# 1,1-Enediamines and β-substituted Enamines in Heterocyclic Synthesis

by

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to my parents

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# ABSTRACT

The work in this thesis mainly deals with 1,1-enediamines and β -substituted enamines (push-pull olefines) and their reactions, leading to the formation of a number of heterocycles.

Various β-substituted enamines were prepared by a 'one pot synthesis' in which a 1,1-enediamine presumably acts as an intermediate. These enamines, various substituted crotonamides and propenamides, were made by using two different orthoesters, various secondary and primary amines and cyanoacetamide. Their structures, mechanism of formation and geometry are discussed.

A synthetic route to various unsymmetrically substituted pyridines was examined. Two substituted pyridinones were obtained by using two different β-substituted enamines and cyanoacetamide. In one case a dihydropyridine was isolated. This dihydropyridine, on heating in acidic conditions, gave a pyridinone, which confirmed this dihydropyridine as an intermediate in this pyridine synthesis.

A new synthetic method was used to make highly substituted pyridinones, which involved the reaction of 1,1-enediamines with the β-substituted enamines. A one pot synthesis and an interrupted one pot synthesis were used to make these pyridinones. Two different orthoesters and three different secondary amines were used. Serendipitous formation of a pyrimidinone was observed when pyrrolidine was used as the secondary amine and triethyl orthopropionate was used as the orthoester. In all cases cyanoacetamide was used as the carbon acid. This pyridine synthesis was designed with a 1,1-enediamine as the Michael donor and the β -substituted enamines as Michael acceptors.

Substituted ureas were obtained in two cases, which was a surprise.

Some pyrimidines were made by reacting two substituted enamines with two different amidines. When benzamidine was used, the expected pyrimidines were obtained. But, when 2-benzyl-2-thiopseudourea (which is also an amidine) was used, of the two expected pyrimidines, only one was obtained. In the other case, an additional substitution reaction took place in which the S-benzyl group was lost.

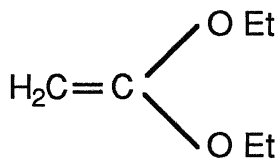
An approach to quinazolone and benzothiadiazine synthesis is discussed. Two compounds were made from 1,1-dimorpholinoethene and a) anthranilamide and b) 2-aminobenzenesulphonamide.

# INTRODUCTION

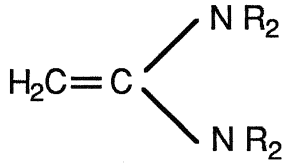
The work in this thesis is based on reactions of 1,1-enediamines and β-susbstituted enamines of the 'push-pull' olefine type. These classes of compounds are briefly reviewed in this section.

## 1,1-Enediamines

1,1-Enediamines are nitrogen analogues of ketene acetals such as (I), in which both the oxygen atoms are replaced by nitrogen. They are also called ketene N,N-acetals or ketene aminals (II).



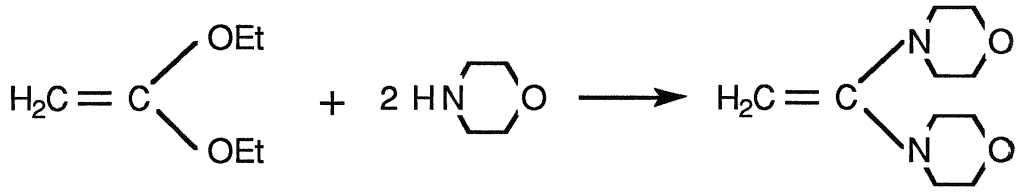

(I)




(II)

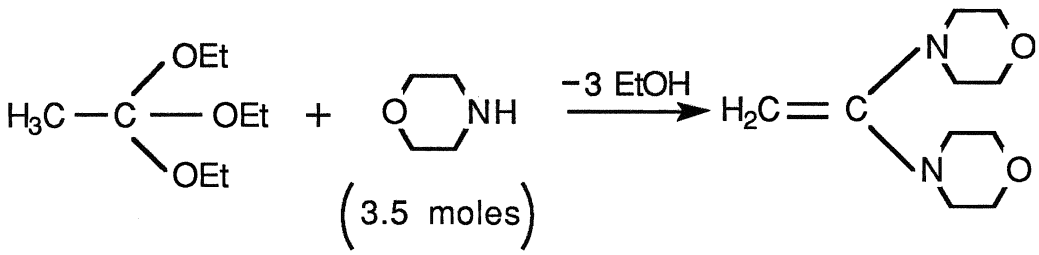
## Preparative Routes to 1,1-Enediamines

Although originally prepared by McElvain and Tate[1] from ketene diethyl acetal and a secondary amine, the first significant preparation of 1,1-enediamines by this route was given by Böhme and Soldan[2]. They reported syntheses of 1,1-dipiperidinoethene and 1,1-dimorpholinoethene from ketene diethyl acetal and the respective secondary amines with yields of 62-64%.



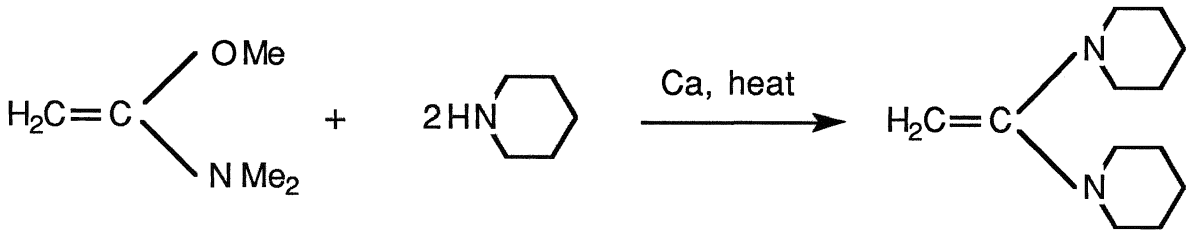
(I)

Later, in 1962, Baganz and Domaschke[3] reported a synthesis using an orthocarboxylic ester instead of the ketene acetal. Their synthesis gave better yields than the Böhme-Soldan synthesis.



p-Toluenesulphonyl chloride was used as a catalyst to speed up the reaction.

Shortly afterwards, Bredereck and co-workers[4] used a ketene O,N-acetal in a similar reaction, e.g.

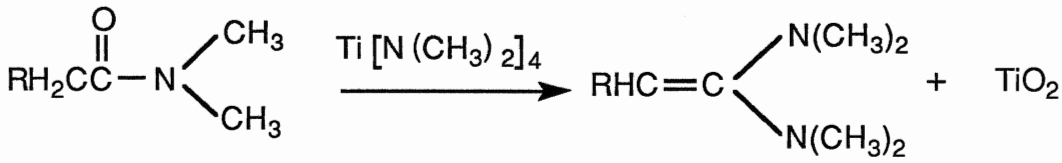


Ketene O,N-acetal

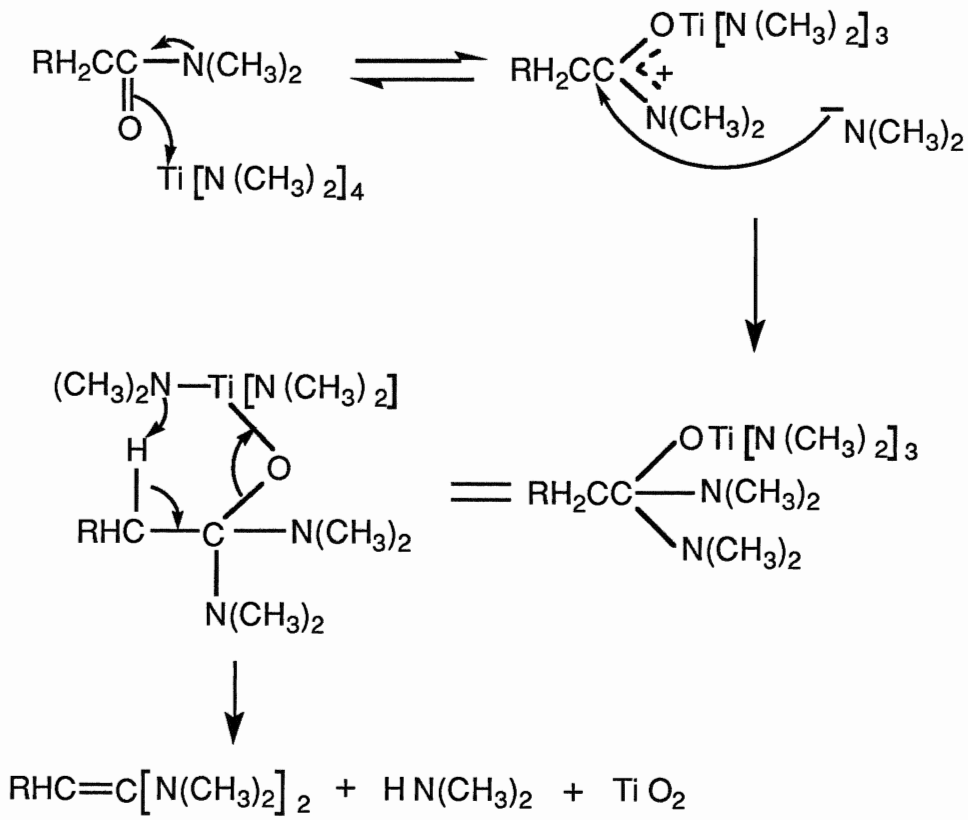
However, triethyl orthoacetate is readily available and therefore is a more obvious choice as starting material in such preparations.

Later, Weingarten and White[5] reported a completely different synthesis of 1,1-enediamines by reaction of carboxylic acid derivatives (amides, free acids, esters,

anhydrides) with tetrakis(dimethylamino)titanium.



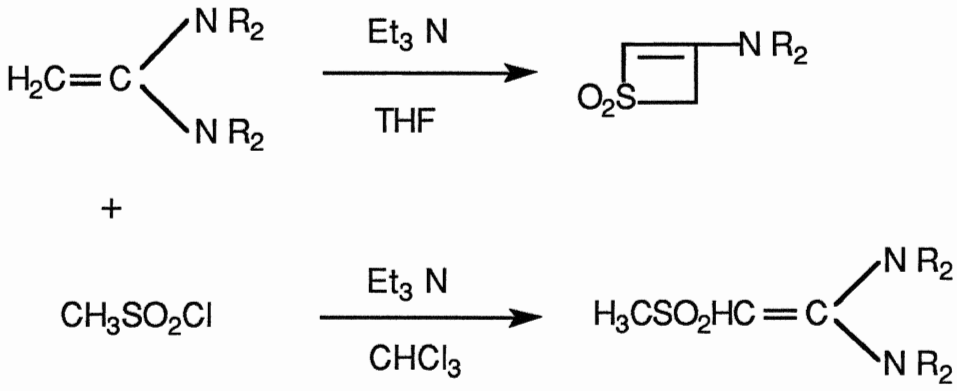

The mechanism given in their paper is shown , slightly modified, below:



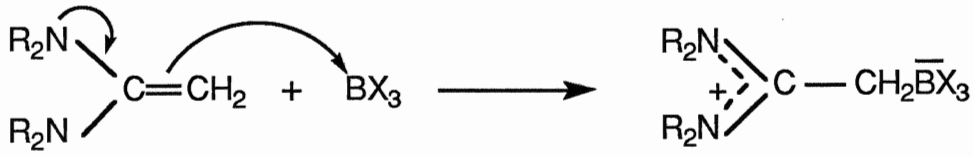
**Properties of 1,1-Enediamines**

The properties and reactions of ketene aminals explained in this section are illustrative but not exhaustive. 1,1-Enediamines would be expected to behave as nucleophiles and much of the research work has been concentrated on the reactions in which they act in this way. Ketene aminals are also electron rich alkenes and can take part in reverse electron demand cycloaddition reactions. An example of both types of behaviour, as a nucleophile and as an electron rich alkene, is seen in the reaction of enediamines with methanesulphonyl chloride.

