

On the basis of the Lewis acidic nature of boron enol ethers, these reagents will also react (in contrast to the lithium enolates) with aminals, species which are much less electrophilic than the iminium salts. In this manner one can also successfully amino methylate even sterically

hindered substrates, in addition; boron enol ethers can be amino-alkylated, with high diastereo selectivity with aminals (only derivatives of non – enolizable aldehydes are suitable.)[11, 96]

1.2.3.6. Alkyl Enol Ethers

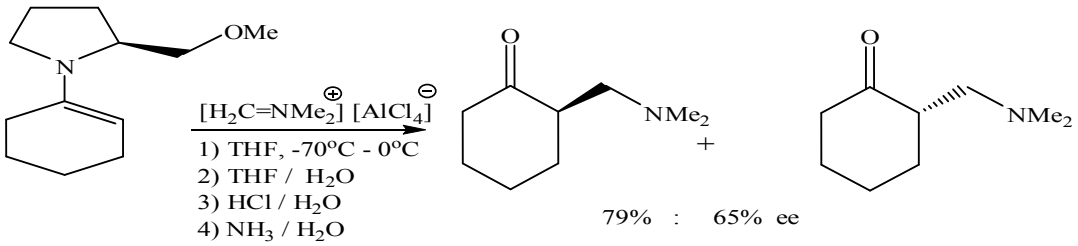
There are relatively few reports of the use of alkyl enol ethers in the Mannich reaction. Thus; alkyl enol ethers can be amino methylated with methylene iminium salts under mild conditions[11, 97]. The use of lanthanide tri flate catalysts such as ytterbium(III) tri flate [$Yb(OTf)_3$] makes possible the synthesis of secondary β-amino ketones by the amino alkylation of alkyl enol ethers with aldehydes and aromatic amines. Kobayashi and Ishitani have proposed that the reaction proceeds via imines formed *in situ*.[11, 97]



Lanthanide tri flate catalysed amino alkylation of alkyl enol ethers in aqueous medium

1.2.3.7. Enamines and Imines

So far, iminium salts have been the preferred reagents for the aminomethylation and amino alkylation of enamines[11,98,99,100,101,102], in comparison to iminium salts, other Mannich reagents such as N,O-acetals[11, 103], aminals[11, 104, 105] and imines[11, 106] have played only a minor supporting role.



Enantioselective synthesis of B-amino ketones by amino methylation of enamines with iminium salts

Ternary iminium salts are extremely good in the amino- alkylation of enamines. Iminium salts can be generated *in situ* almost quantitatively from secondary amines (or their hydrochlorides) and non enolizable aldehydes. These iminium salts can then be used directly, without isolation or purification, in the reaction with enamines or other nucleophiles such as imines or electron- rich arenes (silylogous Mannich reaction), the experimental effort required can be dramatically reduced with this approach[11, 98, 100]. The results (yields, diastereo- selectivities) are essentially indistinguishable from those obtained with preformed iminium salts.[11, 84, 99, 107]

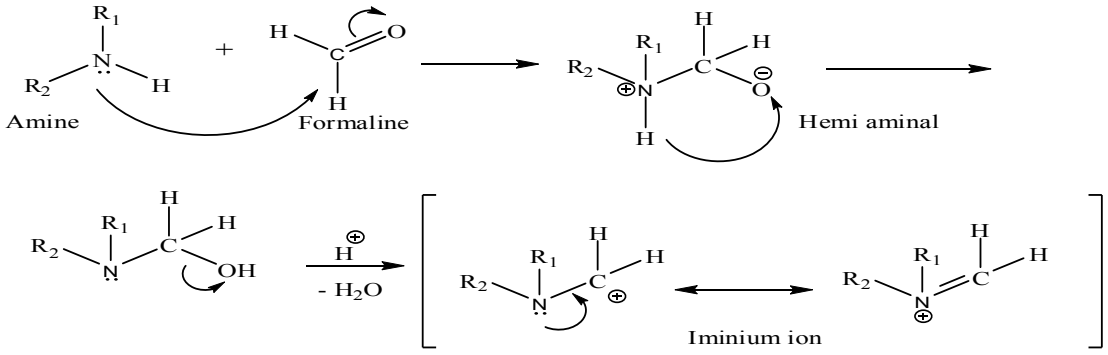
A further benefit is that iminium salts that are otherwise difficult or impossible to obtain can easily be generated (e.g. derivatives of benzyl amine).[11, 108]

1.2.4. Mechanism of Mannich reaction

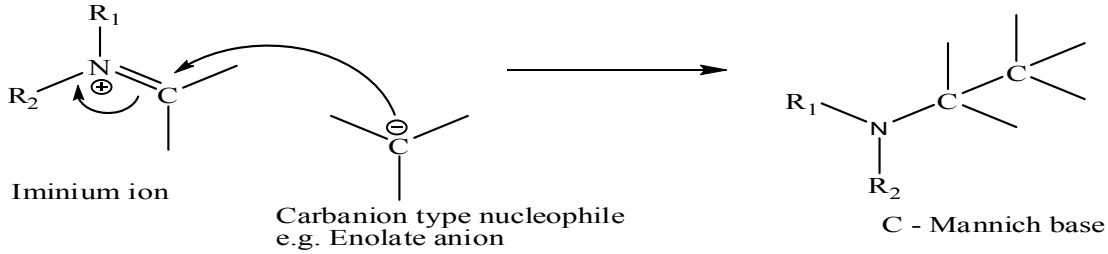
The Mannich reaction apparently proceeds through a variety of mechanisms depending on the reactants and conditions that are employed. Modern recent progresses in asymmetry Mannich reaction were took place such the use of organo catalysis systems.[4, 24]

1.2.4.1. The pathways and Orientation in Mannich reaction

Many pathways were proposed to the mechanism of the Mannich reaction through the kinetic studies in various conditions. Reaction of the secondary amine with the aldehydes forms a hemi aminals which loses molecule of water to form iminium cation in the first step. In the second step of the reaction a carbanion is generated from CH acidic compounds (enol form of the active hydrogen compound)which reacts with the iminium cation to form a β-amino carbonyl compound (a Mannich bases).[3, 10]



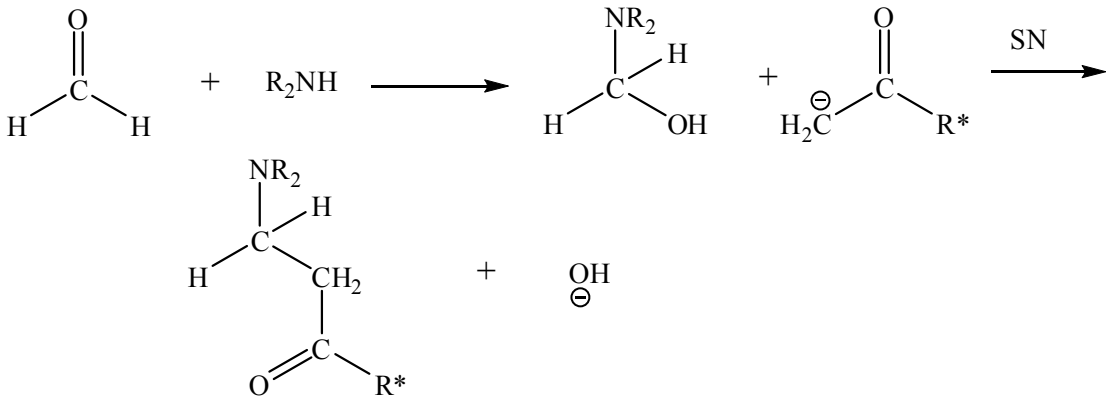
The first step in Mannich reaction mechanism: formation of iminium ion



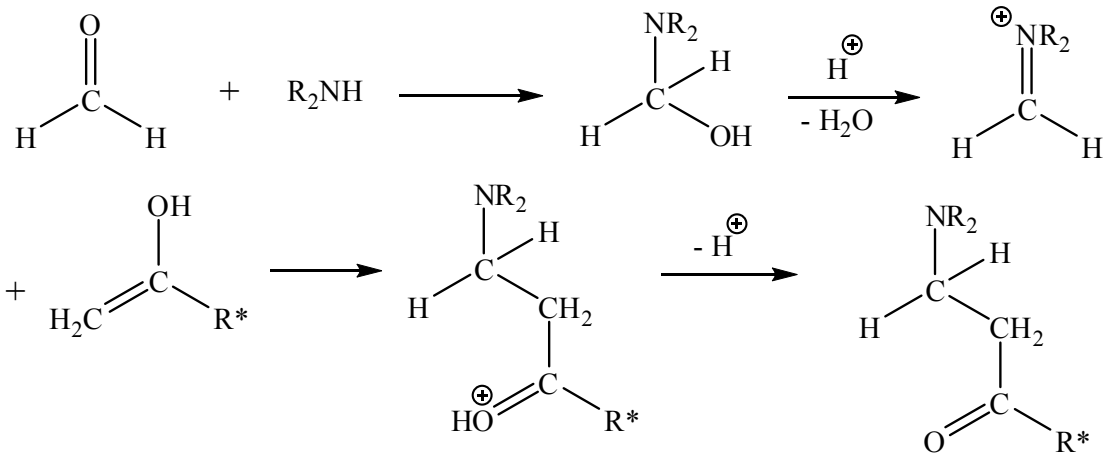
The second step in the Mannich reaction mechanism: nucleophilic addition on to iminium ion.

Studies of the reaction kinetic have led to the following proposal for the mechanism of the Mannich reaction:

The base – catalysed reaction:

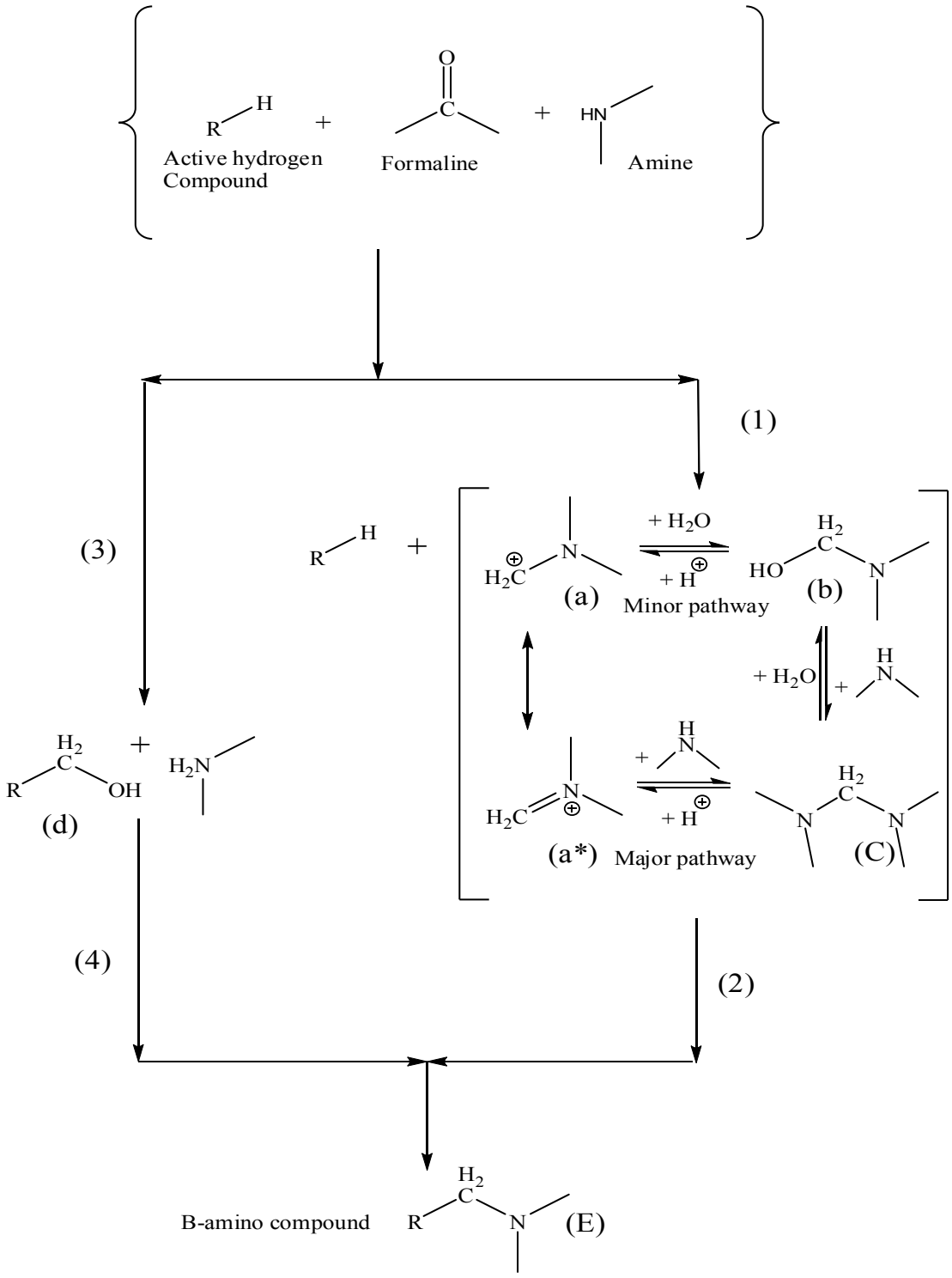


The acid – catalysed reaction:



According to this mechanism, it is the free amine; not the salt that react, even in acid solution; and the active hydrogen compound (in the acid – catalysed process), reacts as the enol when that is possible, there is kinetic evidence for the intermediacy of the iminium ion.[4, 10]

The following scheme illustrated the pathways and bearing compounds in the Mannich reaction[1].


Active hydrogen Compound
Formaline
Amine
(1)
(2)
(3)
(4)
+ H2O
+ H
Minor pathway
Major pathway
(a)
(a*)
(b)
(C)
(d)
(E)
B-amino compound

1.3-Aims of this study

This study was aimed to:

i) Synthesis of some ketonic and phenolic Mannich bases.

ii) Elucidation of the structures of targeted molecules via spectroscopic tools.

iii) Screening targeted molecules for their biological activity.

Chapter Two
Materials and Methods

2- Materials and Methods

2.1- Materials

2.1.1- Chemicals and solvents

Analytical grade reagents (Table 2.1) were used . They were purchased from Sigma – Aldrich company (UK)

Table 2.1 :Chemicals and solvents

Ser . No	Chemical
1	Acetophenone
2	Acetone
3	Acetyl acetone
4	Acetic anhydride
5	2-Aminophenol
6	Benzaldehyde
7	β-Naphthol
8	Dimethyl amine
9	Ethanol (Absolute)
10	Methanol
11	Formalin
12	Hydrochloric Acid
13	Morpholine
14	Paraformaldehyde
15	Salicylic Acid
16	Sodium Hydroxide
17	Ethyl acetate
18	Silica gel G
19	Chloroform

2.2 – Methods

Synthesis protocols:

2.2.1 – Synthesis of 2-naphthylacetate

(0.1 mol) of β-naphthol was dissolved in 50 ml of 3M sodium hydroxide solution . (200g) of crushed ice was added followed by (15ml) acetic acid anhydride. The mixture was shacked vigorously for several minutes. The acetate was separated and then dried on air. The product was recrystallised from 95% ethanol.

2.2.2 – Synthesis of 2-aminophenylacetate

(0.1 mol) of 2-aminophenol was dissolved in (50ml) 3M sodium hydroxide solution , (200g) of crushed ice was added followed by (15ml) of acetic anhydride. The mixture was shacked vigorously for several minutes . The acetate was separated , dried on air and recrystallised from 95% ethanol.

2.2.3- Synthesis of dibenzylidene acetone

A solution of (12.5g) of sodium hydroxide in 125ml of water and 100ml of ethanol was immersed in a bath of cold water and the temperature was kept between 20-25°C. The mixture was stirred vigorously. (1.5ml) of a mixture of benzaldehyde (12.75ml / 0.125mol) and acetone (4.65ml / 0.0625mol) was then added .A flocculent precipitate was formed in 2-3minutes.After 15 minutes the reminder mixture of benzaldehyde – acetone was added and the stirring was continued for a further 30minutes. The yield was filtered off, washed with cold water and dried at room temperature.