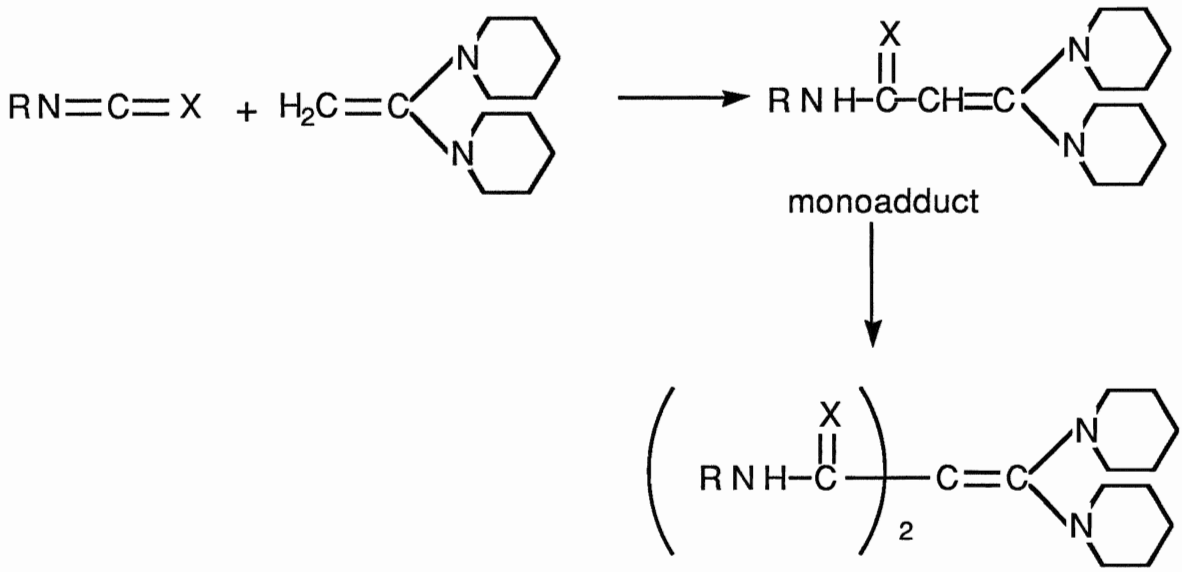
This reaction was reported by three different groups of chemists. Truce and Son[6], Hasek and co-workers[7], and Opitz and Schempp[8] studied the reaction and observed that the product formed is either a cycloadduct (2+2 cycloaddition) or a nucleophilic substitution product , depending on the sulphonyl chloride used and the reaction media, e.g.,




1,1-Enediamines also react with Lewis acids forming a 1:1 adduct via the second carbon atom. This process was examined by Hartman and Keluski[9] at Brock University. In this reaction, a new C-B bond is formed, with the alkene acting as a nucleophile. There is a restricted rotation about the central C-N bond as a result of the amidinium ion's partial double bond character.



The structural relationship of 1,1-enediamines to the ketene acetals prompted a study of the reactions of these compounds with various electrophilic reagents. 1,1-Enediamines show enhanced nucleophilic activity compared to ketene acetals. Clemens, Bell and O'Brien[10] in 1964, examined the reactions of enediamines with isocyanates and isothiocyanates. These produced substituted diaminoethylenes which were not readily accessible by other means.



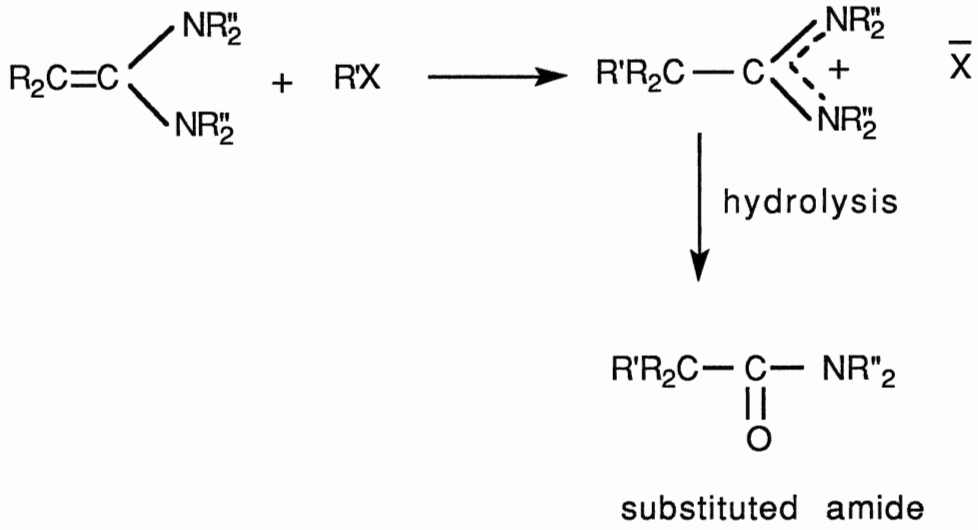
X= O, S

diadduct

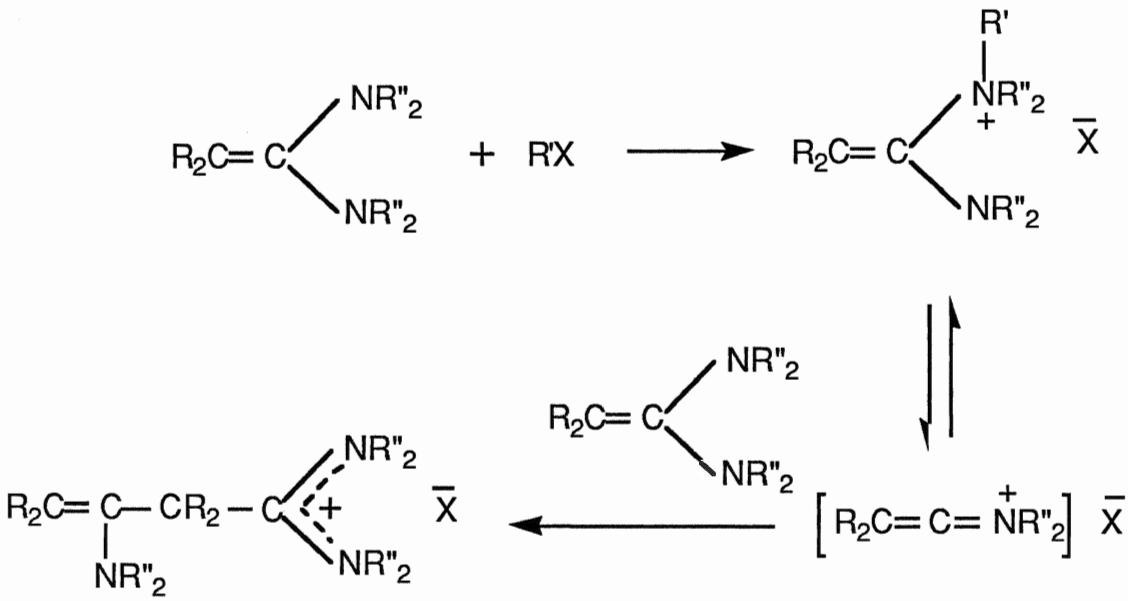
Similar experiments with isocyanates were reported shortly afterwards by Effenberger and co-workers[11].

Alkylation of ketene aminals with alkyl halides has been found to take place at both C and N positions[12,13]. Carbon alkylation afforded amidinium salts which were readily hydrolysed to amides, thus giving a convenient route for synthesis of substituted

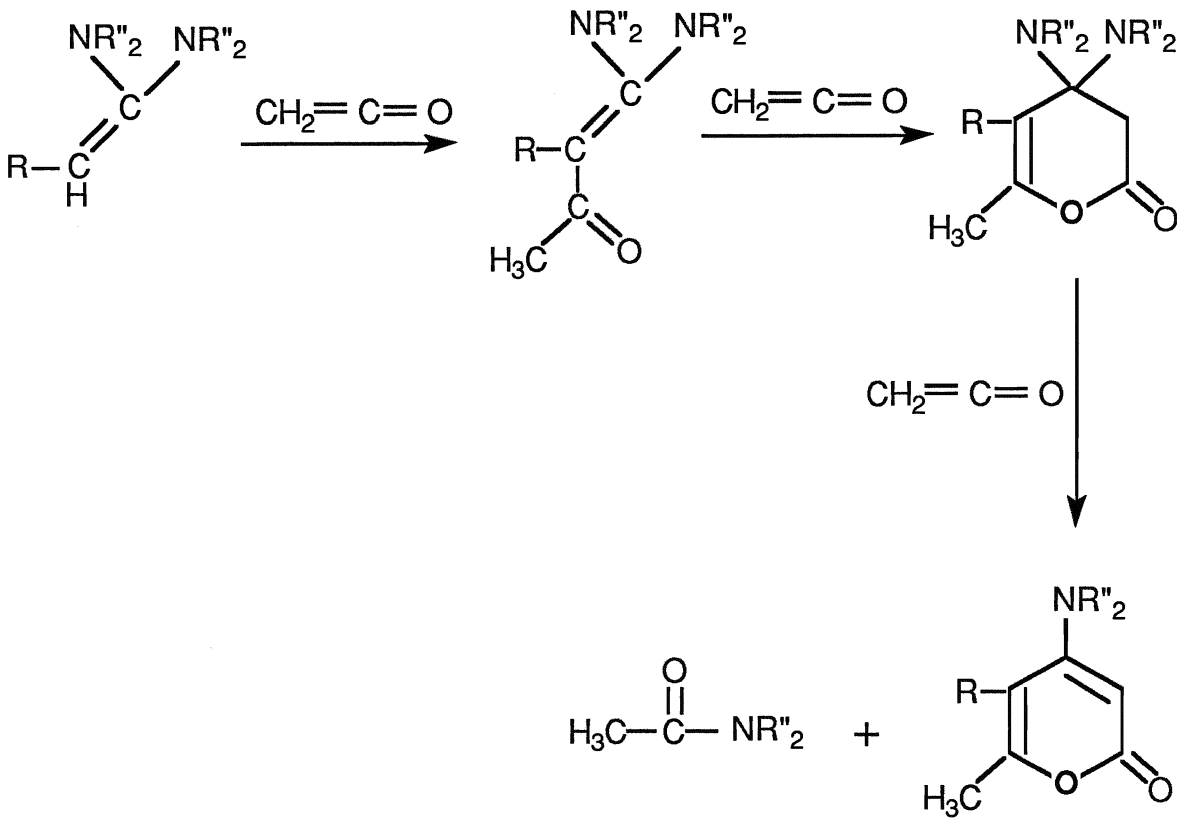
amides and carboxylic acids.



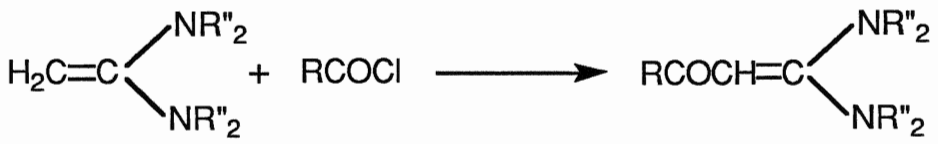

The initial N-alkylation products were found to be unstable, and they reacted with the starting 1,1-enediamine giving condensation products.

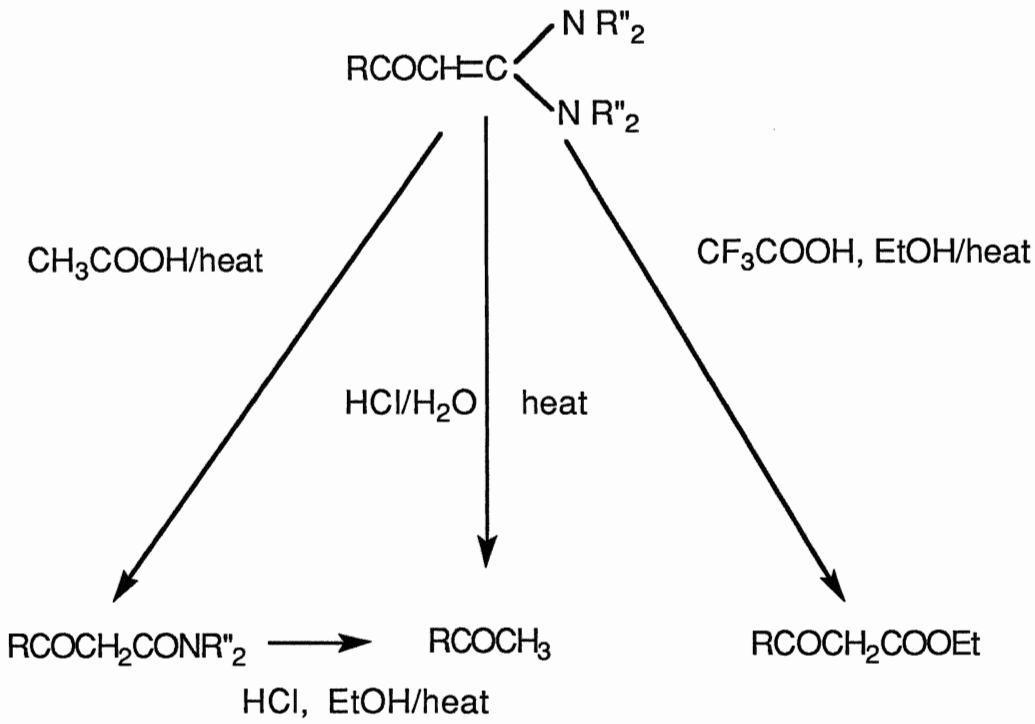


Those ketene aminals or 1,1-enediamines having olefinic hydrogen atoms are converted to 2-pyranone derivatives (2:1adducts) through formation of an intermediate acetyl derivative by reaction with ketenes[14,15].

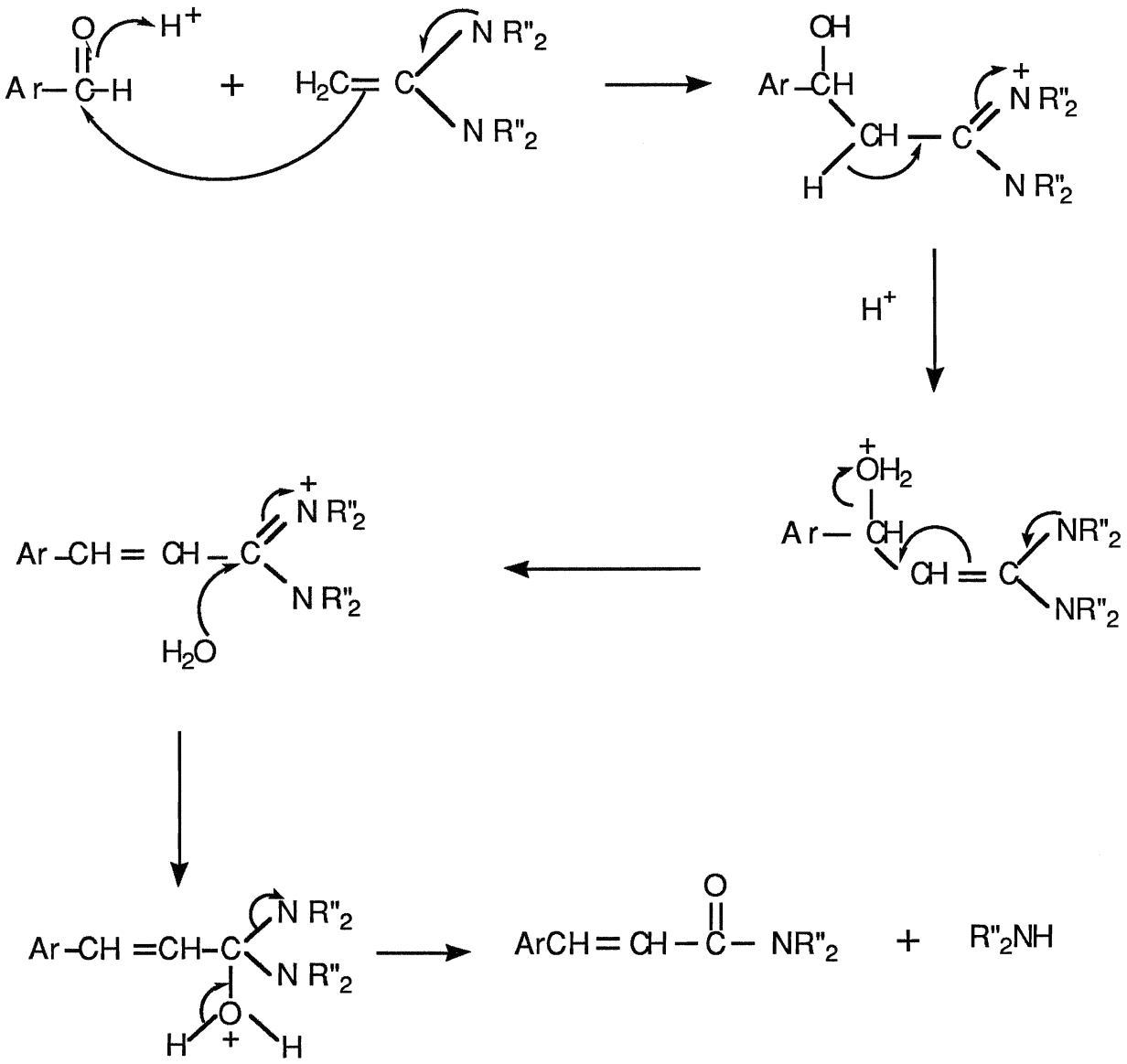



Armati and co-workers[16] explored the reactions of enediamines with aliphatic and aromatic acyl chlorides. These gave acyl derivatives, which can be used as a source of methyl ketones, β–ketoamides and β–ketoesters.

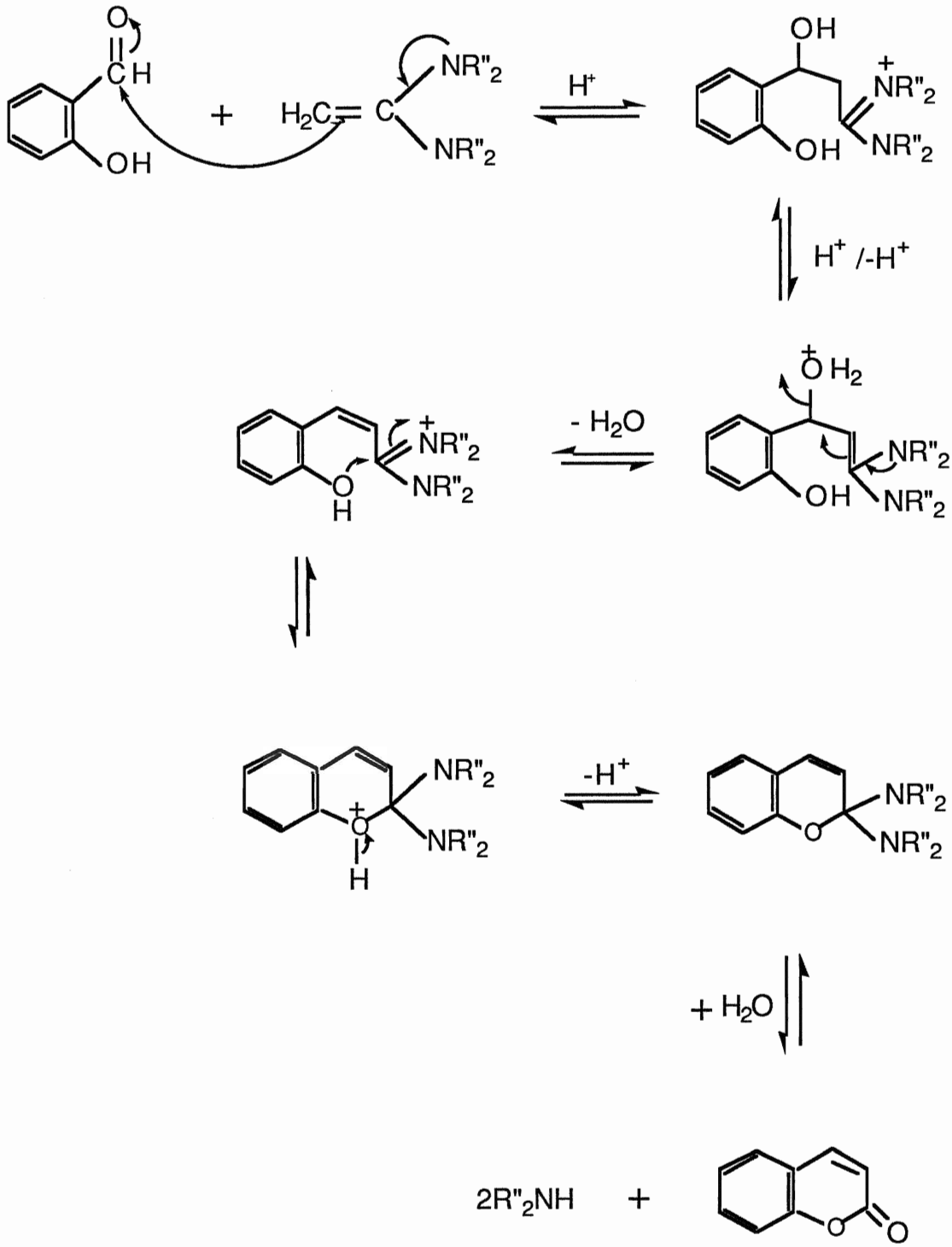



The enediamines also show nucleophilic character at the β–carbon atom in their condensation reactions with other carbonyl compounds, for example with aromatic aldehydes giving substituted cinnamoyl amides as reported by Barton and co-workers[17].