2.2.4- Synthesis of the Mannich base: 1-hydroxymethyl-1-piperidinomethyl-2-naphthylacetate

Formalin(1.6g,20mmol) , 2-naphthyl acetate (3.72g,20mmol) and piperidine hydrochloride (2.45g,20mmol) in a mixture of water and alcohol(1:2,v:v) was refluxed in a water bath for 1 hour and left at room

temperature for 48 hours . Removal of the solvent under reduced pressure gave the Mannich base.

2.2.5- Synthesis of the Mannich base: 1,1-bis-morpholinomethyl-2-naphthylactate

Formalin(1.6g,20mmol) , 2-naphthyl acetate (3.72g,20mmol) and morpholine (1.74g,20mmol) in a mixture of water and alcohol(1:2,v:v) was refluxed in a water bath for 1 hour and left at room temperature for 72 hours . Removal of the solvent under reduced pressure gave the Mannich base.

2.2.6- Synthesis of the Mannich base: 1,1-bis-dimethylaminomethyl-2-naphthylactate

Formalin(1.6g,20mmol) , 2-naphthyl acetate (3.72g,20mmol) and dimethylamine (0.90g,20mmol) in a mixture of water and alcohol(1:2,v:v) was refluxed in a water bath for 1 hour and left at room temperature for 72 hours . Removal of the solvent under reduced pressure gave the Mannich base.

2.2.7- Synthesis of the Mannich base :1,1-bis-dimethylaminomethyl-2-aminophenyl acetate

Formalin(1.6g,20mmol) , 2-aminophenylacetate (3.02g,20mmol) and dimethylamine (0.90g,20mmol) in a mixture of water and alcohol(1:2,v:v) was refluxed in a water bath for 1 hour and left at room temperature for 48 hours . Removal of the solvent under reduced pressure gave the Mannich base.

2.2.8- Synthesis of the Mannich base : 1,3-dibenzylidene-3-hydroxymethyl-1-morpholinomethylpropanone

Formalin(3.2g,40mmol) , di benzylidene acetone (2.34g,20mmol) and morpholine (3.48g,20mmol) in 20ml alcohol was refluxed in a water bath for 1 hour and left at room temperature for 48 hours . Removal of the solvent under reduced pressure gave the Mannich base.

2.2.9 – Synthesis of the Mannich base: 2-hydroxy-3,6-bis-dimethylaminomethylbenzoic acid

Formalin(1.6g,20mmol) , salicylic acid (2.76g,20mmol) and dimethylamine (0.90g,20mmol) in 20ml ethanol was refluxed in a water bath for 1 hour and left at room temperature for 48 hours . Removal of the solvent under reduced pressure gave the Mannich base.

2.2.10 – Synthesis of the Mannich base: 2-hydroxy-3,6-bis-piperidinomethyl benzoic acid

Formalin(1.6g,20mmol) ,salicylic acid (2.76g,20mmol) and piperidine hydrochloride (2.45g,20mmol) in a mixture of water and alcohol(1:2,v:v) was refluxed in a water bath for 1 hour and left at room temperature for 48 hours . Removal of the solvent under reduced pressure gave the Mannich base.

2.2.11 –Synthesis of the Mannic base:1-piperidinomethyl-3-phenylpropanone

Paraformaldehyde(2.25g,0.05mol),acetophenone (6.00g,0.05mol) and piperidine hydrochloride (6.10g,0.05mol) in ethanol(20ml) was refluxed in a water bath for 1 hour and left at room temperature for 48 hours . The reaction mixture was then cooled to afford the Mannich base.

2.2.12– Synthesis of the Mannich base: 3,3-bis-piperidinomethylpentan-2,4-dione

A mixture of piperidine hydrochloride (12.2g,0.1mol), concentrated hydrochloric acid (0.25ml), paraformaldehyde (4.50g,0.15mol) and acetyl acetone (2g ,0.02mol) in ethanol (30ml) was heated under reflux for one hour, then paraformaldehyde (3g,0.1mol) was added to the mixture and the refluxing was continued for 2 hours. The resulting solution was cooled slowly, and the product was filtered off.

2.2-13- Biological activity

2.2.13.1- Preparation of bacterial suspension

One ml aliquots of 24 hours broth culture of the test organisms were aseptically distributed onto nutrient agar slopes and incubation at 37^{o} C for 24 hours. The bacterial broth was harvested and washed off with 100 ml sterile normal saline to opacity of matched barium chloride turbidity (standard). The suspension was stored in the refrigerator at 4^{o}C till used.

2.2.13.2- Preparation of fungal suspensions

The fungal cultures were maintained on Sabouraud dextrose agar, incubated at 25^{o} C for 4 days. The fungal growth was harvested and washed off with 100 ml sterile normal saline and the suspension was stored in the refrigerator at 4^{o} C till used.

2.2.13.3- Testing for antibacterial activity

The cup-plate agar diffusion method was adopted with some minor modification to assess the antibacterial activity of the prepared extracts. One ml of the standardized bacterial stock suspension 10^{8} – 10^{9} C.F.U/ml were thoroughly mixed with 100 ml of molten sterile nutrient agar which was maintained at 45^{o} C. (20 ml aliquots of this inculcated nutrient agar were distributed in- to sterile Petri-dishes. The agar was left

to settle and in each of these plates 4 cups (10 mm in diameter) were cut using a sterile cork borer and agar discs were removed. Alternate cups were filled with 0.1 ml of compounds which dissolved in DMSO (0.1g of compound / 1ml of solvent) using automatic microlitre pipette, and allowed to diffuse at room temperature for two hours. The plates were then incubated in the upright position at 37^{o} C for 18 hours. After incubation the diameters of the resultant growth inhibition zones were measured.

2.2.13.4- Testing for antifungal activity

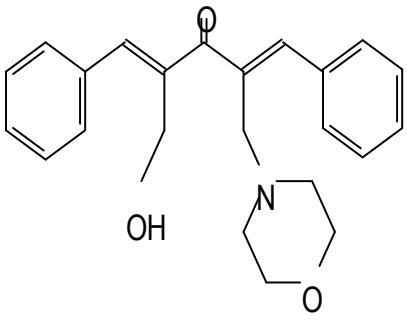
the same method as for bacteria was adopted. Instead of Muller Hinton agar, Sabouraud dextrose agar was used. The medium was incubated at 25^{o} C for two days for *Candida Albicans* and three days for *Aspergillum Niger*.

Chapter Three
Results and Discussion

3-Results and Discussion

A targeted series of phenolic and ketonic Mannich bases were synthesized via a general strategy involving the condensation of an active hydrogen compound with different secondary amines in presence of formalin. The targeted molecules were evaluated for their antimicrobial activity.

3.1-Synthesis of the Mannich base(I)



1,3-dibenzylidene-3-hydroxymethyl-1-morpholinomethylpropanone

I

The Mannich base I was synthesized by refluxing a mixture of formalin , dibenzylidene acetone and morpholine in absolute ethanol for one hour.

The UV spectrum of compound I (Fig.1) showed λ_{max} (MeOH) 230,325nm which is characteristic of an enone absorption extended by phenyl rings.

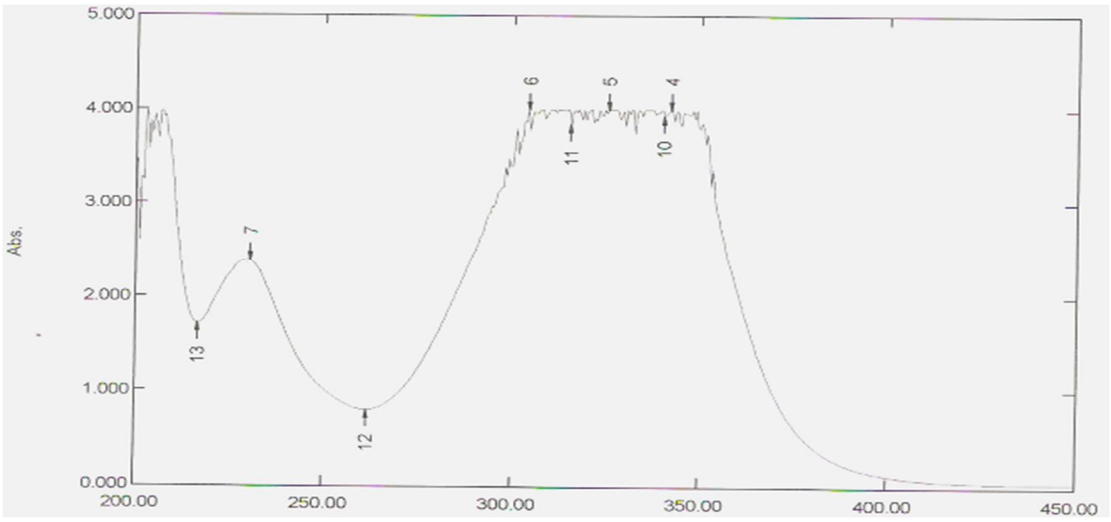


Fig.1: UV spectrum of compound I

The IR spectrum (Fig.2) showed v(KBr) 694,757,850(C-H, Ar., bending) , 1191(C-N) ,1446,1494, 1591(C=C, Ar) , 1650(C=O) 2792(C-H, aliphatic), 3236(NH) cm^{-1}(OH).

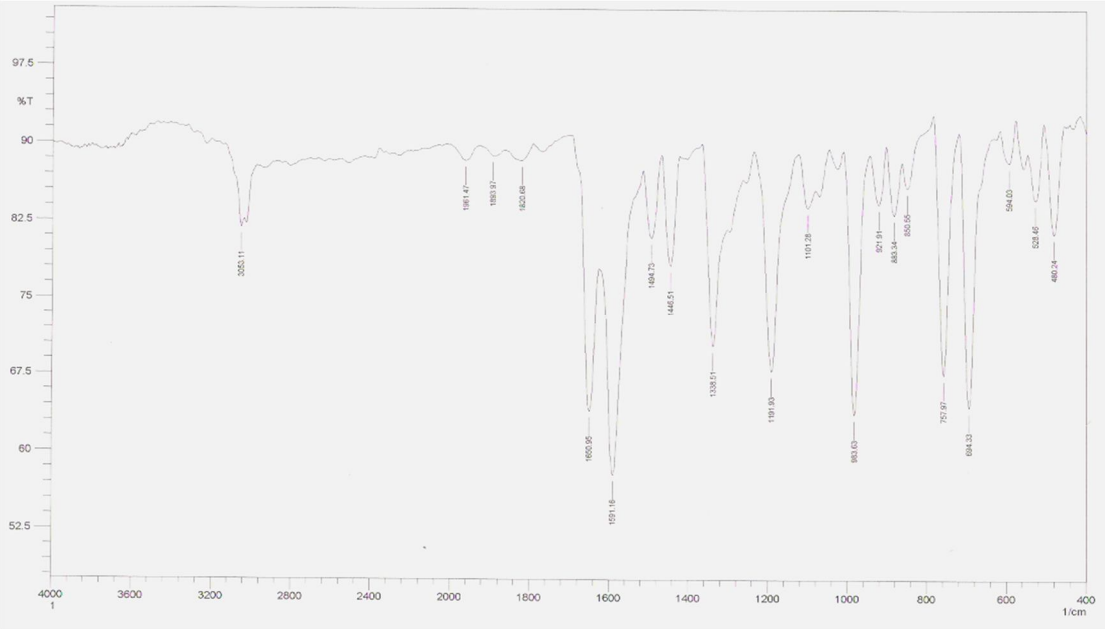


Fig.2: IR spectrum of compound I

The ^{1}H NMR spectrum (Fig.3) revealed the following signals:

δ 2.49	Singlet	8H
δ3.30	Singlet	4H
δ 732	doublet	4H
δ7.47	singlet	4H
δ 7.80	singlet	2H

The signal at δ 2.49(8H) accounts for four methylenes ( and ), while the resonance at δ3.30(4H) is characteristic of (). The aromatic protons resonate at δ7.32,7.47 and 7.80ppm.

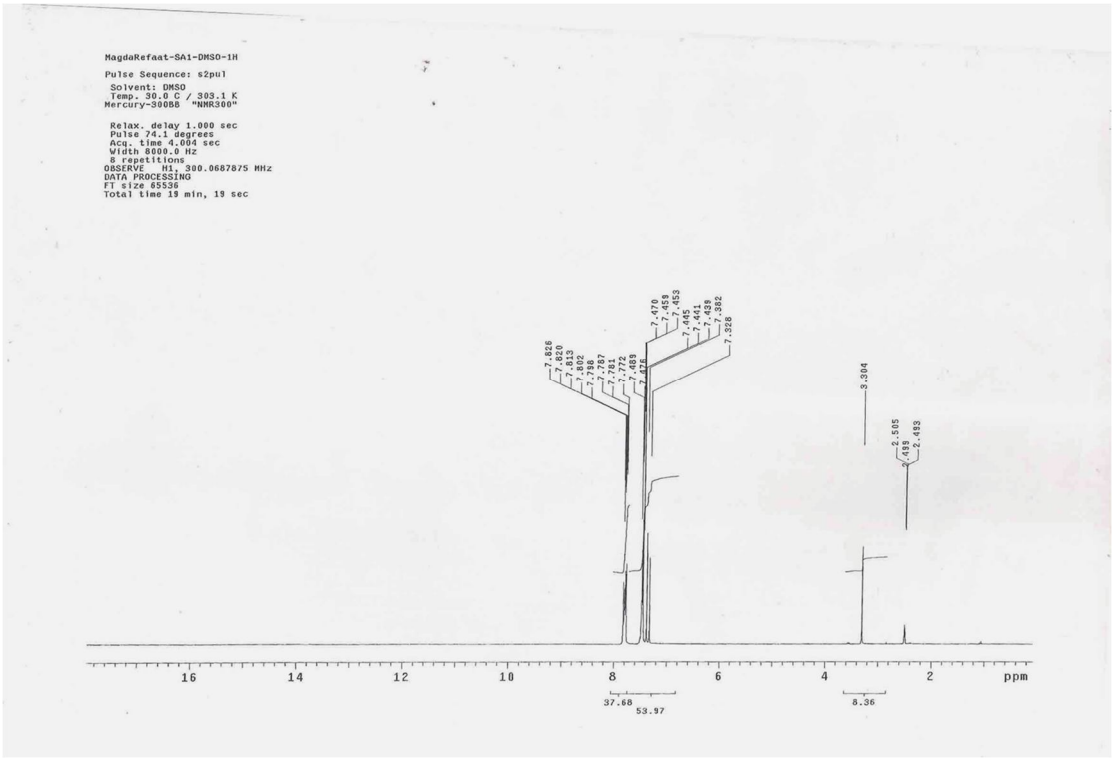


Fig. 3:[1]H NMR spectrum of compound I

The Mass spectrum (Fig.4) gave m/z366 for the molecular ion.

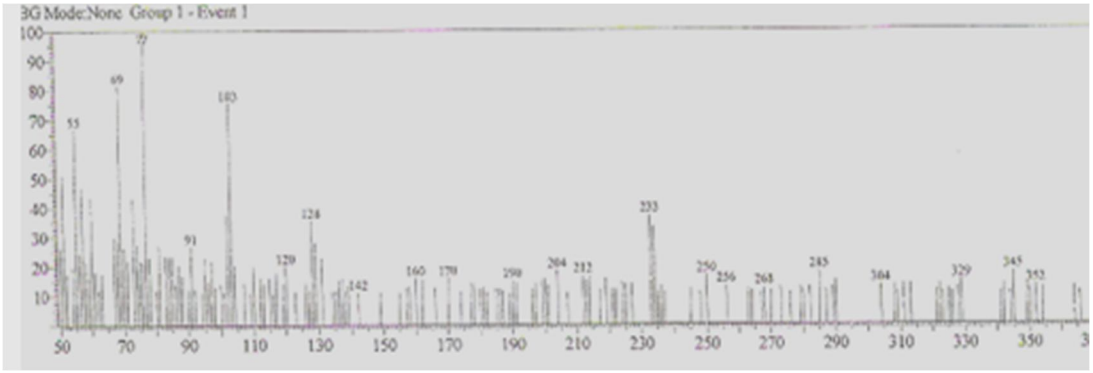
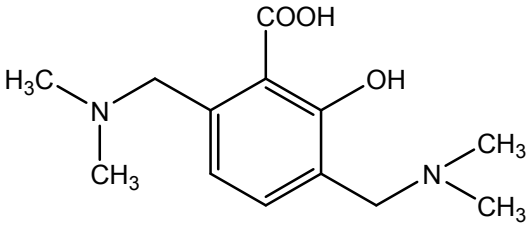


Fig.4: Mass spectrum of compound I

On the basis of the above spectral data structure I above was assigned for this Mannich base.