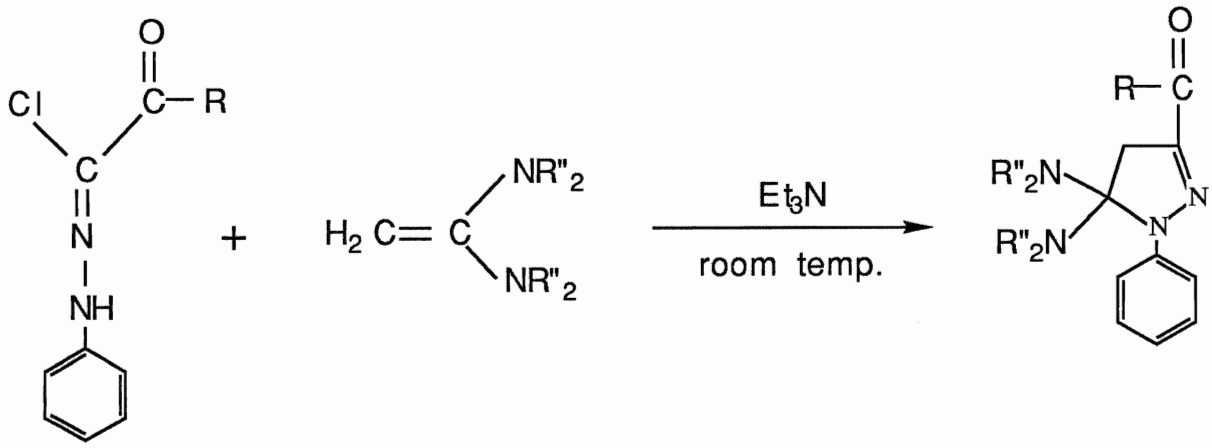


Salicylaldehyde on reaction with 1,1-enediamine gave a coumarin derivative. A reaction mechanism was given by Barton, which we shown in modified form below:




The electron rich double bond of the enediamine has also been found to participate in cycloaddition reactions of the 1,3- dipolar[18,19], reverse electron

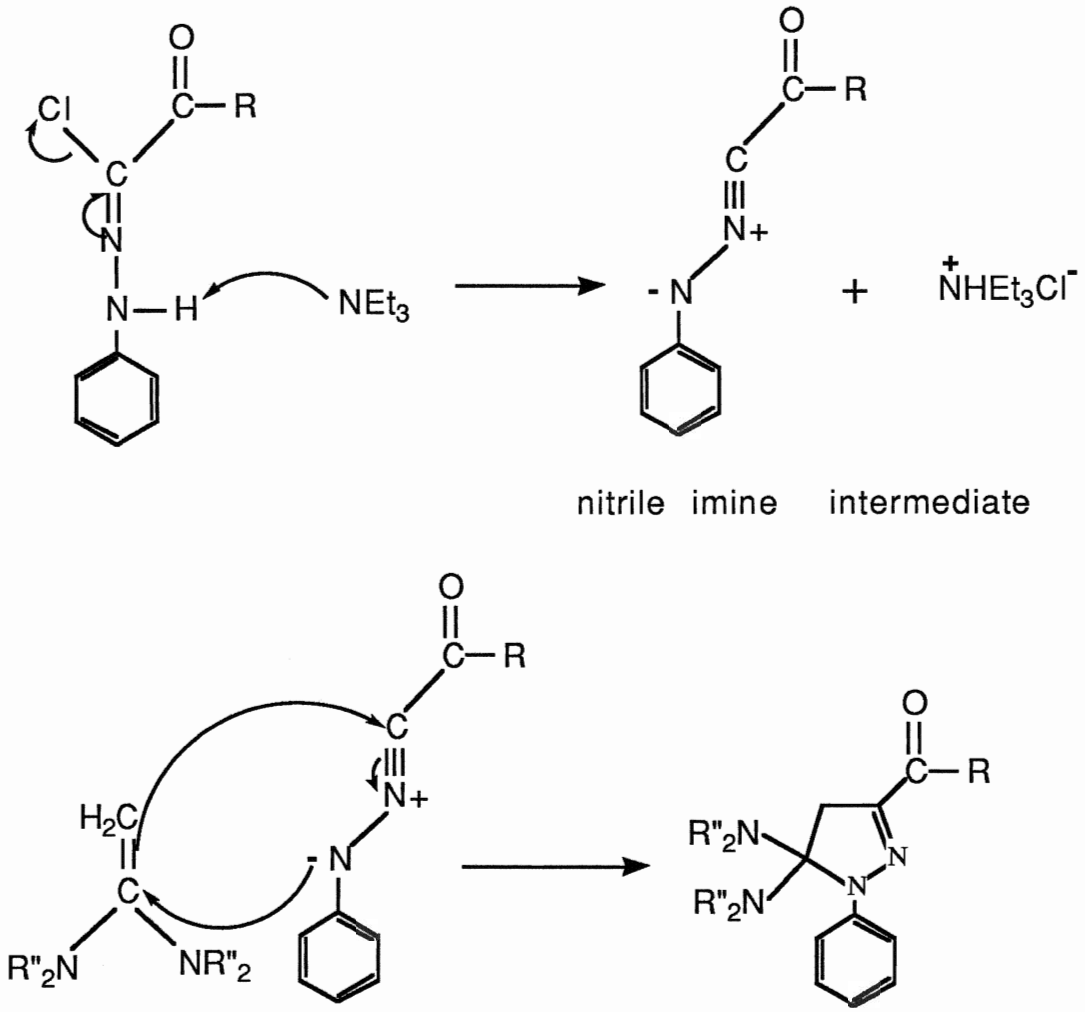
demand Diels-Alder[20,21] and (2+2) types[6,7,8,22]. Thus, Pocar and co-workers[18] reported in brief the synthesis of dihydropyrazoles by reaction of 1,1-enediamines with nitrile imines, generated *in situ* .



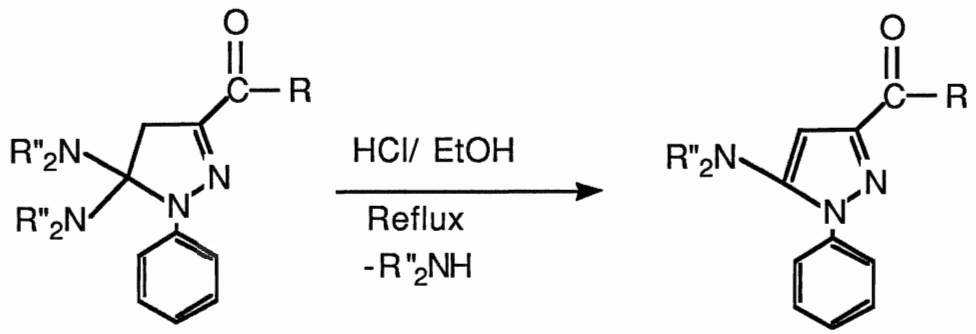

(III)

This reaction is believed to proceed as a 1,3-dipolar cycloaddition reaction, and the probable mechanism is shown below.

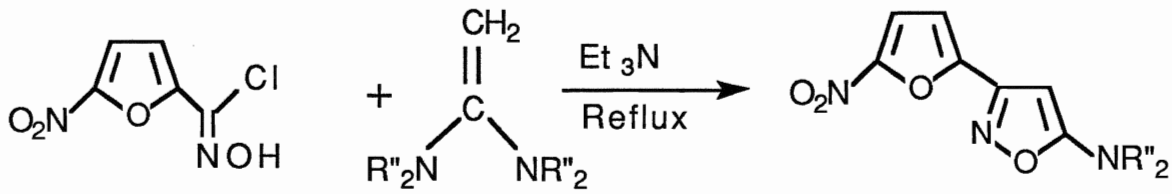
The base $Et_3N$ probably abstracts a proton from the hydrazonoyl halide (III), thus providing a nitrile imine intermediate. This intermediate would then react with the 1,1-enediamine giving the dihydropyrazole.



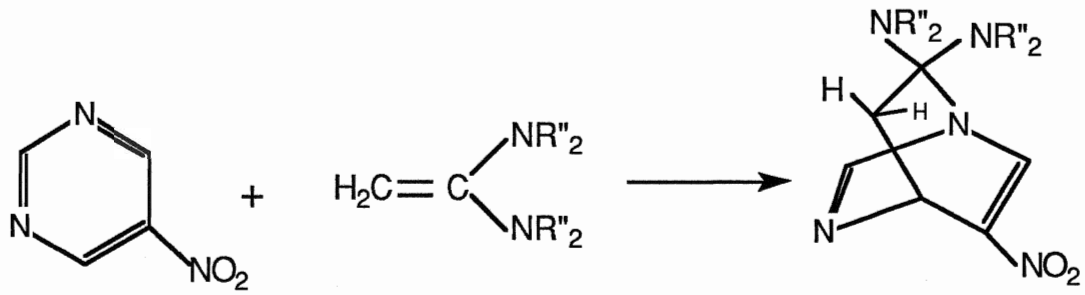

This dihydropyrazole loses a molecule of amine when refluxed with HCl/EtOH to give the pyrazole.



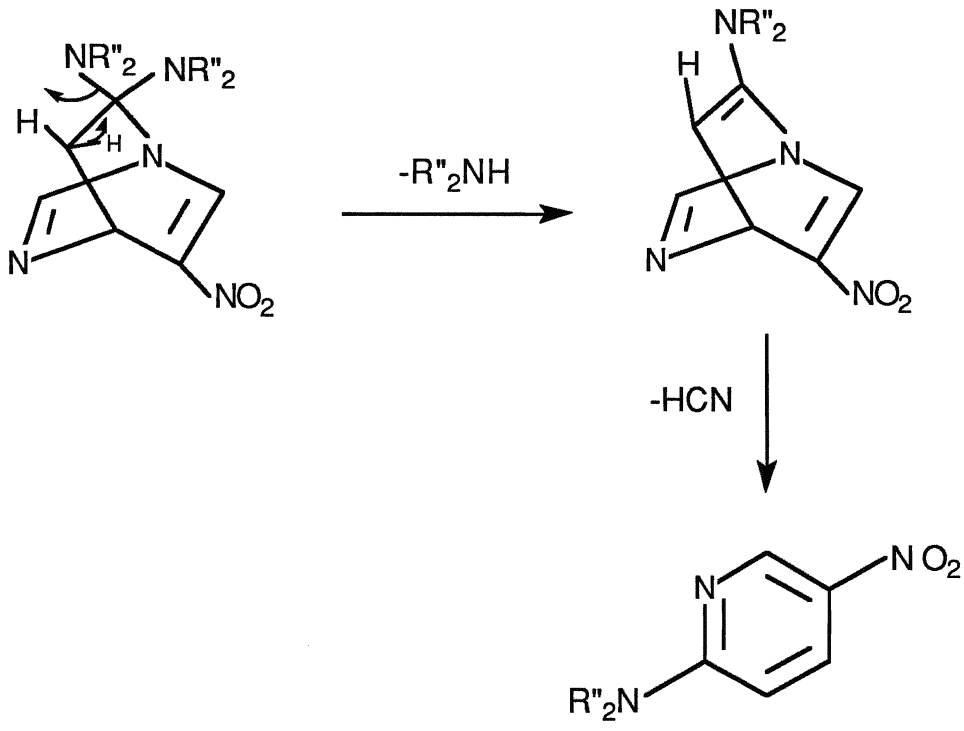

A similar approach using hydroxamoyl chlorides and enediamines was employed by Minami and Matsumoto[19] to synthesize a variety of potential bactericides and fungicides.