3.2-Synthesis of the Mannich base(II)



2-hydroxy-3,6-bis-dimethylaminomethylbenzoicacid

II

The Mannich base II was synthesized by refluxing a mixture of formalin, salicylic acid and dimethylamine in absolute ethanol for one hour.

The UV spectrum of compound II (Fig.5) showed λ_{max} (MeOH) 245,295,325nm.

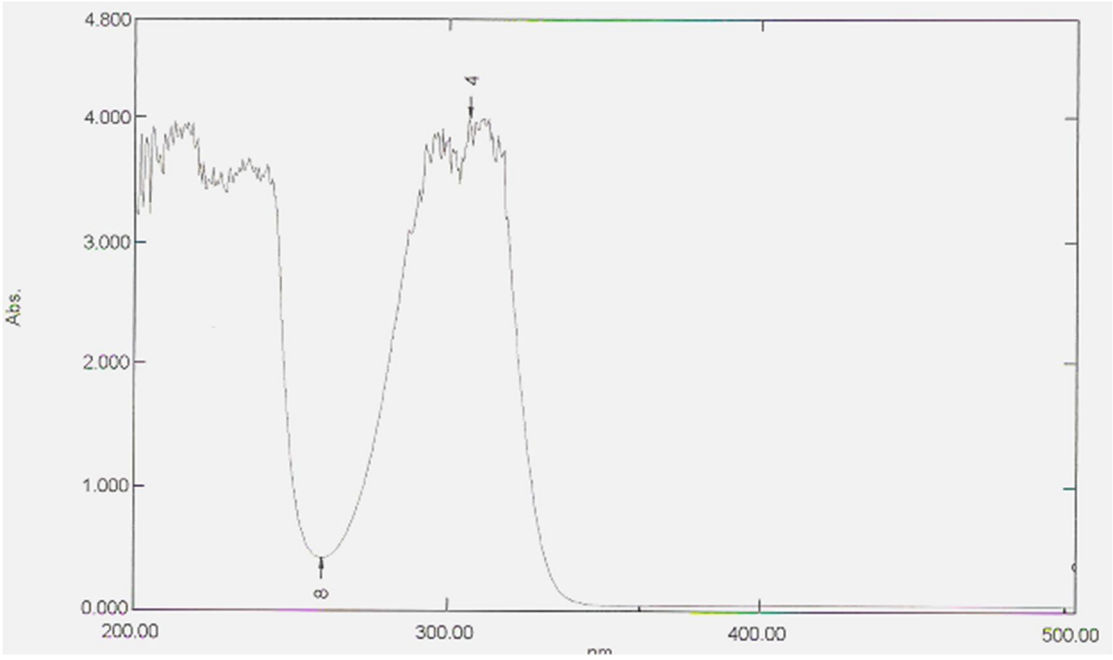


Fig.5: UV spectrum of compound II

The IR spectrum (Fig.6) showed v(KBr) 655,759,891(C-H, Ar., bending) , 1151(C-N) ,1442,1481, 1575(C=C, Ar) , 1658(C=O) 2858(C-H, aliphatic), and 3236cm^{-1}(OH).

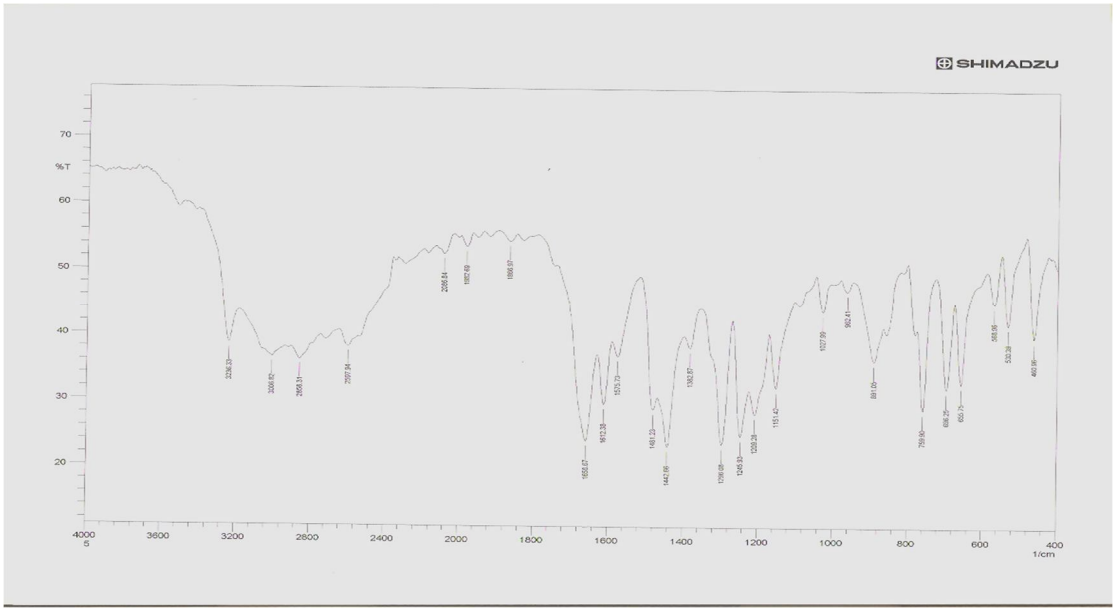


Fig.5: IR spectrum of compound II

The ^{1}H NMR spectrum (Fig.6) revealed the following signals:

δ 2.50	Singlet	12H
δ 2.69	Singlet	4H
δ 6.80	doublet	1H
δ 7.49	Doublet	4H

The signal at δ 2.50(12H) was assigned to four methyl groups, while the resonance at δ 2.69(4H) accounts for two methylene moieties. The ortho coupled aromatic protons at C_4 and C_5 resonate as a double doublet at δ 6.80 and δ 7.49 ppm respectively.

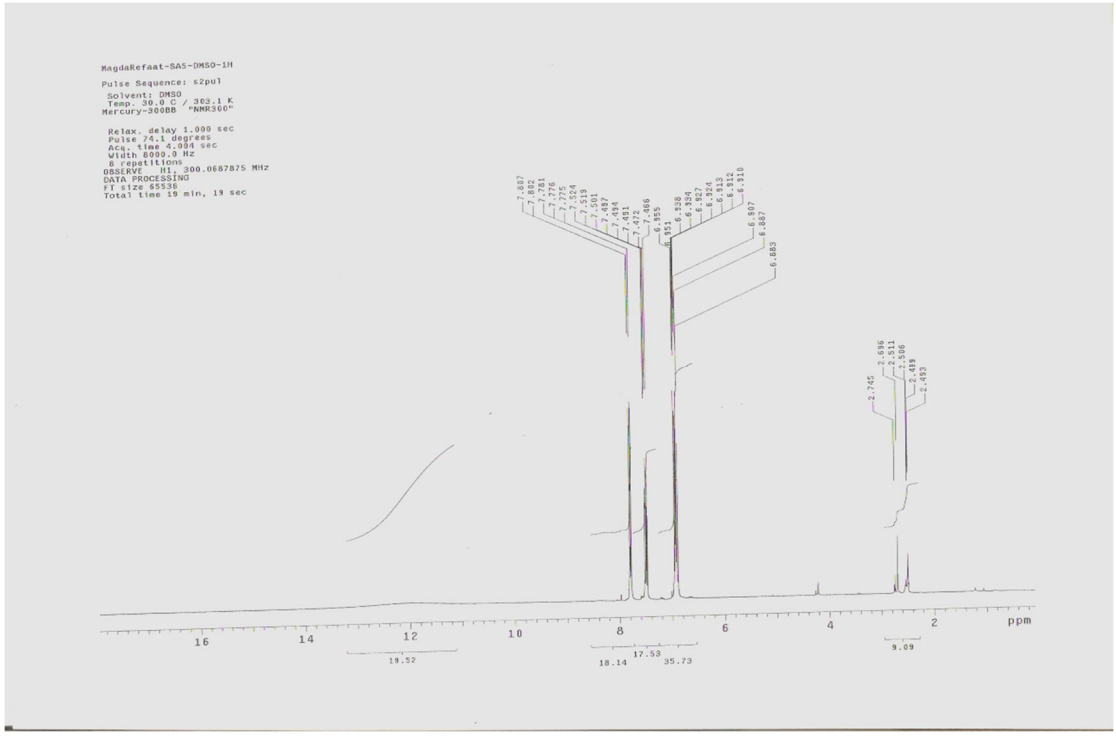


Fig. 6:[1]H NMR spectrum of compound II

The Mass spectrum (Fig.7) gave m/z222 for the molecular ion.

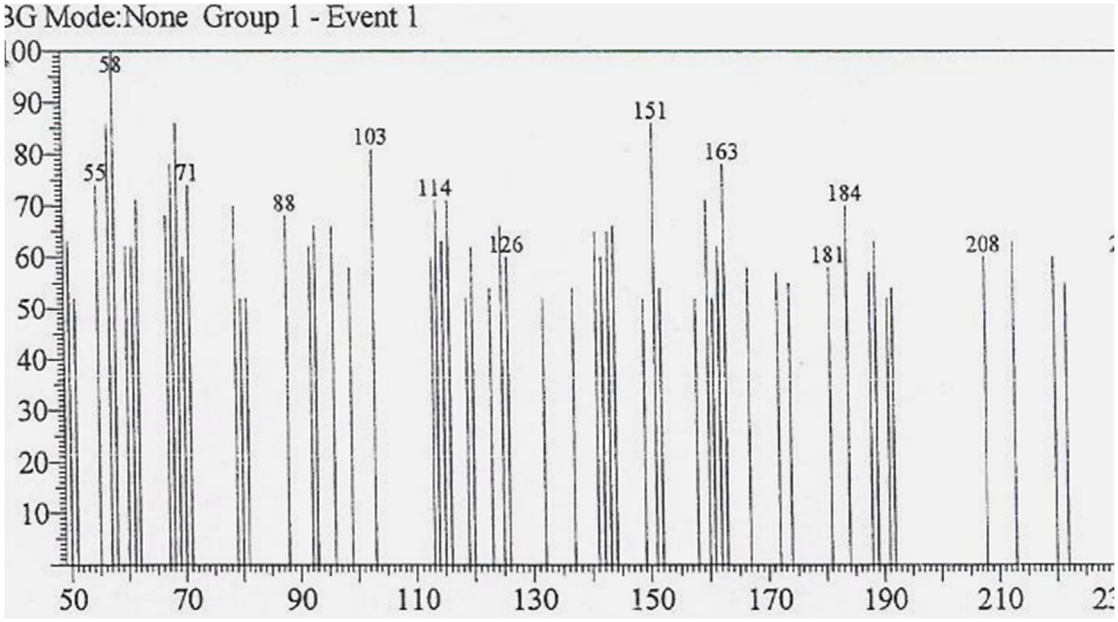
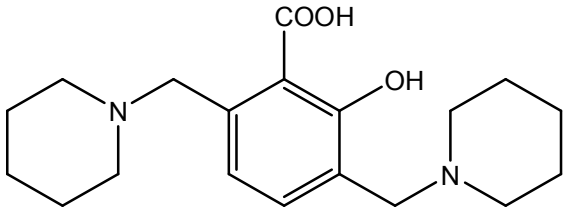


Fig.7: Mass spectrum of compound II

On the basis of such cumulative data structure II above was assigned for this Mannich base.

3.3-Synthesis of the Mannich base(III)



2-hydroxy-3,6-bis-piperidinomethylbenzoicacid

III

The Mannich base III was synthesized by refluxing a mixture of formalin , salicylic acid and piperidine in absolute ethanol for one hour.

The UV spectrum of compound II (Fig.8) showed λ_{max} (MeOH) 230,310nm .

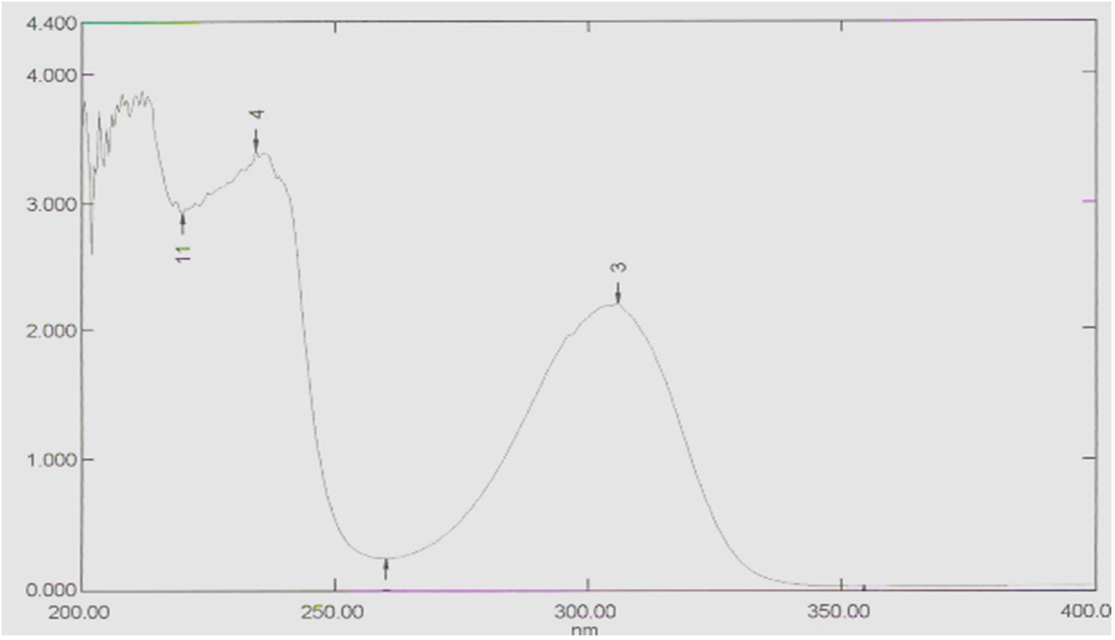


Fig.8: UV spectrum of compound III

The IR spectrum (Fig.9) showed v(KBr) 659,759,802(C-H, Ar., bending) , 1157(C-O) ,1444,1483, 1586(C=C, Ar) , 1658(C=O) 2808(C-H, aliphatic), and 3240cm^{-1}(OH).

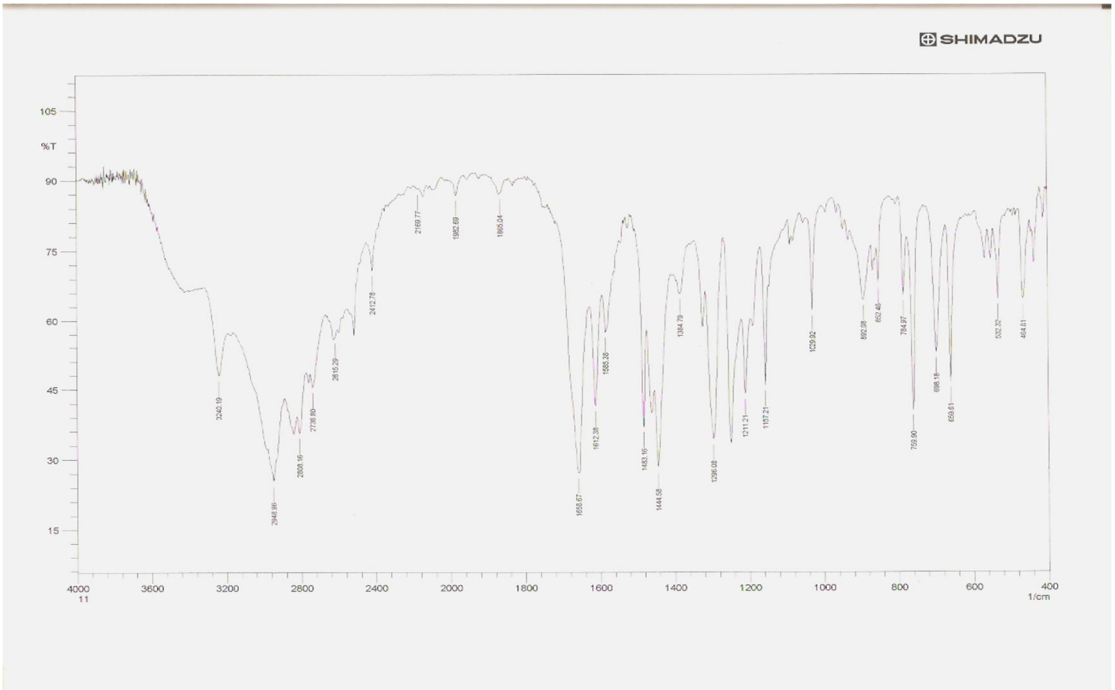


Fig.9: IR spectrum of compound III

The ^{1}H NMR spectrum (Fig.10) revealed the following signals:

δ 1.52	Singlet	12H
δ 1.66	Singlet	8H
δ 3.33	Singlet	4H
δ 6.93	Doublet	1H
δ 7.47	Doublet	1H

The signal at δ 2.52(12H) was assigned to six methylene moieties(neighboring oxygen in piperidine moiety), while the resonance at δ 1.66(8H) accounts for four methylenes(.

The singlet at δ 3.33(4H) was assigned for two methylenes linked to an aromatic ring. The ortho coupled aromatic protons at C_4 and C_5 resonate as a double doublet at δ 6.93 and δ 7.47 ppm respectively.

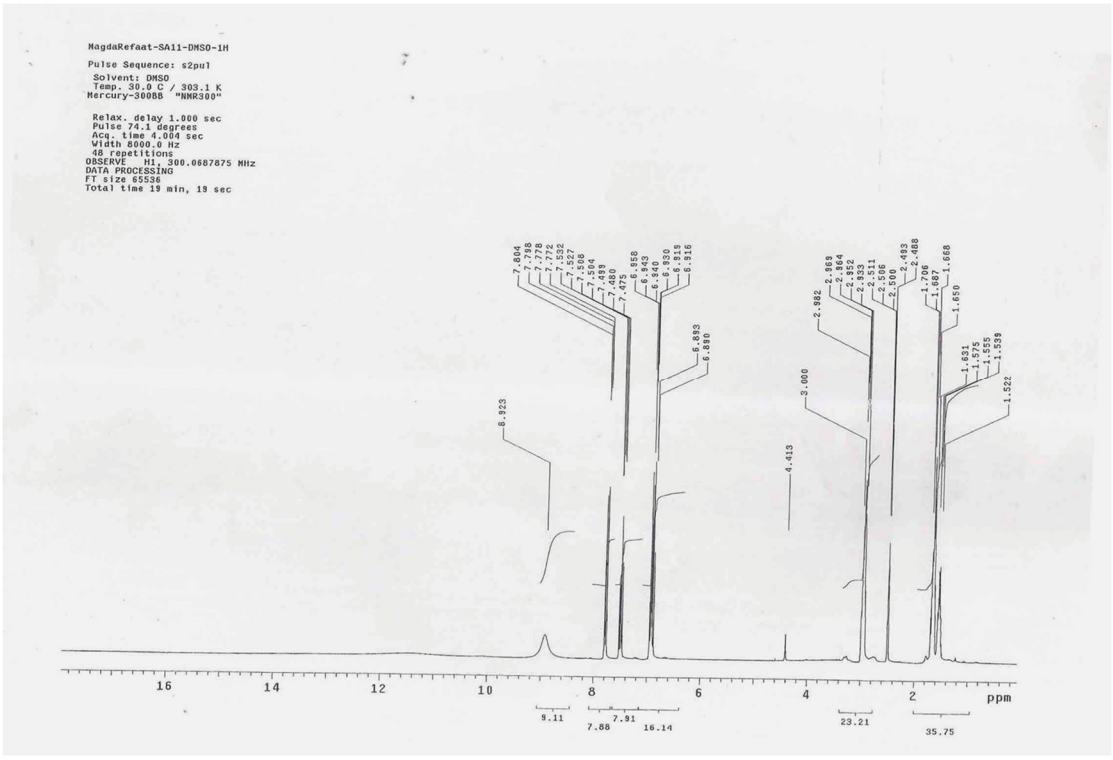


Fig. 10:[1]H NMR spectrum of compound III

The Mass spectrum (Fig.11) gave m/z318 for the molecular ion.

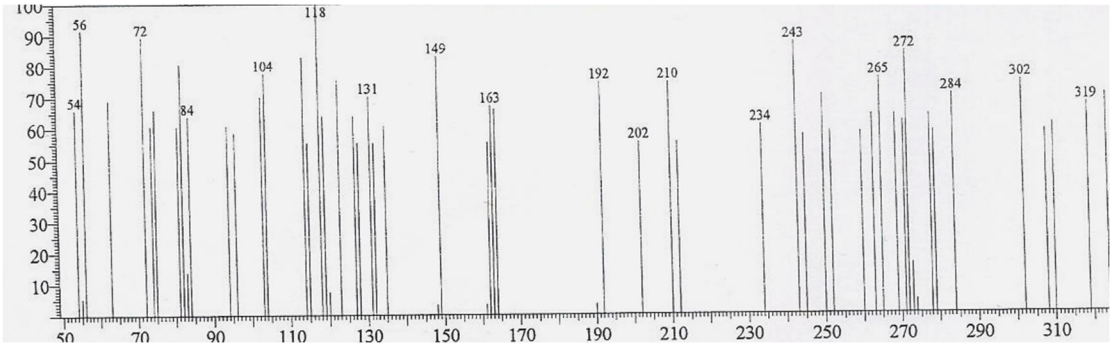
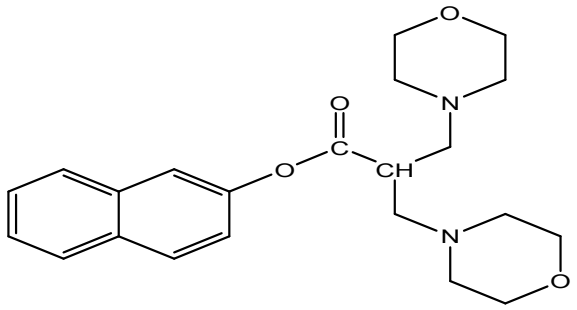


Fig.11: Mass spectrum of compound III

On the basis of such accumulative data structure III above was assigned for this Mannich base.

3.4-Synthesis of the Mannich base(IV)



1,1-bis-morpholinomethyl-2-naphthylacetate

IV

The Mannich base IV was synthesized by refluxing a mixture of formalin ,2-naphylacetate and morpholine in absolute ethanol for one hour.

The UV spectrum of compound IV (Fig.12) showed λ_{max} (MeOH) 275,332nm.

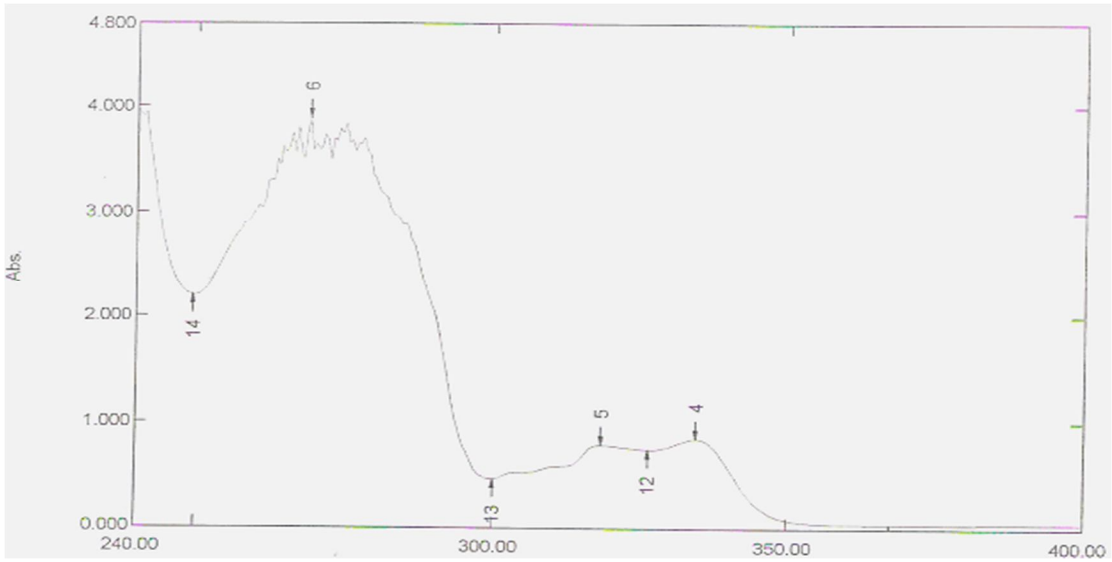


Fig.12: UV spectrum of compound IV

The IR spectrum (Fig.13) showed v(KBr) 705,817(C-H, Ar., bending) , 1114(C-O) ,1417,1458, 1593(C=C, Ar) , 1757(C=O) 2850(C-H, aliphatic)cm^{-1}.

Fig.13: IR spectrum of compound IV

The ^{1}H NMR spectrum (Fig.14) revealed the following signals:

δ 2.33	Singlet	12H
δ 2.52	Singlet	8H
δ 3.56	Singlet	2H
δ 7.07	Doublet	1H
δ 7.27	Doublet	1H
δ 7.33	Doublet	1H
δ 7.67	Doublet	1H

The signal at δ 2.33(12H) was assigned to six methylene moieties in (CH_2-N), while the resonance at δ2.52(8H) accounts for four methylenes (N). The methine proton resonates as singlet at δ 3.56ppm. The resonances at δ 7.07,7.23,7.33 and δ 7.67 ppm account for the aromatic protons.

Fig. 14:^{1}H NMR spectrum of compound IV

The Mass spectrum (Fig.15) gave m/z281 for the molecular ion.

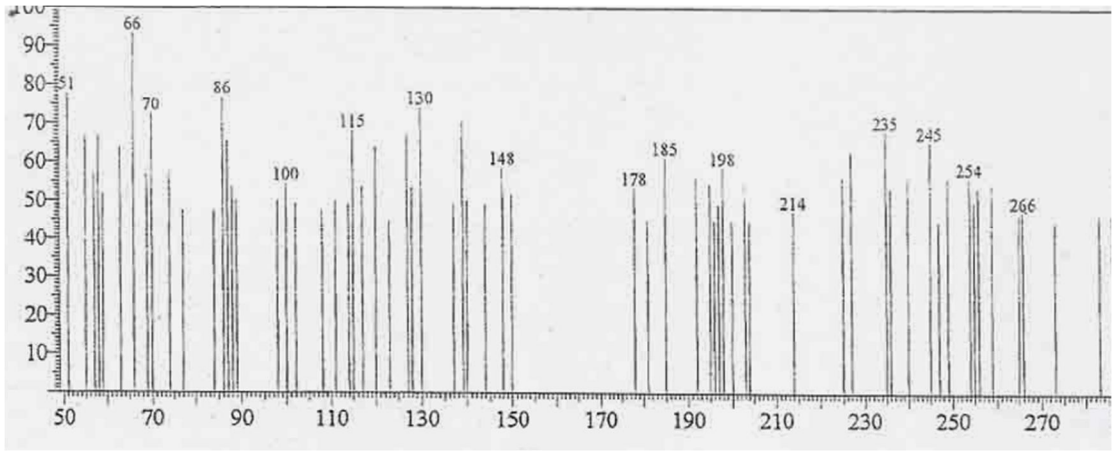
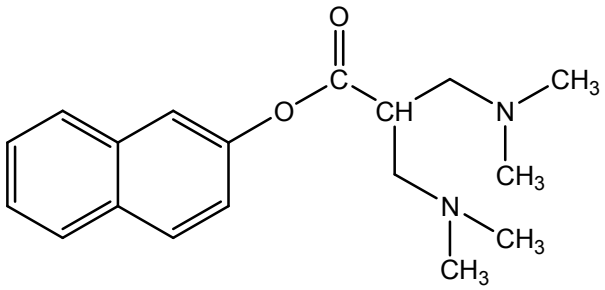


Fig.15: Mass spectrum of compound IV

On the basis of such cumulative data structure IV above was assigned for this Mannich base.

3.5-Synthesis of the Mannich base(V)



1,1-bis-dimethylaminomethyl-2-naphthylacetate

V

The Mannich base V was synthesized by refluxing a mixture of formalin , 2-naphylacetate and dimethylamine in absolute ethanol for one hour.

The UV spectrum of compound V (Fig.16) showed λ_{max} (MeOH) 274,317nm .

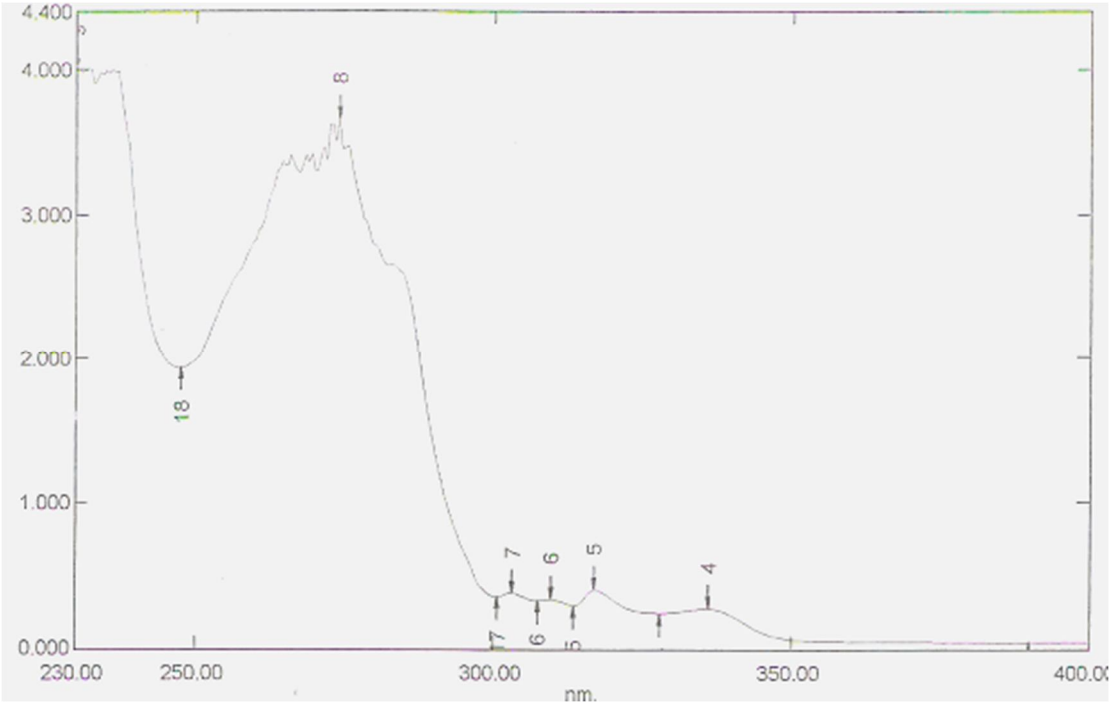


Fig.16: UV spectrum of compound V

The IR spectrum (Fig.17) showed v(KBr) 609,752,819(C-H, Ar., bending) , 1213(C-O) ,1434,1461, 1508(C=C, Ar) , 1755(C=O) and 3058 cm^{-1} (C-H, aliph.).