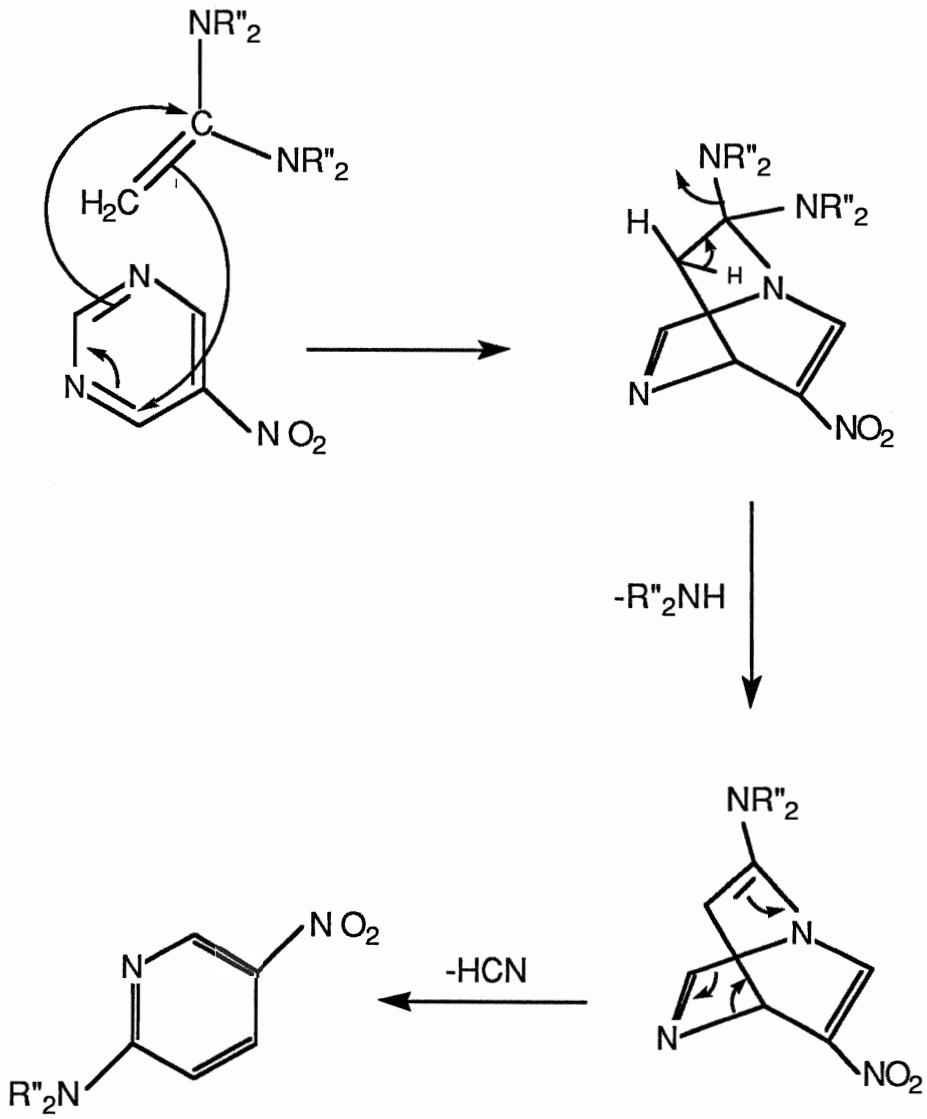

A very interesting reaction has been observed[20,21] in which the electron rich enediamine reacts as a dienophile in its reaction with the electron deficient 5-nitropyrimidine. This is a type of Diels-Alder reaction with inverse electron demand where the HOMO of the dienophile delivers electron density to the LUMO of the "diene".



The primary adduct then loses a molecule of amine and then, in a reverse Diels-Alder type reaction, a molecule of HCN giving a substituted pyridine derivative.

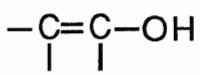



The mechanism for this reaction can be explained as follows,

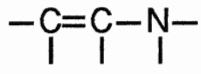

NR"2
C
NR"2
H2C
N
N
N O2
NR"2
NR"2
H
H
N
N
NO2
-R"2NH
NR"2
N
N
NO2
-HCN
N O2
N
R"2N

## Enamines

Wittig and Blumenthal[23] introduced the term 'enamine' in 1926. Enamines are the nitrogen analogues of 'enols'.

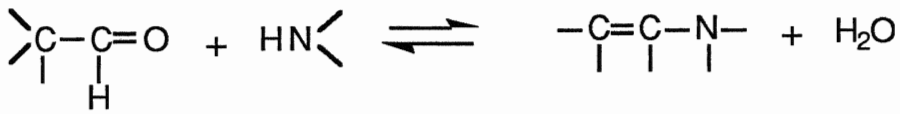


enol



enamine

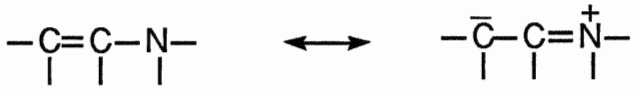
The most frequently used method for the preparation of enamines was given by Mannich and Davidsen[24] in 1936. They discovered that the reaction of aldehydes and secondary amines in the presence of anhydrous potassium carbonate at $0^0$C gave enamines.



This method was further explored by Herr and Heyl[25] in 1952 and later by Stork et al.[26] Stork's method involved reflux of a carbonyl compound with a secondary amine in an anhydrous solvent such as dry benzene or toluene, with azeotropic removal of water to give an enamine. p-Toluenesulphonic acid was used as a catalyst in cases of slow reactions.

Enamines can also be prepared from other sources such as ketals[27], lactams and Grignard reagents[28], and imines[27].

Due to overlap of the lone pair of electrons of the nitrogen atom with the $\pi$-electrons, enamines can be drawn in two mesomeric forms[29], (IV) and (V).



(IV) (V)

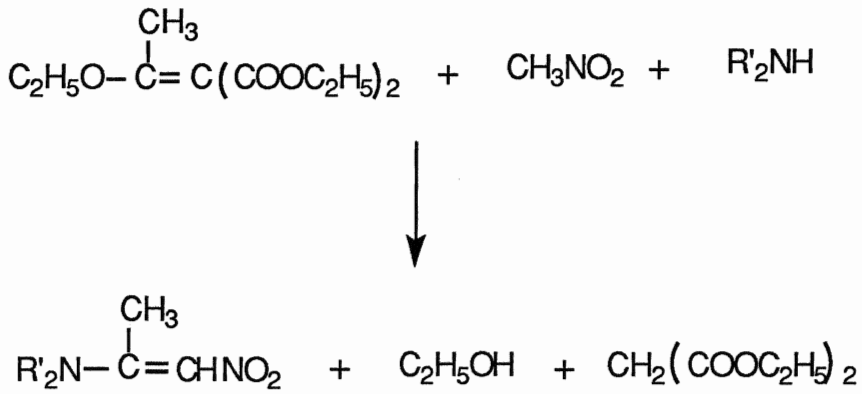
The structure of the enamine suggests the possibility of electrophilic attack either on the nitrogen atom or on the carbon atom $\beta$ to the nitrogen, thus implying that enamines should behave as nucleophiles.

Previously, enamines with a tertiary nitrogen atom were often said to be more basic than the corresponding saturated amine, but questions were raised on this generalisation. It was found that the basicity depends on the presence of substituents on the α- or β- positions[27]. α-Alkyl substituents were found to increase the basicity, whereas β-alkyl substituents decrease the basicity. The 1,1-enediamines discussed earlier can be regarded as α-aminoenamines.

There are many reactions illustrated in the literature in which enamines are used as a nucleophile. Some of these are alkylation[30,31,32], protonation[33,34], reactions with olefines which have an electron attracting group attached to the double bond, with acetylenes, esters, carbonyl compounds, and various other electrophiles[27,29].

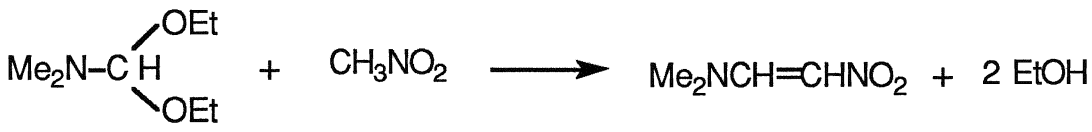
Up until now enamines were used as nucleophiles in a variety of reactions. Enamines could in principle be made to undergo nucleophilic attack by creating an electrophilic centre in the structure. This could, in principle, be achieved by attaching an electron withdrawing group to the carbon atom β to the nitrogen. We will refer to such enamines as β-substituted enamines; they are also representatives of the class of compounds described as 'push-pull' olefines.

There are many examples of such substituted enamines. An early preparation of β-nitroenamines was given by Hurd and Sherwood[35]. They reported a series of these compounds made from the reaction of malonate ester derivatives, nitromethane and a secondary amine. One example is shown below:

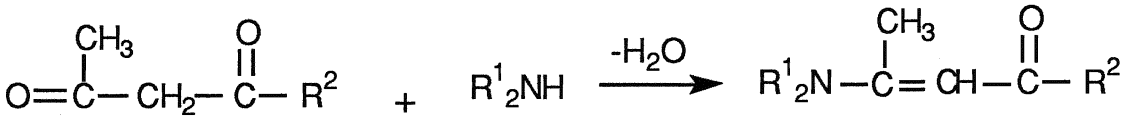


More common methods of preparation for β-nitroenamines have been reviewed

by Rajappa[36] and include the reaction of amide acetals with nitromethane [37]. An example is shown below,



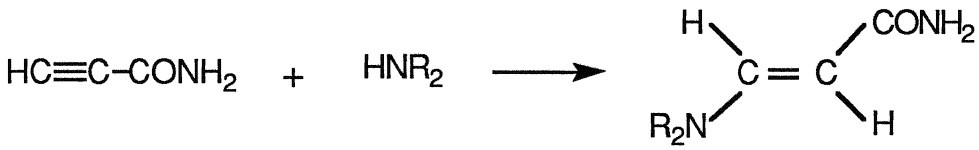
Preparations of other β-substituted enamines such as β-enaminoketones and β-enaminoesters from β-diketones and β-ketoesters respectively have also been reported in a useful publication by Hickmott and Sheppard[38]. In these examples, the reaction of only one carbonyl group with an amine to give the substituted enamine was noted.



$R^1$= morpholine, piperidine etc; $R^2$= methyl in case of enaminoketones and OEt in case of enaminoesters.

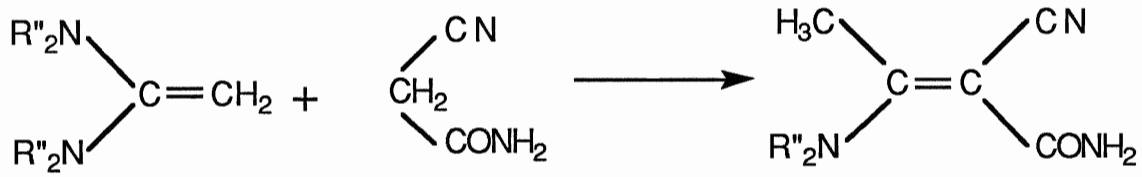
The mechanism of this reaction is explored in the Discussion section.