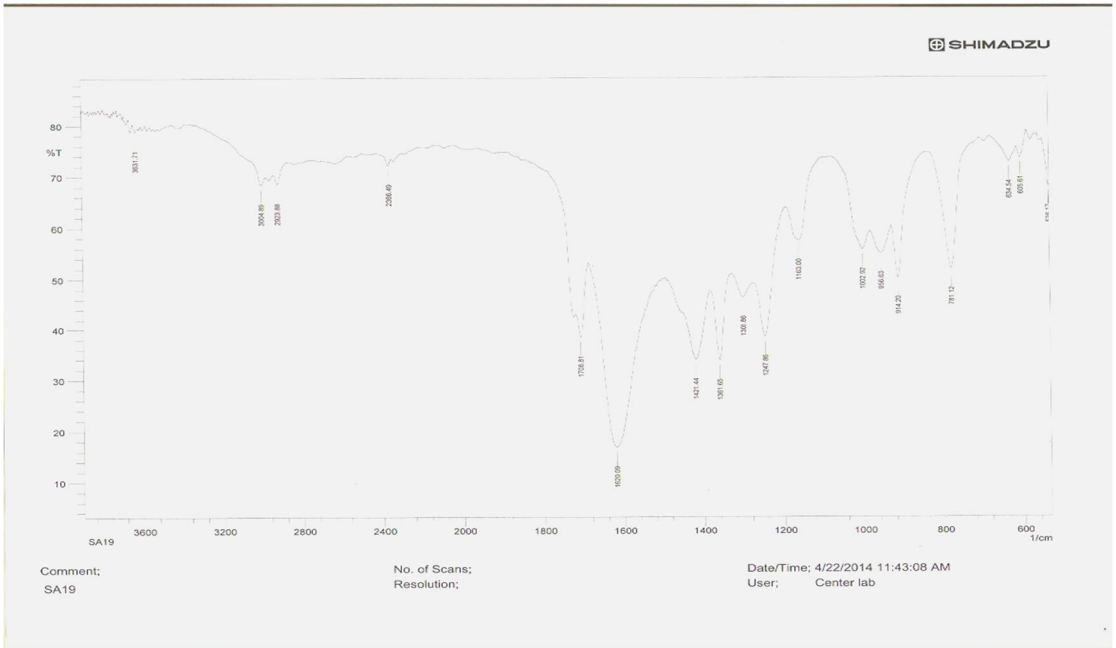


Fig.17: IR spectrum of compound V

The ^{1}H NMR spectrum (Fig.18) revealed the following signals:

δ 2.33	Singlet	12H
δ 2.50	Singlet	4H
δ 3.31	Singlet	2H
δ 7.07	Doublet	1H
δ 7.27	Doublet	1H
δ 7.33	Doublet	1H
δ 7.67	Doublet	1H

The signal at δ 2.33(12H) was assigned to six methyl's, while the resonance at δ2.50(8H) accounts for two methylenes . The methine proton resonates as singlet at δ 3.31ppm.The resonances at δ 7.07,7.27,7.33 and δ 7.67 ppm account for the aromatic protons.

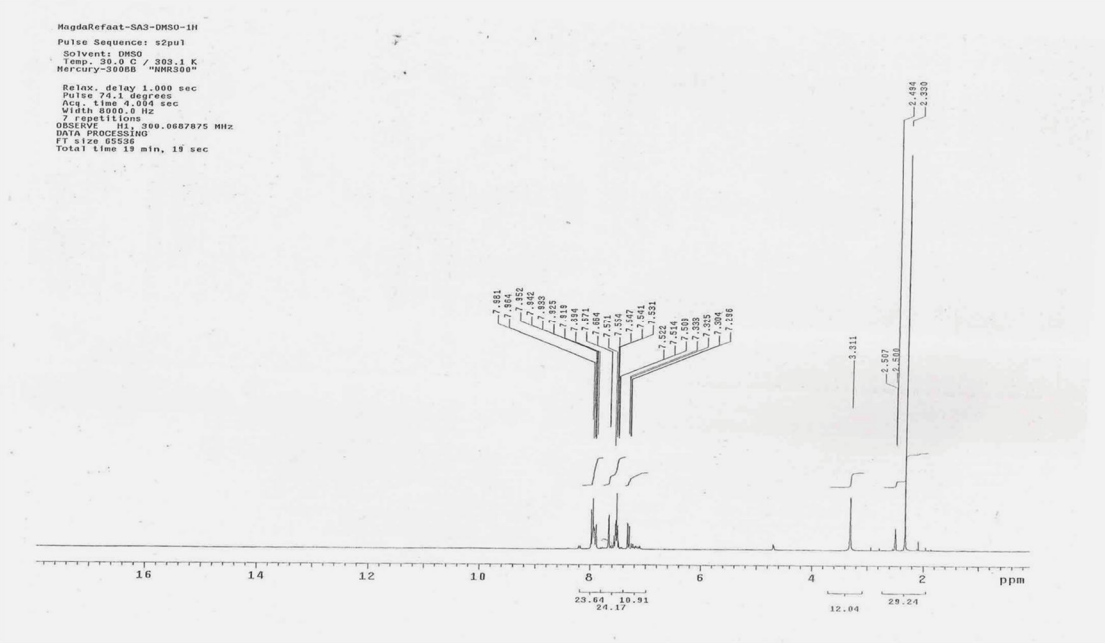


Fig. 18:[1]H NMR spectrum of compound v

The Mass spectrum (Fig.19) gave m/z299 for the molecular ion.

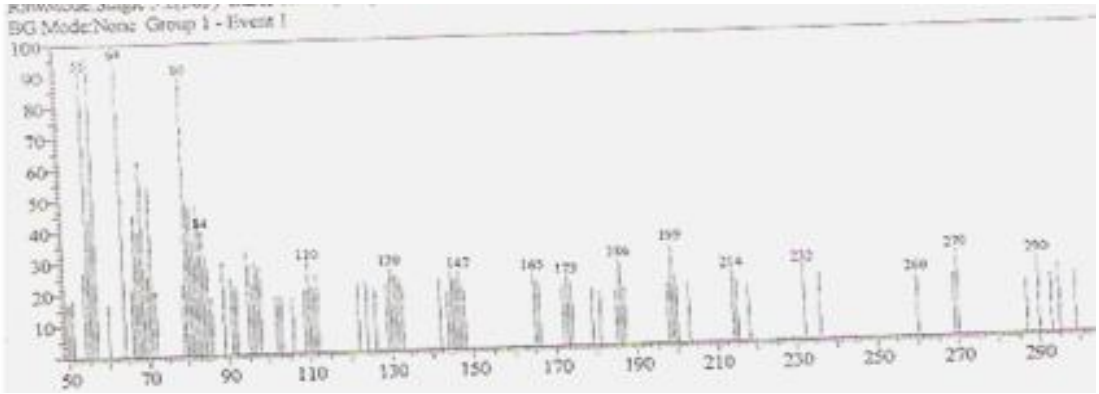
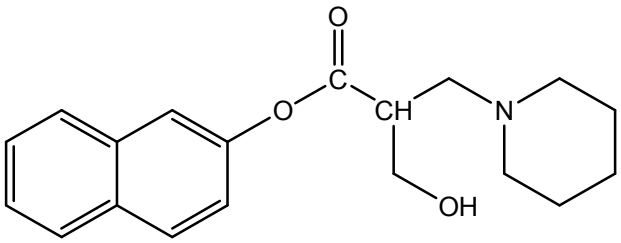


Fig.19: Mass spectrum of compound V

On the basis of such cumulative data structure V above was assigned for this Mannich base.

3.6-Synthesis of the Mannich base (VI)



1-hydroxymethyl-1-piperidinomethyl-2-naphthylacetate

VI

The Mannich base III was synthesized by refluxing a mixture of formalin , 2-naphylacetate and piperidine in absolute ethanol for one hour.

The UV spectrum of compound VI (Fig.20) showed λ_{max} (MeOH) 219,274,317nm.

Fig.20: UV spectrum of compound VI

The IR spectrum (Fig.21) showed v(KBr) 761,823,925(C-H, Ar., bending) , 1215(C-O) ,1460,1508, 1591(C=C, Ar) , 1755(C=O),2948 (CH, aliphatic).

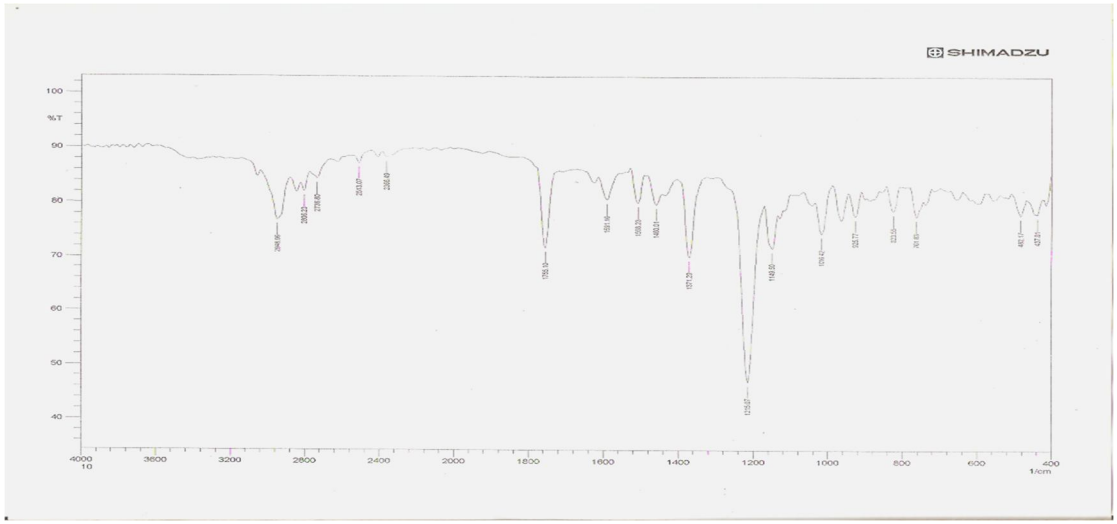


Fig.21: IR spectrum of compound VI

The ^{1}H NMR spectrum (Fig.22) revealed the following signals:

δ 1.64	Doublet	2H
δ 2.32	Singlet	6H
δ 2.49	Singlet	6H
δ 3.11	Singlet	1H
δ 7.29	Doublet	1H
δ 7.55	Doublet	1H
δ 7.96	Doublet	1H

The signal at δ 1.64(2H) was assigned for a methylene moiety $-CH_2-OH$,The resonance at δ 2.32(6H) is characteristic of three methylenes ( ), while the resonance at δ2.49(6H) accounts for three methylenes in ( ).The methine proton resonates as singlet at δ 3.11ppm.The resonances at δ 7.29,7.55 and δ 7.96 ppm account for the aromatic protons.

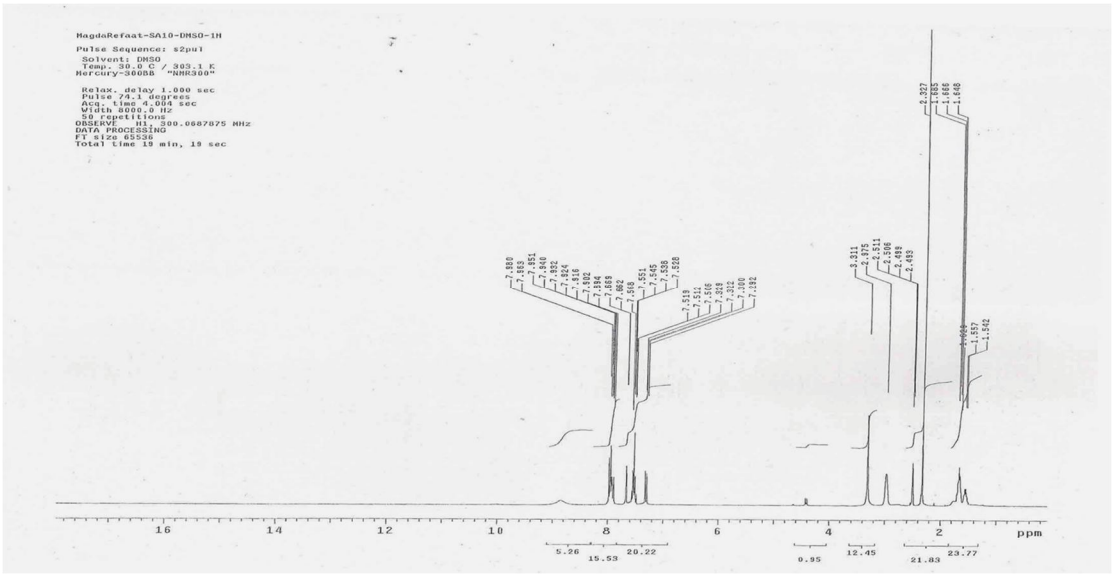


Fig.22: ^{1}H NMR spectrum of compound VI

The Mass spectrum (Fig.23) gave m/z312 for the molecular ion.

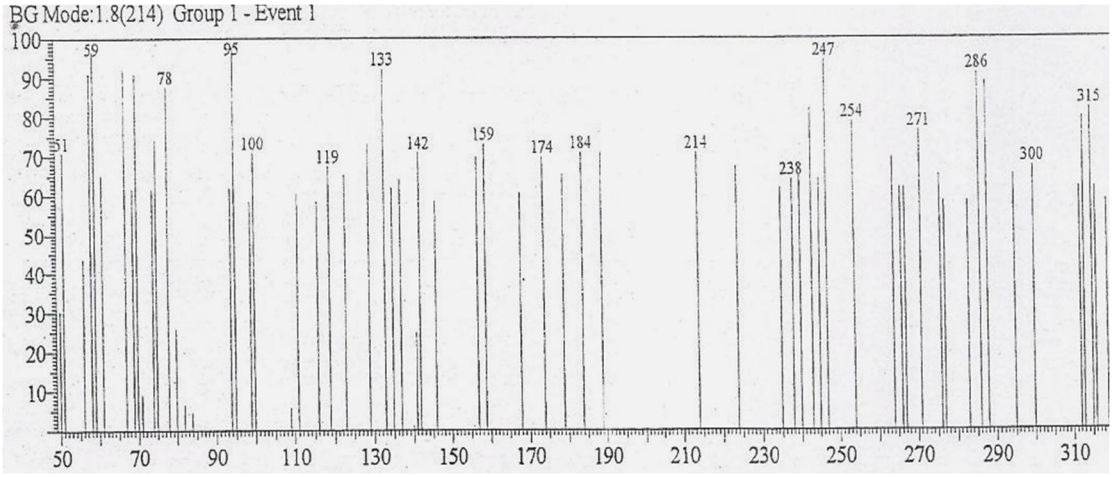
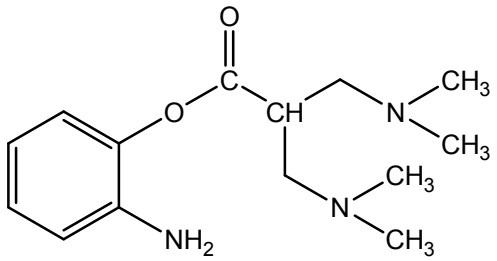


Fig.23: Mass spectrum of compound VI

On the basis of such evidence structure VI above was assigned for this Mannich base.

3.7-Synthesis of the Mannich base (VII)



1,1-bis-dimethylaminomethyl-2-aminophenylacetate

VII

The Mannich base VII was synthesized by refluxing a mixture of formalin, 2-aminophenylacetate and dimethylamine in absolute ethanol for one hour.

The UV spectrum of compound VII (Fig.24) showed λ_{max} (MeOH) 243,386nm .