A recent synthesis of β-enaminoamides has been given by Paglietti and coworkers[39]. They reacted acetylenic amides with secondary amines, e.g.



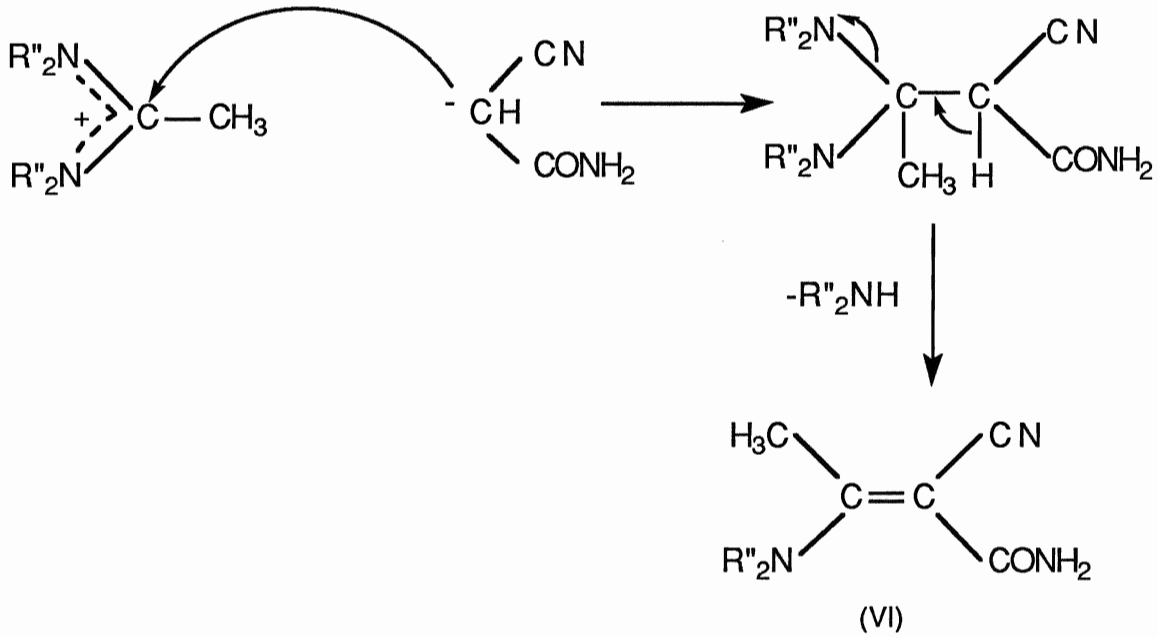
**A relationship between 1,1-enediamines and β-substituted enamines**

Gandhi and Gibson[40] reported the reactions of 1,1-enediamines with carbon acids and so established a relationship between 1,1-enediamines and β-substituted enamines. An example is shown below.



(VI)

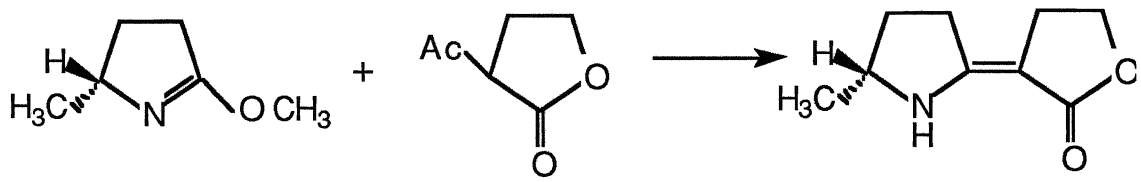
Gandhi explained this reaction in terms of the enediamine abstracting a proton from the carbon acid forming an amidinium ion and the anion of the active methylene compound. Now, presumably this anion of the carbon acid acts as a nucleophile and adds to the protonated 1,1-enediamine. This reaction leads to the formation of a β-substituted enamine (VI). The probable mechanism can be explained as follows,



(VI)

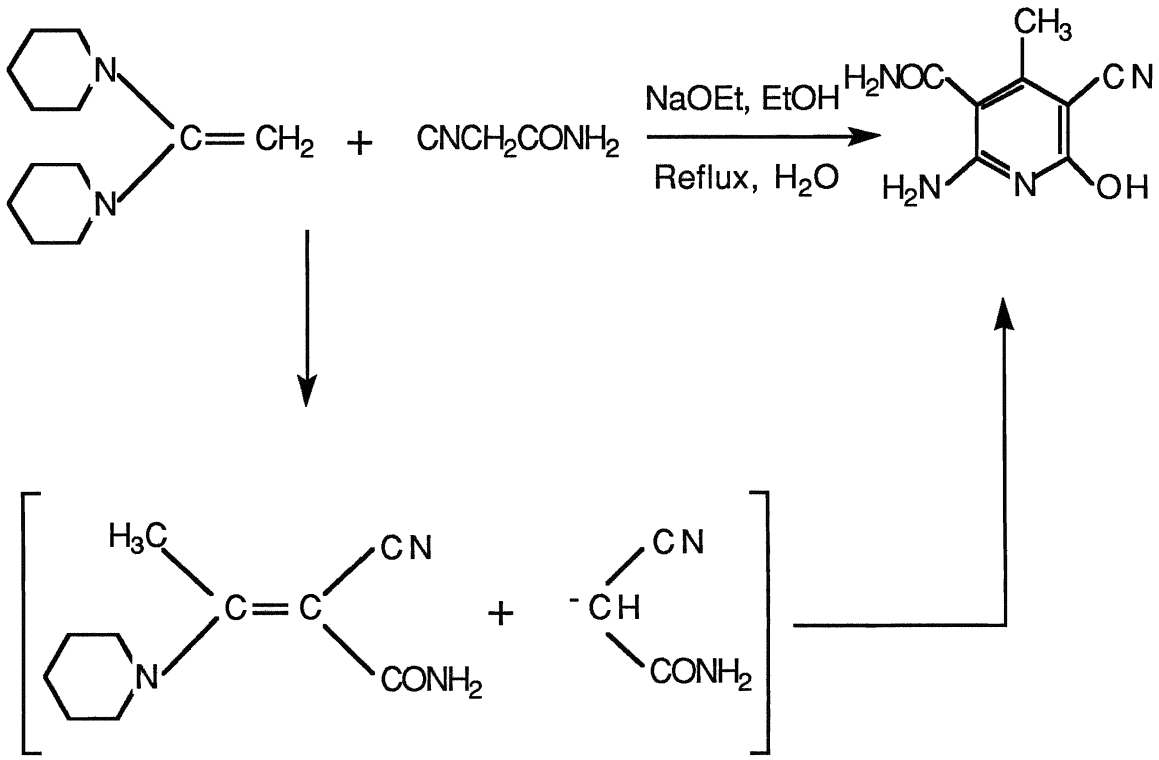
This reaction seems to be general, and is thus a useful additional route to β-

substituted enamines. Specific compounds of this type had been made by other methods, as noted earlier. It is interesting to note that a similar approach has been adopted by Provot and co-workers[41] in a recent synthesis of a β-enaminolactone. They reported a reaction of a lactim ether with 2-acetylbutyrolactone which gave the β-enaminolactone as shown below:

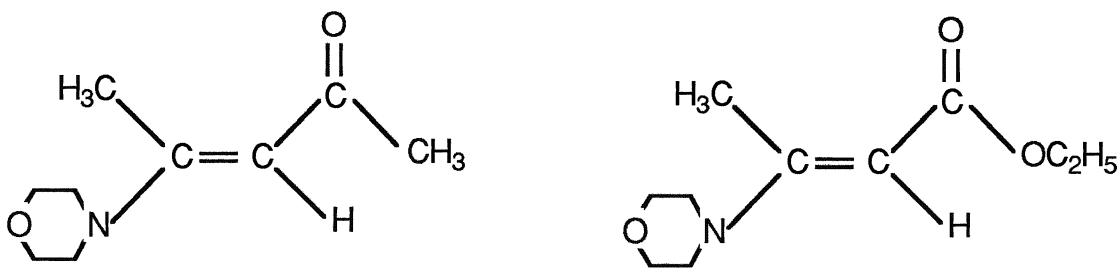


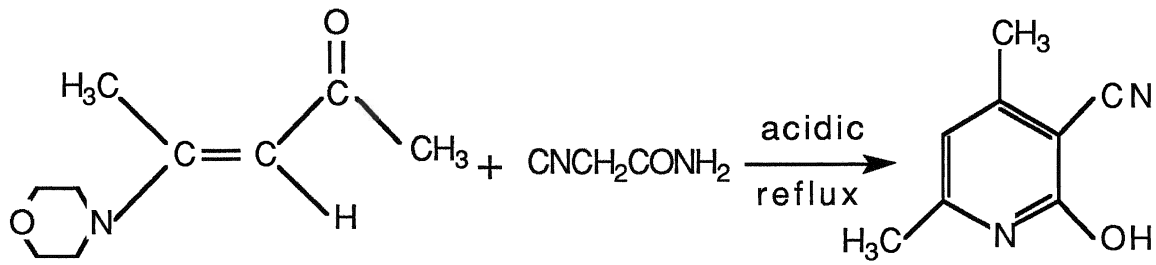

Gandhi briefly examined the reaction of 1,1-dipiperidinoethene with cyanoacetamide in a basic medium and actually obtained a substituted pyridine derivative. Incidently, this pyridine compound was not intended to be prepared; it was a byproduct in an experiment designed to prepare a β-substituted enamine .

Gandhi interpreted the process leading to this pyridine as involving a Michael addition of cyanoacetamide (anion) to β-substituted enamine intermediate , followed by loss of piperidine and ring closure by dehydration. The intermediate is presumably formed by the reaction of cyanoacetamide and 1,1-dipiperidinoethene, as explained earlier.




In our laboratory, Ratemi[42] developed this idea using the β - substituted enamines as shown below. These were prepared by Hickmott and Sheppard's method[38] and then reacted with several carbon acids. One example is shown below.

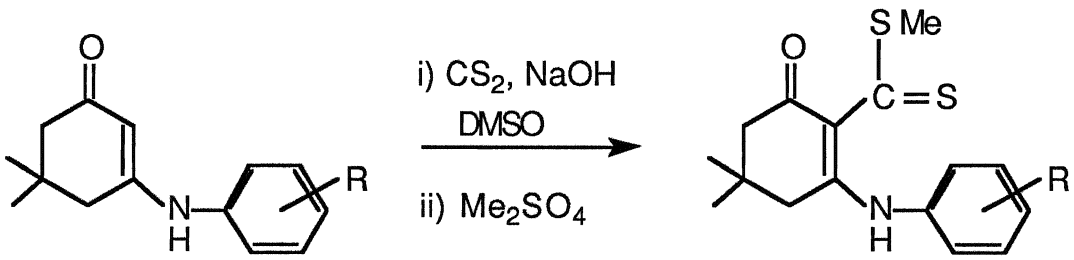





The β-substituted enamine shown in this example is an α,β-unsaturated carbonyl compound, and raises the possibility of its undergoing a Michael addition at the carbon alpha to the amine group when treated with active methylene compounds.

**Objectives of the present research**

1,1-Enediamines are electron rich alkenes that can act as nucleophiles, as has been illustrated in this brief review. Further, β-substituted enamines of the 'push-pull' olefine type can, in principle, show nucleophilic character at the carbon atom β to the amino-group and electrophilic character at the carbon atom α to the amino-group. This nucleophilic character is nicely illustrated in a reaction of β-anilinocyclohexenones,(enaminones), with carbon disulfide reported recently by Tominaga and coworkers [43].




The primary interest in this research has been in 1,1-enediamines as nucleophiles and β-substituted enamines as electrophiles ( as mentioned above). The reactions of 1,1-enediamines with β-substituted enamines have been explored as a possible route to unsymmetrically substituted pyridines. The reactions of other nucleophiles, such as amidines, with such enamines have also been examined in this work.

A further objective was to use the 1,1-enediamines as reagents for the synthons $CH_2=C^+-NR_2$ and $CH_2=C^{+2}$ in synthesis of β-substituted enamines and of other heterocycles.

# DISCUSSION

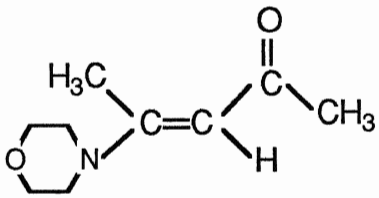
The Discussion is divided into four sections. The first section deals with b-substituted enamines. It contains their method of preparation, structure, mechanism of formation, and geometry. The pyridine synthesis is discussed in the second section. It involves various synthetic routes to substituted pyridines, scope and limitations, and some miscellaneous experiments. The pyrimidine section is discussed next and lastly a short section is devoted to quinazolone and benzothiadiazine.

Conclusions and suggestions for future work follow the Discussion.

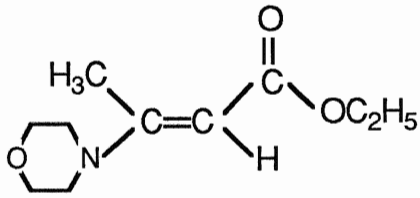
## β - Substituted Enamines

Our plan was first to prepare a series of β – substituted enamines and then to use them for further reactions.

The two enamines listed below were prepared in our laboratory using the Hickmott and Sheppard method [38].



(i)

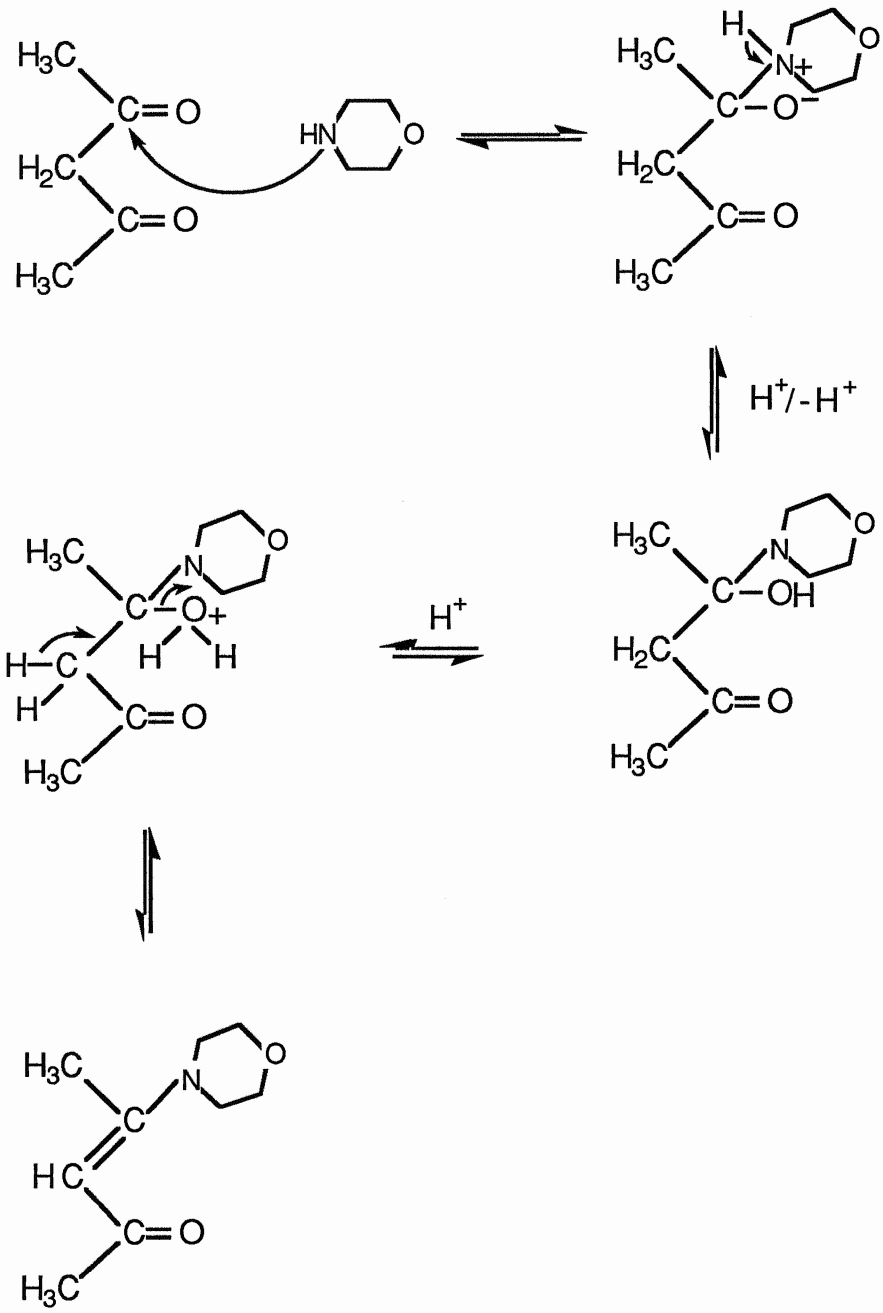


(ii)

These enamines were made by condensation of a secondary amine and a β - dicarbonyl compound. The secondary amine used was morpholine in both cases, but for compound (i) acetylacetone was the dicarbonyl compound whereas for compound (ii) ethyl acetoacetate was used. Benzene was used as solvent. The water formed in the reaction was removed by azeotropic distillation. This method was preferred due to its simplicity, the ready availability of the chemicals used, and its good yields.

It is interesting to note that only one carbonyl group reacts with the secondary amine in both cases. When acetylacetone was used, it being a symmetrical compound either one of the carbonyl groups can react, but in the case of ethyl acetoacetate the keto- carbonyl is more reactive than the ester carbonyl group (due to resonance stabilisation the ester carbonyl is less reactive).

The formation of enamine (i) could be mechanistically explained as in Scheme (I).



(i) Scheme (I)

The mechanism involves the nucleophilic addition of the morpholine ring to the carbonyl carbon. Due to the use of an acid catalyst, the oxygen atom of the carbonyl group is likely to get reversibly protonated. The final dehydration step gives the enamine

(i). The formation of enamine (ii) can also be explained in a similar way.

The structures of enamines (i) and (ii) were confirmed by spectral analysis, which were comparable with those reported by Hickmott and Sheppard [38] and by Ratemi[42] in our laboratory.

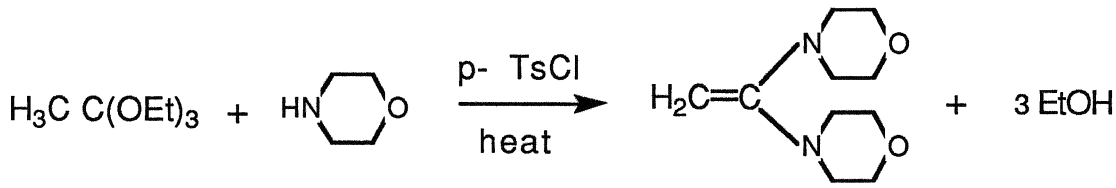
Looking at the structures of enamines (i) and (ii), we can see the presence of conjugation which is important for future reactions. This conjugation of the double bond makes the system quite reactive by decreasing the electron density at C4 in (i) and at C3 in (ii), making these carbons prone to nucleophilic additions. This extended conjugation is an example of what is known as the 'push-pull' effect[44,45], as mentioned on page 17 in the Introduction. In general, alkenes having this type of system, where conjugated electron donor and electron acceptor groups are present, are called 'push-pull' alkenes.

We planned to use enamines (i) and (ii) in Michael type reactions; these are discussed further in the next part of the Discussion.

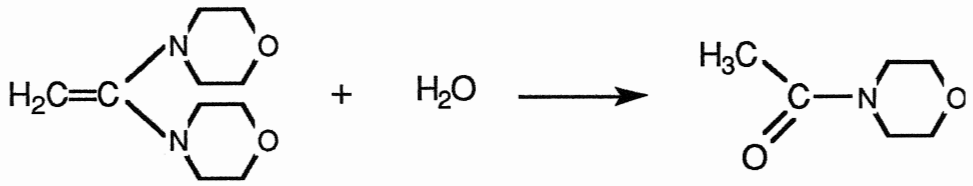
Let us now consider the synthesis of various β-substituted enamines or 'push-pull' type alkenes from 1,1-enediamines and a compound containing an active methylene group (Introduction p -19).

The required 1,1-enediamines were prepared by the Baganz and Domaschke method[3]. This method was preferred over the others due to its high yields and the ready availability of the chemicals needed.

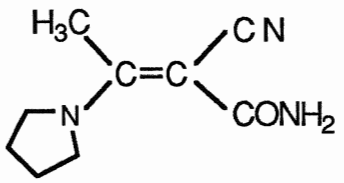
1,1- Dimorpholinoethene was prepared by reaction of triethyl orthoacetate and morpholine in the presence of a catalytic amount of p-toluenesulphonyl chloride.



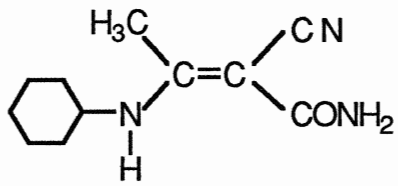

This particular 1,1-enediamine was found to be very hygroscopic. On exposure to air and moisture it readily hydrolyses to N- acetylmorpholine. Therefore the freshly prepared product was used for the various enamine preparations.



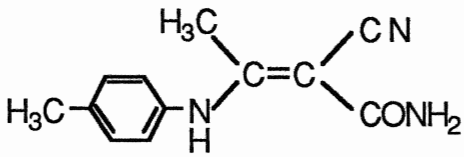
This difficulty actually gave us the idea of doing the overall reaction as a so-called 'one pot synthesis'. In this synthesis, equimolar quantities of triethyl orthoacetate, the secondary amine, and an active methylene compound were mixed together and refluxed. The idea behind this was to generate the 1,1-enediamine *in situ* ; it should then react with the active methylene compound present in the reaction mixture to give the desired β- substituted enamine. Keeping this in mind, a series of enamines were prepared.



(iii)



(iv)



( v )

Compound (iii) was prepared using pyrrolidine as the required secondary amine, whereas (iv) and (v) were made by using different primary amines. Cyanoacetamide was used as the active methylene compound in all three cases. Compound (iii) was made by heating a mixture of equimolar quantities of triethyl orthoacetate, pyrrolidine and cyanoacetamide. During the reflux, the ethanol produced in the reaction was distilled off.