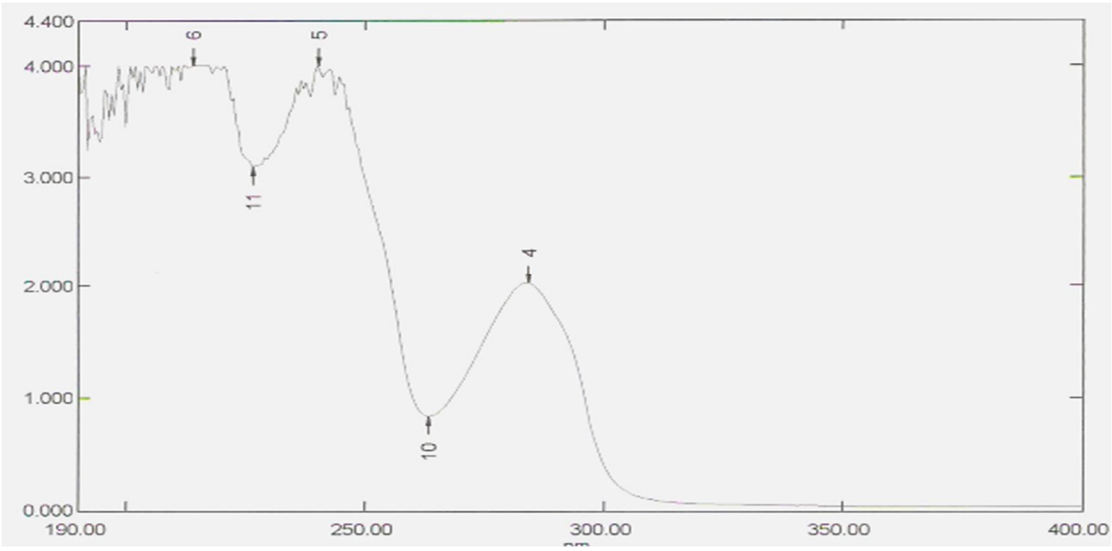


Fig.24: UV spectrum of compound VII

The IR spectrum (Fig.25) showed v(KBr) 661,785,842(C-H, Ar., bending) , 1282(C-O) ,1450,1541(C=C, Ar) , 1658(C=O) 2881 cm^{-1} (C-H, aliphatic).

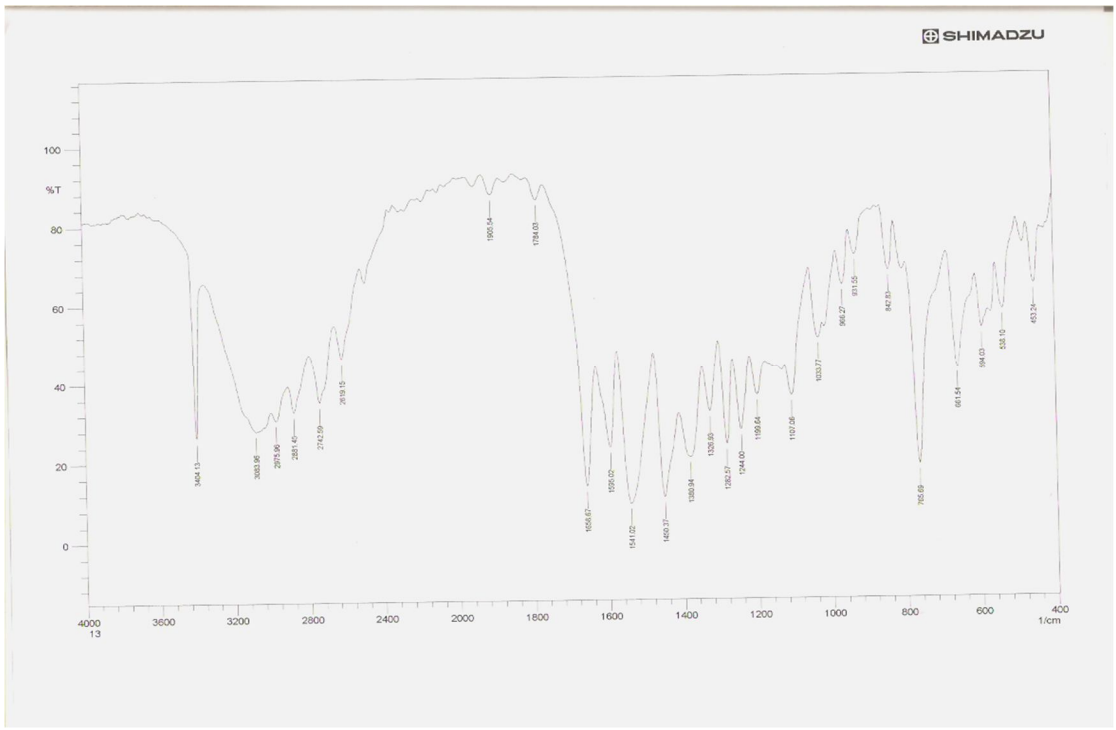


Fig.25: IR spectrum of compound VII

The ^{1}H NMR spectrum (Fig.26) revealed the following signals:

δ 2.08	Singlet	12H
δ 2.50	Singlet	4H
δ 6.72-6.86	Multiplet	4H
δ 6.93	Singlet	1H

The signal at δ 2.08(s,12H) was assigned for four methyl's. The resonance at δ 2.50(s,4H) is characteristic of two methylenes , while the multiplet at δ2.49(6H) accounts for the aromatic protons . The protons of the amino function resonate well downfield as singlet at δ 6.93ppm.

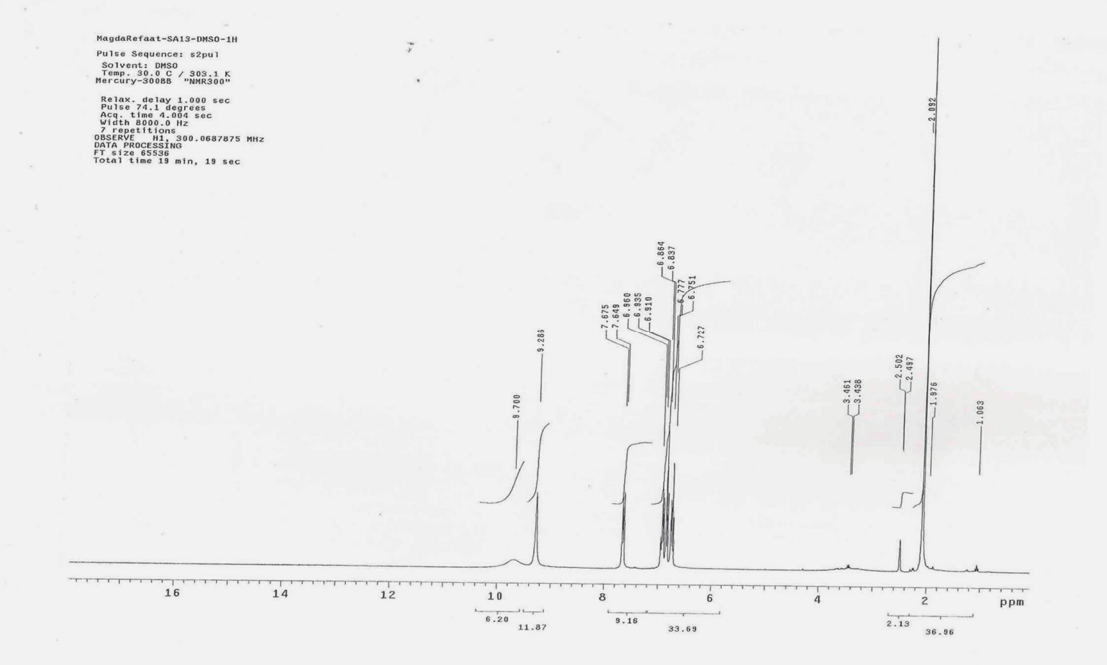


Fig. 26:[1]H NMR spectrum of compound VII

The Mass spectrum (Fig.27) gave m/z263 for (M^+ + 2H).

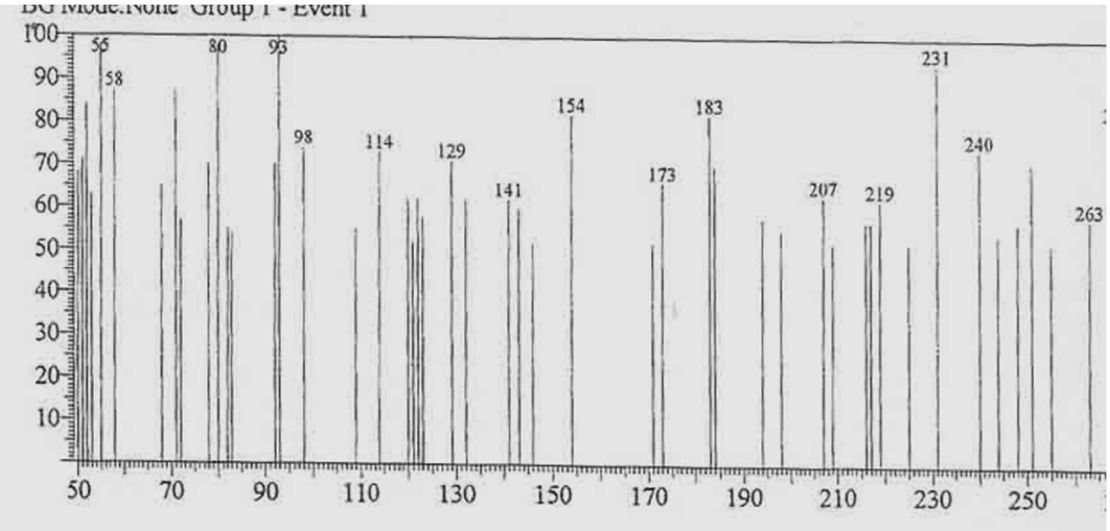
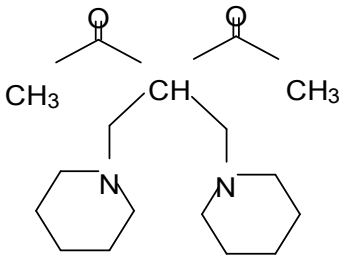


Fig.27 Mass spectrum of compound VII

On the basis of such spectral data structure VII above was assigned for this Mannich base.

3.8-Synthesis of the Mannich base (VIII)



3,3-bis-piperidinomethylpentan-2,4-dione

VIII

The Mannich base VIII was synthesized by refluxing a mixture of formalin , acetyl acetone and piperidine in absolute ethanol at 0^0C.

The UV spectrum of compound VIII (Fig.28) showed λ_{max} (MeOH) 230,335nm .

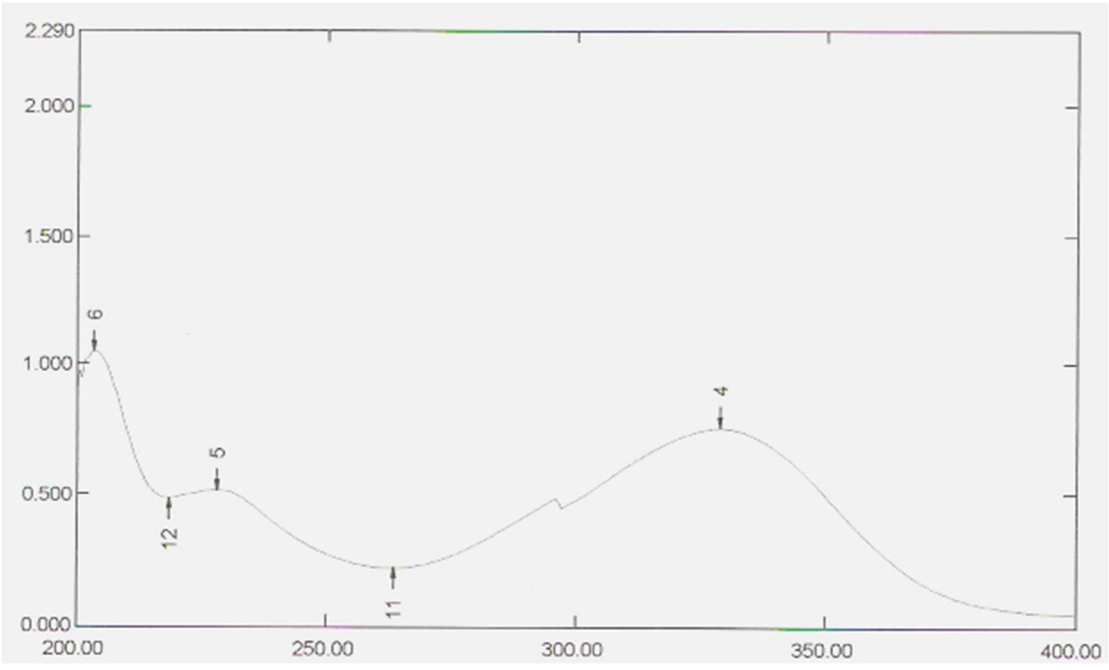


Fig.28: UV spectrum of compound viii

The IR spectrum (Fig.29) showed ν(KBr) 624,864,945(C-H, Ar., bending) , 1080(C-N) ,1480,1591(C=C, Ar) , 1676(C=O) 2952 cm^{-1} (C-H, aliphatic).

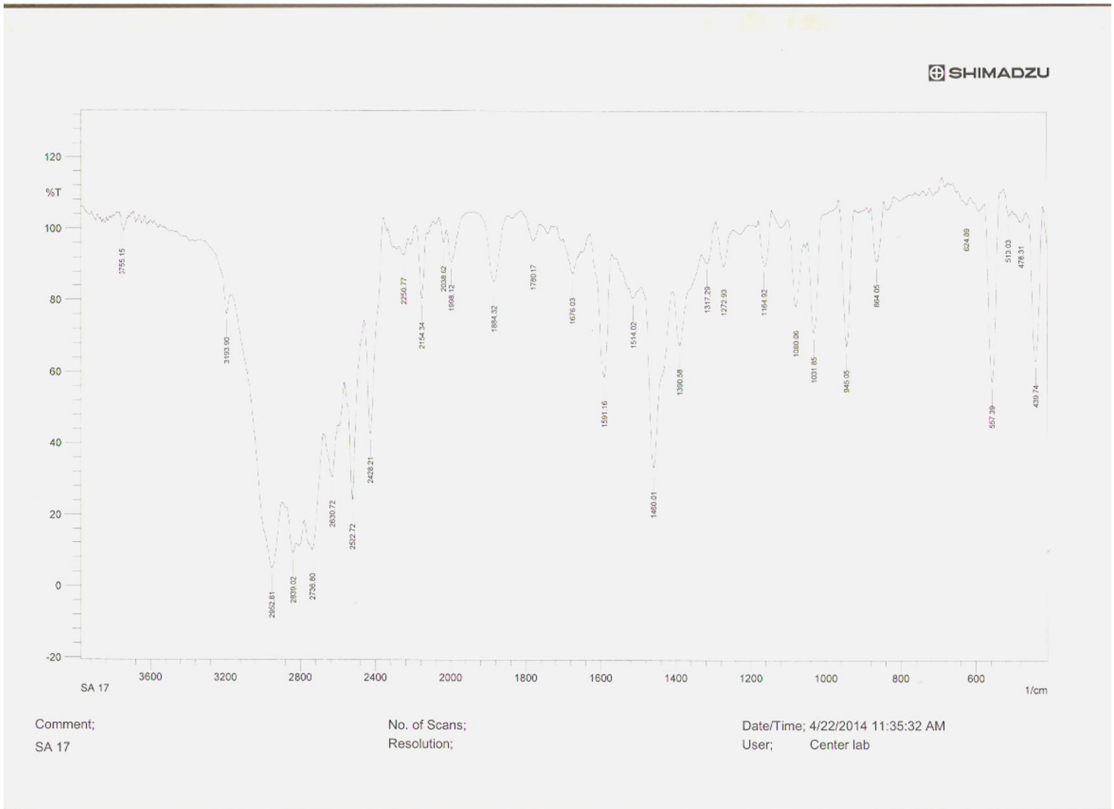


Fig.29: IR spectrum of compound viii

The ^{1}H NMR spectrum (Fig.30) revealed the following signals:

δ 1.59	Singlet	6H
δ 1.64	Singlet	4H
δ 2.88	Singlet	4H
δ 6.93	Singlet	1H

The signal at δ 1.59(s,6H) was assigned for two methyl's , while the resonance at δ 1.64(s,12H) is characteristic of six methylenes in (⟩). The singlet at δ2.88(4H) accounts for two methylene moieties . The methine proton resonates well downfield as singlet at δ 3.01ppm.

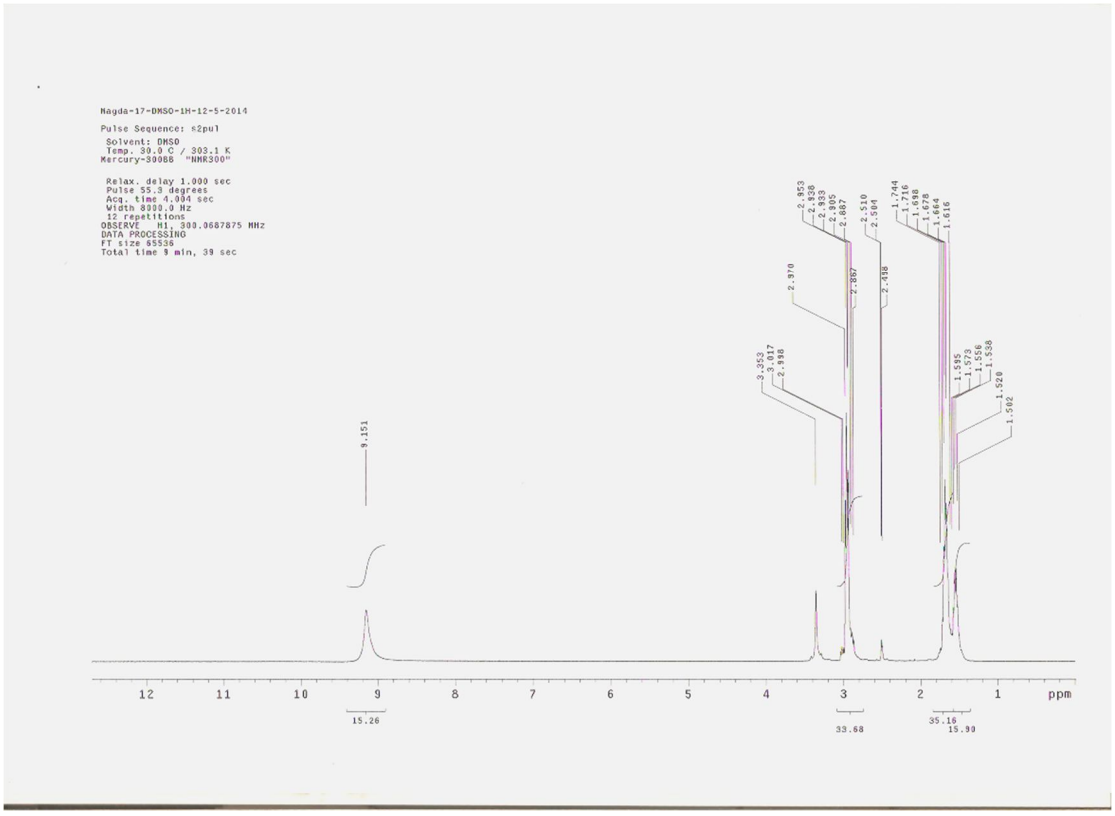


Fig. 30:[1]H NMR spectrum of compound VII

The Mass spectrum (Fig.31) gave m/z312 for the molecular ion.

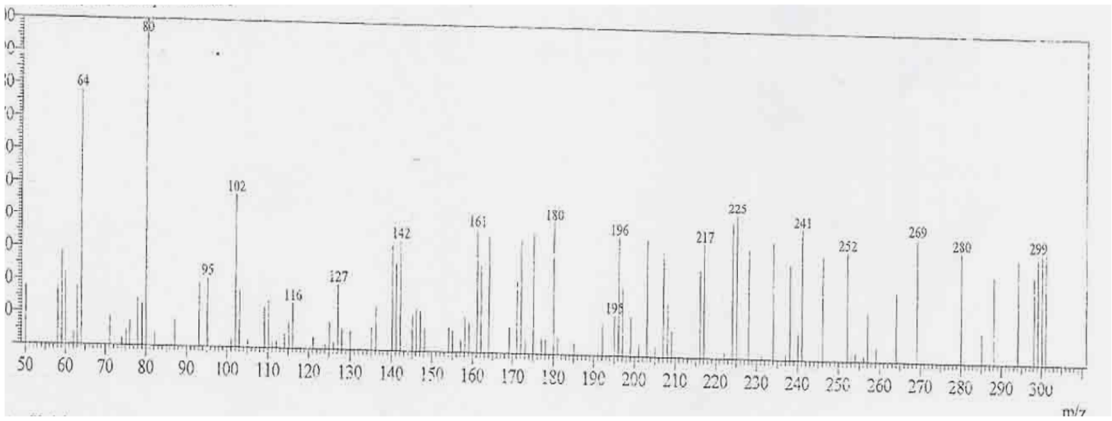
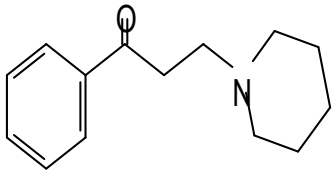


Fig.31: Mass spectrum of compound VIII

On the basis of such cumulative data structure VIII above was assigned for this Mannich base.

3.9-Synthesis of the Mannich base (IX)



1-Piperidinomethyl-3-phenylpropanone

IX

The Mannich base IX was synthesized by refluxing a mixture of formalin, acetophenone and piperidine in absolute ethanol for one hour.

The UV spectrum of compound IX (Fig.32) showed λ_{max} (MeOH) 265,276nm .

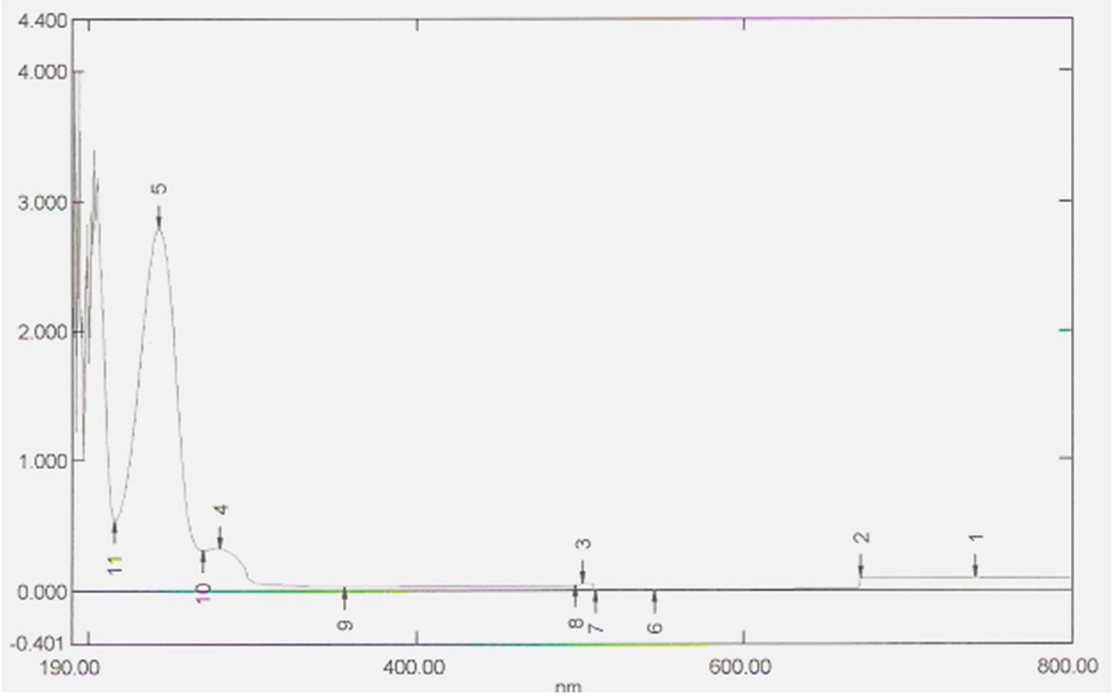


Fig32: UV spectrum of compound IX

The IR spectrum (Fig.33) showed v(KBr) 698,880(C-H, Ar., bending) , 1224(C-N) ,1458,1591(C=C, Ar) , 1681(C=O) 2945 cm^{-1} (C-H, aliphatic).

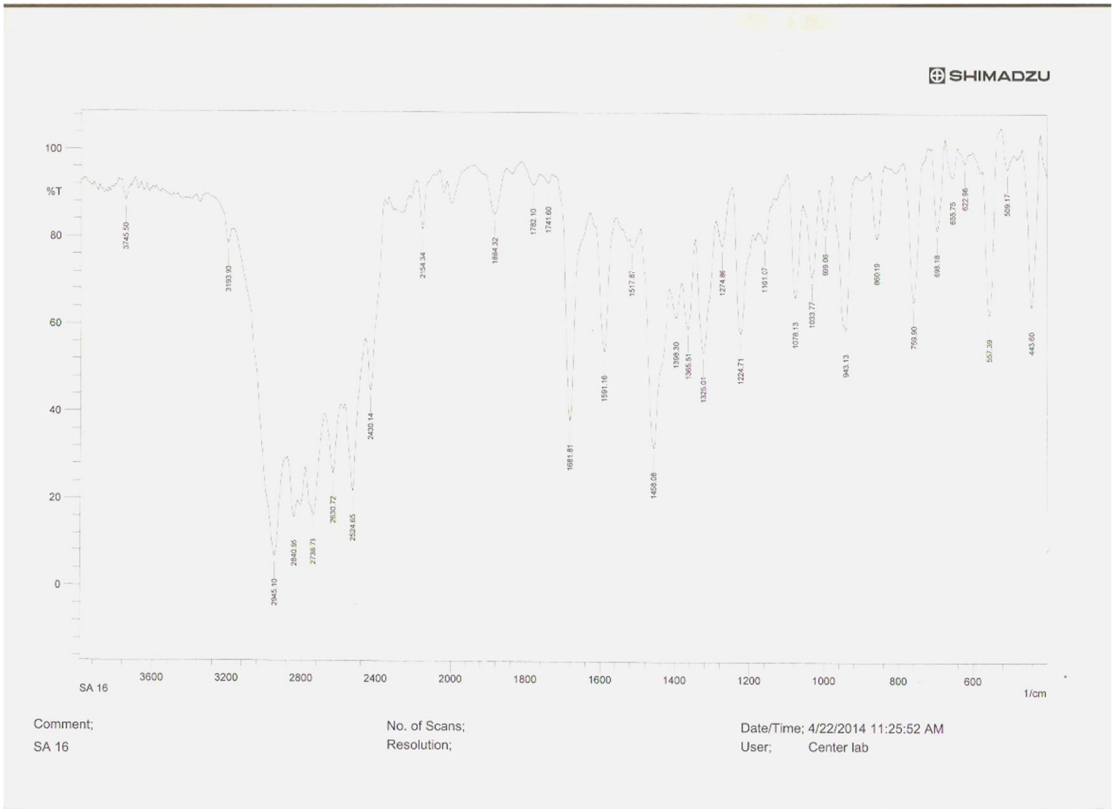


Fig.33: IR spectrum of compound IX

The ^{1}HNMR spectrum (Fig.34) revealed the following signals:

δ 2.08	Singlet	6H
δ 2.49	Singlet	6H
δ 3.32	Singlet	2H
δ 6.72-6.95	Multiplet	5H
δ 7.65	Doublet	1H

The signal at δ 2.08(s,6H) was assigned for( ) , while the resonance at δ 2.49(s,6H) is characteristic of three methylenes in ( ) .The singlet at δ3.32(2H) accounts for a methylene moiety being shifted downfield due to the deshielding influence of the neighboring keto function. .The multiplet at δ 6.72-6.95 and the doublet at δ 7.65 account for the aromatic protons.

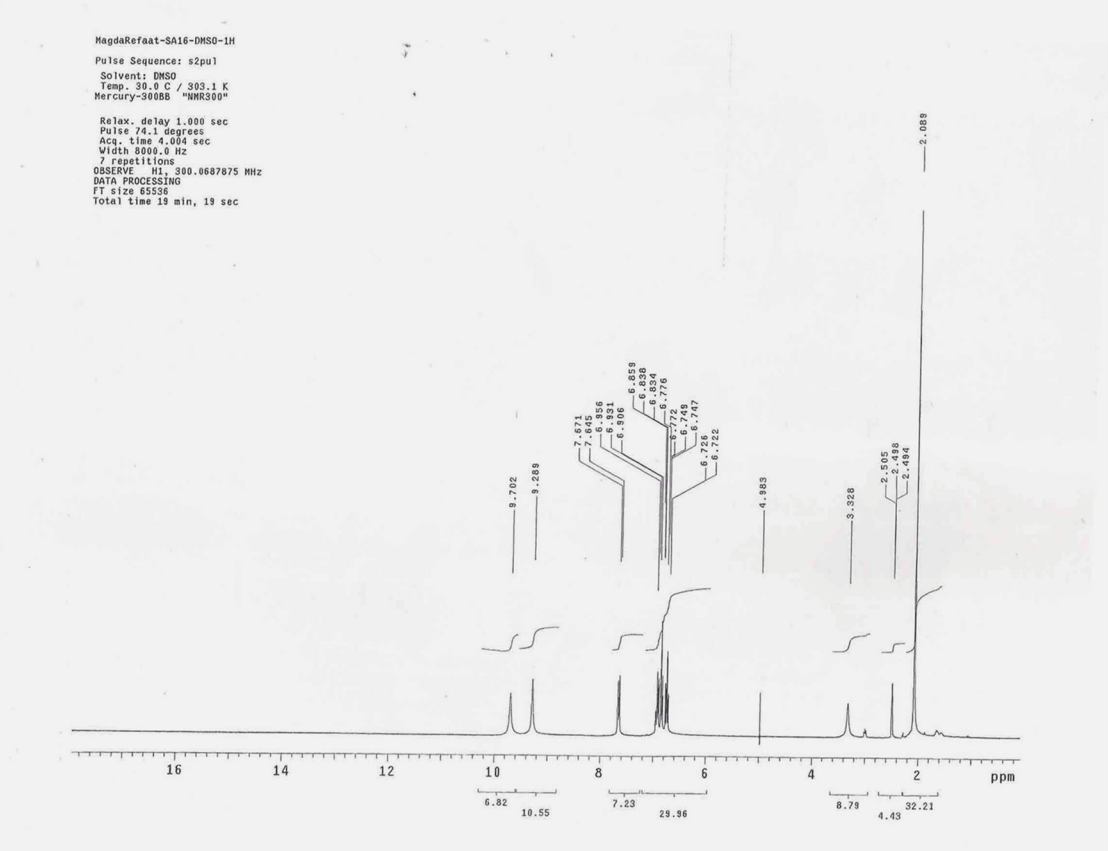


Fig. 34:[1]H NMR spectrum of compound IX

The Mass spectrum (Fig.35) gave m/z212 for the molecular ion.

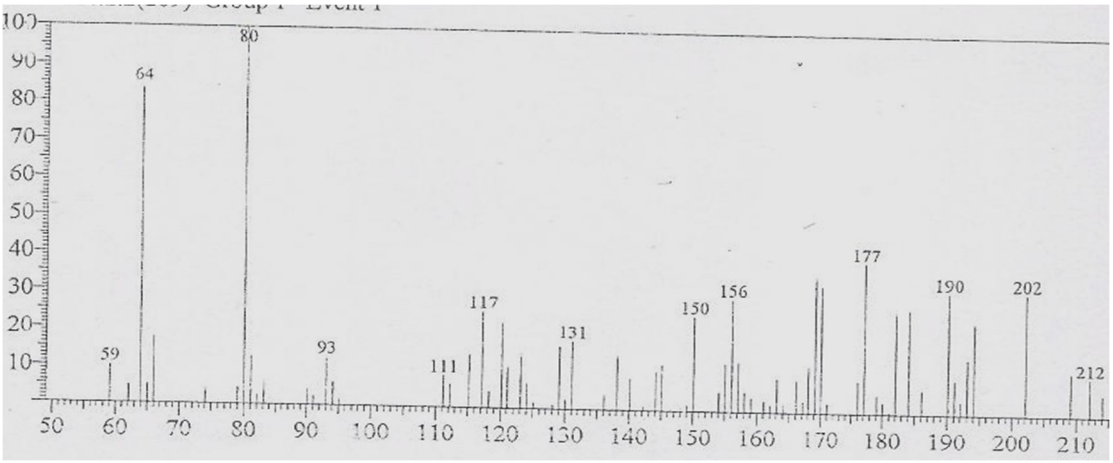


Fig. 35:Mass spectrum of compound IX

On the basis of such accumulative data structure IX above was assigned for this Mannich base.

3.10- Biological activity

The synthesized Mannich bases were evaluated for their antimicrobial activity against some standard human pathogens namely, *Staphylococcus aureus* (S.a), *Escherichia coli* (E.c.), *Pseudomonas aeruginosa* (Ps.a), *Bacillus subtilis* (B.s.), *Aspergillus Niger* (A.n.), and *Candida albicans* (C.a)-table 3.1.

Table 3.1: Test organisms

Ser. No	Micro organism	Type	Source
1	*Staphylococcus aureus*	G+ve	ATCC**25923
2	*Pseudomonas aeruginosa*	G-ve	NCTC* 6750
3	*Escherichia coli*	G-ve	ATCC**25922
4	*Bacillus subtilis*	G+ve	ATCC**25925
5	*Aspergillus Niger*	fungi	ATCC** 9736
6	*Candida albicans*	fungi	NCTC* 10716

NCTC*. National Collection of Type Culture, Colindale, England.

ATCC**. American Type Culture Collection, Maryland, USA.

The cup-plate agar diffusion method was adopted with some minor modifications. The diameters of inhibition zones are depicted in table 3.2.

Table 3.2: Diameter of inhibition zones of synthesized Mannich bases

Organism	Compound								
	I	II	III	IV	V	VI	VII	VIII	IX
Bacillus subtilis	14	25	25	16	15	22	15	23	20
Escherichia coli	15	27	29	15	13	21	18	18	20
Pseudomonas aeruginosa	16	25	26	15	16	22	16	21	23
Staphylococus aureus	15	23	23	14	13	19	17	17	21
Candida albicans	15	30	30	21	20	24	25	14	15
Aspergillus niger	17	35	35	20	21	30	16	15	21

Compound I showed activity against all test organisms except for B.s. Compound II exhibited significant antimicrobial activity against all test organisms . The same trend was observed for compound III- both compounds were derived from salicylic acid.

Compound IV showed significant antifungal activity , but it was inactive against S.a. Also compound V exhibited significant antifungal activity, but was inactive against E.c.

Significant activity was exhibited by compound VI . It showed activity against all test organisms. Compound VII exhibited promising activity . However , compound VIII gave weak antifungal activity, but significant antibacterial activity. `Promising antifungal and significant antibacterial activity was given by IX.

References

References:

(1). Tramontini, M., *Synthesis*, **63**, 702-720, (1973).

(2).Jack Li and et al, ″Modern Organic Synthesis in the Laboratory″, Oxford University Press, New York, U.S.A., (2007).

(3). Solomon's, T.W. and Fryhle, C.B., ″Organic Chemistry″, 10thed, John Wiley and Sons, U.S.A., (2011).

(4). Carey, F.A. and Sandburg, R.J., ″Advanced Organic Chemistry; Part B: Reactions and Synthesis″, 5thed, Springer, New York, U.S.A., (2007).

(5). Gatterman, L., ″Laboratory Methods of Organic Chemistry″, 24thed, The McMillan Company, New York., U.S.A., (1937).

(6). Fieser, L.F. and Williamson, K.L., ″Organic Experiments″, 7thed, D.C. Health and Company, U.S.A., (1992).

(7). Monson, R.S., ″Advanced Organic Chemistry; Methods and Techniques″, Academic Press, New York, U.S.A., (1971).

(8).McMurry, J., ″Organic Chemistry″, 7thed, Thomson Learning, U.S.A., (2008).

(9). McMurry, J., ″Organic Chemistry″, 5thed, Brooks / Cole, U.S.A., (2000).

(10). Smith, M.B. and March, J., ″Advanced Organic Chemistry″, 6thed, pp., John Wiley and Sons, U.S.A., (2007).

(11). Risch, N. and *et al*, *Angew. Chem. Int. Ed.*, **37**, 1044-1075, (1998).

(12). Overmann, L.E. and Rica, D.J., *In Comprehensive Organic Synthesis*, Vol. **2**, 1007, Oxford, Pergamon, (1991).

(13). Schreiber, J. and *et al*, *Angew. Chem.*, **83**, 355, (1971); *Angew. Chem. Int. Ed. Engl.*, **10**, 330, (1971).

(14). Donishefsky, S. and *et al*, *J. Am. Chem. Soc.*, **98**, 6715, (1976).

(15). Zaragoza, F.D., ″Side Reaction in Organic Synthesis″, Wiley-VCH, Weinheim, Germany, ( ).

(16). Robinson, R., *J. Chem. Soc.*, **111**, 762, (1917).

(17). Blick, F.F., The Mannich reaction, (Adams, R. and et al). ″Organic reaction″, Vol. **1**, John Wiley and Sons, New York, U.S.A, (1942).

(18). Jerry, M., ″Advanced Organic Chemistry; Reactions, Mechanisms and Structure″, 4thed, John Wiley and Sons Inc., New York, U.S.A., (1992).

(19). Mannich and Ritsert, *Ber.*, **57**, 1116, (1924).

(20). Mannich and Curtis, *Arch. Pharm.*, **264**, 741, (1926).

(21). Mannich and Braun, *Ber.*, **53**, 1874, (1920).

(22). Decombe, *Compt. Rend.*, **197**, 258, (1933).

(23). Mannich and Kather, *Arch. Pharm.*, **257**, 18, (1919).

(24). Xiao-Hue and *et al*, , *Eur. J. Chem.*, **3**(2), 258-266, (2012).

(25). Mannich and Ball, *Arch. Pharm.*, **65**, 264, (1926); Mannich and Ritsert, *Ibid*, **264**, 164, (1926).

(26). Mannich and Abdullah, *Ber.*, **68**, 113, (1935).

(27). Schäfer and Tollens, *Ber.*, **39**, 2181, (1906).

(28). Mannich and Krösch, *Arch. Pharm.*, **250**, 647, (1912).

(29). Mannich, Lesser and Silten, *Ber.*, **65**, 378, (1932).

(30). Mannich and Wielder, *Ber.*, **53**, 385, (1932).

(31). Mannich and Ganz, *Ber.*, **55**, 3486, (1922).

(32). Mannich and Bauroth, *Ber.*, **57**, 108, (1924).

(33). Mannich and Kather, *Ber.*, **53**,1368, (1920).

(34). Mannich and Schuman, *Ber.*, **69**, 2299, (1936).

(35). Mannich and Viet, *Ber.*, **68**, 506, (1935).

(36). Mannich and Moths, *Ber.*, **63**, 608, (1930).

(37). *Ger. Pat.*, **92**, 309; *Frdl.*, **4**, 103, (1899).

(38). Decombe, *Compt. Rend.*, **196**, 866, (1933).

(39). Bruson and McMullen, *J. Am. Chem. Soc.*, **63**, 270, (1941).

(40). Caldwell and Tampson, *J. Am. Chem. Soc.*, **61**, 765, (1939).

(41). Burke, W.J. and et al, *J. Org. Chem.*, **29**, 407, (1964).

(42). Bucherle, A. and et al, *Chin. Ther.*, **2**, 410; *C. A.*, **61**, 14630, (1964).

(43). Mathai, K.P., *Indian J. Chem. Soc.*, **43**, 421; *C. A.*, **65**, 18577, (1966).

(44). Burke, W.J. and *et al*, *J. Org. Chem.*, **30**, 3423, (1965).

(45). Stavrovskaya, V.I. and *et al*, *Poluch. Poluprod. Prom. Org. Sin.*, **164**, (1967); *C.A.*, **68**, 12820. (1968).

(46). Nobles, W.L. and et al, *J. Pharm. Sci.*, **52**, 600, (1963).

(47). Magarian, R.A. and Nobles, W.L., *J. Pharm. Sci.*, **56**: 987, (1967).

(48). Mehta, R.H., *Indian J. Chem.*, **2**, 336; *C. A.*, **61**, 14630, (1964).

(49). Fernandez, J.E. and Calderazzo, J.M., *J. Chem. Eng. Data.*, **10**, 402, (1965).

(50). Tseou, H. F., *Comp. Rend.*, **192**, 1242, (1931).

(51). *Ger. Pat.*, **497**, 907; *Frdl.*, **16**, 2669, (1931).

(52). Joule, J.A. and Mills, K., *Heterocyclic Chemistry*, 5thed, John Wiley and Sons, U.K., (2010).

(53). Hank, A. and Kutscher, W.Z., *Physiol. Chem.*, **338**, 272, (1964).

(54). Fuhlhage, D.W. and Vanderwerf, C.A., *J. Am. Chem. Soc.*, **80**, 6249, (1958).

(55). Temelli, B. and Unaleroglu, C., *Tetrahedron Lett.*, **46**, 7941, (2005).

(56). Smith, G.F., *Adv. Heterocycle Chem.*, **2**, 287,(1963); Zhao, Y., Beddoes, R.L. and Joule J.A., *J. Chem. Res.*(**S**), 42-44, (1997); (**M**), 0401-0429, (1997).

(57). Hartough, H.D. and Meisel, S.L., *J. Am. Chem. Soc.*, **70**, 4018, (1948).

(58). Barker, J.M., Huddleston, P.R. and Wood, M.L., *Synth. Commun.,* **59**, (1975).

(59). Dowle, M.D. and *et al*, *Synthesis*, **73**, (1983).

(60). Harwood, L.M. and *et al*, *Chem. Commun.*, **1953**,(1996); Petasis, N.A., Goodman, A. and Zavialov, I.A., *Tetrahedron*, **53**, 16463, (1997).

(61). Gill, E.W. and Ing, H.R., *J. Chem. Soc.*, 4728,(1958); Eliel, E.L. and Peckham, P.A., *J. Am. Chem. Soc.*, **72**, 1209, (1950).

(62). Heaney, H., Papageorgiow, G. and Wilkins, R.F., (1988). *Tetrahedron Lett.*, **29**, 2377.

(63). Padwa, A. and *et al*, (2003). *Tetrahedron*, **59**, 4939, (1966).

(64). Swaminathan, S. and Narisimhan, K., *Chem. Ber.*, **99**, 889, (1966).

(65). Kühn, H. and Stein, O., *Chem. Ber.*, **70**, 567, (1937).

(66). Kozikowski, A.P. and Ishida, H., *Heterocycles*, **14**, 55, (1980).

(67). Yadav, J.S. and *et al*, *Synthesis*, **719**, (2008).

(68). Xie, W. and *et al*, *Syn. Lett.*, **498**, (1999).

(69). Lei, F. and *et al*, *Syn. Lett.*, **1160**, (2003).

(70). Hahn, G. and Ludewig, H., *Chem. Ber.*, **67**, 2031, (1934).

(71). Narayaman, K. and Cook, J.M., *Tetrahedron Lett.*, **31**, 3397, (1990).

(72). Katritzky, A.R., Rewcastle, G.W. and Fan, W.Q., *J. Org. Chem.*, **53**: 5685, (1988).

(73). Gerard, A.L. and *et al*, *Tetrahedron Lett.*, **48**, 4123, (2007).

(74). Tramontini, M. and Angiolini, L.,″ Mannich base: Chemistry and Uses″, Crc, Boca Raton, Fl, (1994).

(75). Yi, L. and *et al*, *Synthesis*, **717**, (1991).

(76). Kleemann, A., Linder, E. and Engel, J., *Arznemittel*, VCH, Weinheim, Germany, (1987).

(77). Cannarsa, M.J., *Chem. Ind.(London)*, **374**, (1996).

(78). Deslong, C.P., ″Stereo electronic Effects in Organic Chemistry″, Oxford, Pergamon, (1983).

(79). Heathcock, C.H. and *et al*, *J. Am. Chem. Soc.*, **100**: 8036, (1978).

(80). Carruthers, W. and Moses, R.C., *J. Chem. Soc. Chem. Commun.*, **509**, (1987).

(81). Hong, C.Y. and *et al*, *J. Am. Chem. Soc.*, **115**, 11028, (1993).

(82). Juaristi, E., ″Enantio Selective Synthesis of β-Amino acids″, VCH, N.Y., U.S.A, (1997).

(83). Risch, N. and Arend, M., *Methoden. Org. Chem.(Houben-Weyl)*, 4thed, Vol. **E 21/b**, 1908, (1952).

(84). Pawlenko, S., *Reviews*: *Methods in Organic Chemistry*, Vol. **E 14/b**, 4thed, p. 222, Houben – Weyl, (1952).

(85). Kleinmann E.F., *In Comprehensive Organic Synthesis*, Vol. **2**, p. 893, Oxford, Pergamon, (1991).

(86). Ha, H.-J. and Ann, Y.-G., *Synth. Commun.*, **25**, 969, (1995).

(87). Verkade, J. and *et al*, *J. T. Chem. Soc. Rev*., **37**, 29-41, (2008).

(88). Paukstelis, J.V. and Cook, A.G., *Reviews*: *Enamines*: *Synthesis*, *Structure & Reactions*, 2^{ed}ed, p. 275, Dekker, N.Y., U.S.A, (1988).

(89). Winterfledt, *J. Prakt. Chem.*, **91**, 336, (1994).

(90). Polniaszek, R.P. and Bell, S.J., *Tetrahedron Lett.*, **37**, 575, (1996).

(91). Kinast, G. and Tietze, L.F., *Angew. Chem.*, **88**: 261; *Angew. Chem. Int. Ed. Engl.*, **15**, 239, (1976).

(92). Ahond, A. and *et al*, *J .Am. Chem. Soc.*, **90**, 5622, (1968).

(93). Zhao, Q.-Y. and *et al*, *Tetrahedron Asymmetr.*, **21**, 943-951, (2010).

(94). Lou, S. and *et al*, *J. Org. Chem.*, **72**, 9998-10008, (2007).

(95). Nolen, E.G. and *et al*, *Tetrahedron Lett.*, **32**: 73, (1991).

(96). Katritzky, A.R. and *et al*, *Synth. Commun.*, **26**, 357, (1996).

(97). Arend, M. and Risch, N., Abstract paper, p. 90, *11th international conference organic synthesis*, Amsterdam, The Netherlands, (1996).

(98). Risch, N. and Arend, M., *Ibid.*, **106**: 2531; *bzw,* **33**, 2422, (1994).

(99). Arend M., (1996). *Dissertation*, Universität-Gesamthochschule Paderborn.

(100). Rangaishenvi, M.V. and *et al*, *Indian J. Chem.*, **21B**: 56, (1982).

(101). Gloede, J. and *et al*, *Arch. Pham. (Weinheim Ger.)*, **302**: 354. (1969).

(102). Shono, T. and *et al*, *J. Am. Chem. Soc.*, **104**, 5753, (1982).

(103). Souquet, F. and *et al*, *Synth. Commun.*, **26**, 357, (1996).

(104). Katritzky, A.R. and *et al*, *J. Org. Chem.*, **59**, 5207, (1994).

(105). Aben, R.W.M. and *et al*, *J. Org. Chem.*, **52**, 365, (1987).

(106). Arend, M. and Risch, N., *Angew. Chem.*, **107**, 2861; *Angew. Chem. Int. Ed. Engl.*, **34**, 2639, (1995).

(107). Witt land, C. and *et al*, *Synthesis*, **367**, (1996).

(108). Becker, H.G.O. and *et al*, *Wiss. Z. Techn.*, **11**: 38; *C. A.*,(1970). **71**, 60938, (1968).

(109). Vogel's, ″Text book of Practical Organic Chemistry″, 5thed, Long man group, U.K., (1989).

(110). Pavia, L.D., Lamp man, M.G. and Kris, S.G., ″Introduction to Spectroscopy″, 3rded, Thomson Learning Inc., U.S.A., (2001).

(111). Silverstein, R.M., Webster, F.X. and Kimble, D.J., ″Spectrometric Identification of Organic Compounds″, 7thed, John Wiley and Sons, U.S.A., (2005).

(112). Stuart, B.,″ Infra red Spectroscopy: Fundamentals and Applications″, pp., John Wiley and Sons, U.S.A., (2004).