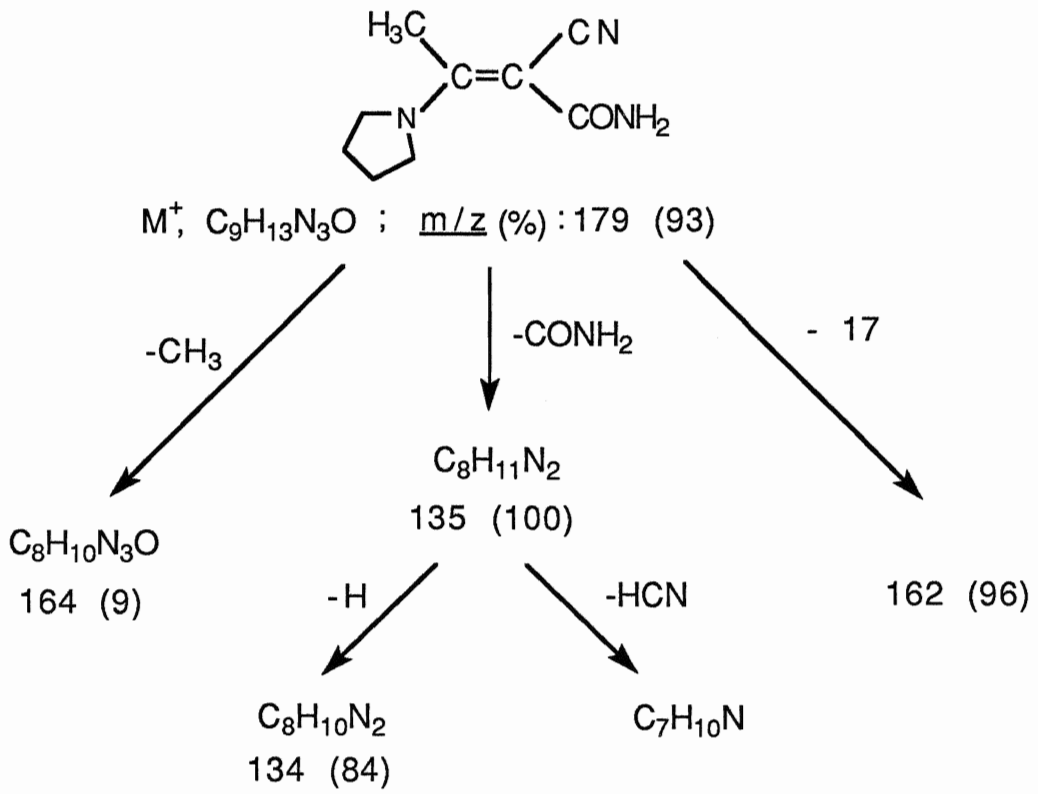
The structure of compound (iii) was confirmed by $^{1}H$ NMR, $^{13}C$ NMR, mass and infra red spectral interpretation. The mass spectrum gave the molecular ion at the

expected m/z value 179. The proton NMR spectrum should show four different chemical signals, based on proton environments, but the actual spectrum shows only three. A broad multiplet was observed at the δ value 1.01-1.61, integrating for 8 protons of the pyrrolidine ring. A singlet at δ 2.41 for the methyl group was observed. The observed downfield chemical shift of this methyl group could be attributed to the presence of the amino substituent and the double bond. A doublet at δ 5.51 was observed, integrating for the 2 protons of the amide $NH_2$ group, and was exchangeable with $D_2O$.

The $^{13}C$ NMR spectrum showed the presence of required signals at appropriate chemical shifts. The C2 carbon appeared at δ 51.7 whereas the C3 carbon signal appeared at δ 166.8.

The large difference in the δ values of the two olefinic carbons C2 and C3 will be discussed later on in this part of the Discussion.

The EI mass spectrum showed the molecular ion at the expected m/z value (179). The fragmentation mode for compound (iii) can be explained as in Scheme (II).




Scheme (II)

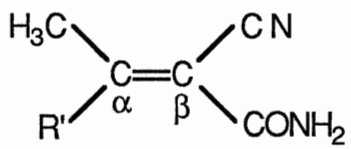
The other two enamines, (iv) and (v), were prepared in a similar way but instead of pyrrolidine, cyclohexylamine and p-toluidine were used respectively. In the case of compound (iv), several crystallisations were needed to obtain the pure product (thin layer chromatography showed one spot only); however, the yield was poor (33%).

The structures for compounds (iv) and (v) were also assigned through spectral data interpretation. The proton NMR spectrum for compound (iv) showed only four different types of signals. The cyclohexyl ring protons appear at δ 1.27-2.04 as a multiplet. The NH signal appears quite downfield (δ 10.8) and is separate from that observed for the amide ($NH_2$) protons at δ 5.52.

In case of compound (v), nuclei splitting which is expected for the aromatic protons, is observed in a clear AA'BB' pattern at δ 7.02-7.36. The aromatic NH group appears at a chemical shift of δ 12.2 which is far downfield from that for the pure amine $NH_2$( δ 1.00-2.00).

The $^{13}C$ NMR signals for the carbons in (iv) and (v) were also assigned accordingly.

Now, let us look at the chemical shifts of the olefinic carbons C2 and C3 (or $C_\beta$ and $C_\alpha$) observed in all these three enamines.



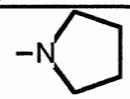
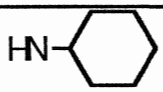
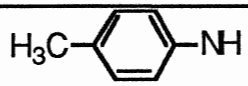
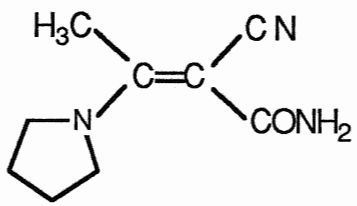
| Enamine | R' | $\delta C_\alpha$ | $\delta C_\beta$ |
|---|---|---|---|
| (iii) |  | 166.8 | 51.7 |
| (iv) |  | 166.7 | 70.3 |
| (v) |  | 167.6 | 72.8 |

TABLE 1

As we can see from Table 1, there is a large difference between the δ values of $C_\alpha$ and $C_\beta$. Due to the presence of extended conjugation in the β - substituted enamine structure, a partial positive charge exists at the carbon α to the amine nitrogen and a partial negative charge exists at the carbon β to the amine nitrogen. This may be the reason why $C_\alpha$ appears at a chemical shift which is so far downfield and $C_\beta$ at a chemical shift which is upfield. A similar incident was observed by Thomas[46] in 1979.

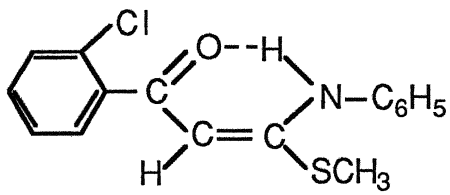
The probable mechanism for the formation of compound (iii) can be summarised as follows : first, formation of 1,1-dipyrrolidinoethene (or 1-ethoxy-1-pyrrolidinoethene) *'in situ'* ; second, the anion of cyanoacetamide, which is presumably present in the reaction mixture at low concentrations, acts as a nucleophile and adds to the protonated species from the enediamine to give the desired enamine (iii). This follows from the explanation given on page 19 in the Introduction.




(iii)

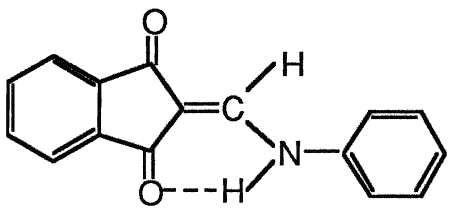
In a similar way, the formation of other two enamines (iv) and (v) may be explained.

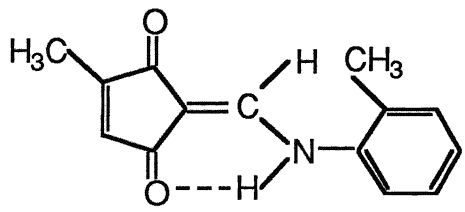
The geometry of enamines (i), (ii), and (iii) was assigned as (E)-geometry. This was based on comparisons with data reported[40] for other enamines with (E)-geometry. Compounds (iv) and (v) were tentatively assigned (Z)- geometry. This was based on the possible hydrogen bonding present in these molecules which can be confirmed by the IR and proton NMR data. The N-H stretch in the IR specrum for compound (iv) is observed at 3050 $cm^{-1}$, which is a shift of about 150 $cm^{-1}$ from the observed frequency for the unassociated amines. Even the NH chemical shift observed in the proton NMR is far downfield (δ value 10.8). A similar case was observed by Rudorf and coworkers[47]. They suggested the presence of hydrogen bonding in enamines of the push-pull olefine type reported in their paper; an example is shown below with the δ value of the NH.




$\delta_{NH}$ ($CDCl_3$): 11.76

More recently, Barnish and Gibson[48] reported some enaminodiones with cyclic keto-substituents attached to the β carbon (very similar to our enamines which also have a carbonyl group attached to the β carbon atom). They also observed the chemical shift of the NH to be far downfield, from about δ10.33 to 12.40 .



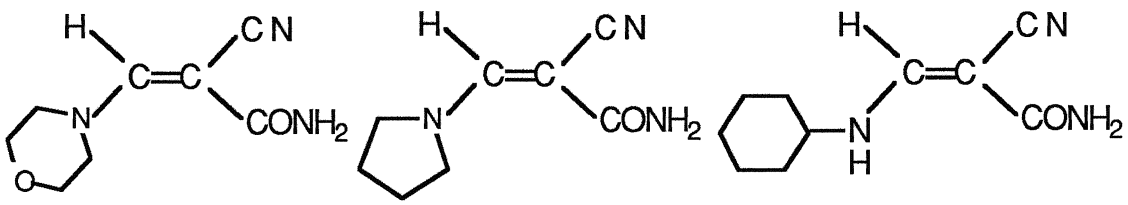




$\delta_{NH}$ (DMSO-$d_6$): 10.99 $\delta_{NH}$ ($CDCl_3$): 10.33

All of these β - substituted enamines were found to be stable in nature compared to simple enamines, which are reported in the literature to be unstable and requiring

storage at low temperature. But our work has shown that these β - substituted enamines are quite stable; e.g., they do not tautomerise or undergo self condensation at room temperature. The absence of tautomerism in compounds (i), (ii), and (iii) is due to the amino substituent being tertiary in nature; more generally, as mentioned earlier, the delocalisation of the electrons associated with the 'push-pull effect' adds to the overall stability of the system. However, though stable, these β - substituted enamines are not unreactive. We have found them to be reactive towards nucleophiles and, depending upon their reaction either with a carbon acid or a 1,1-enediamine, they give different products. Indeed, in some cases, the β-substituted enamines could not even be isolated and, instead, reacted further giving artefacts. This in fact led us to the idea of generating such β-substituted enamines *in situ* for one pot syntheses of other compounds. These matters will be explored in the next part of our Discussion.

A series of β-substituted enamines were also prepared by using a one pot synthesis method. Equimolar quantities of triethyl orthoformate, a secondary or primary amine, as required, and cyanoacetamide were refluxed in a round-bottomed flask. After work up and crystallisation, the substituted enamines were obtained.

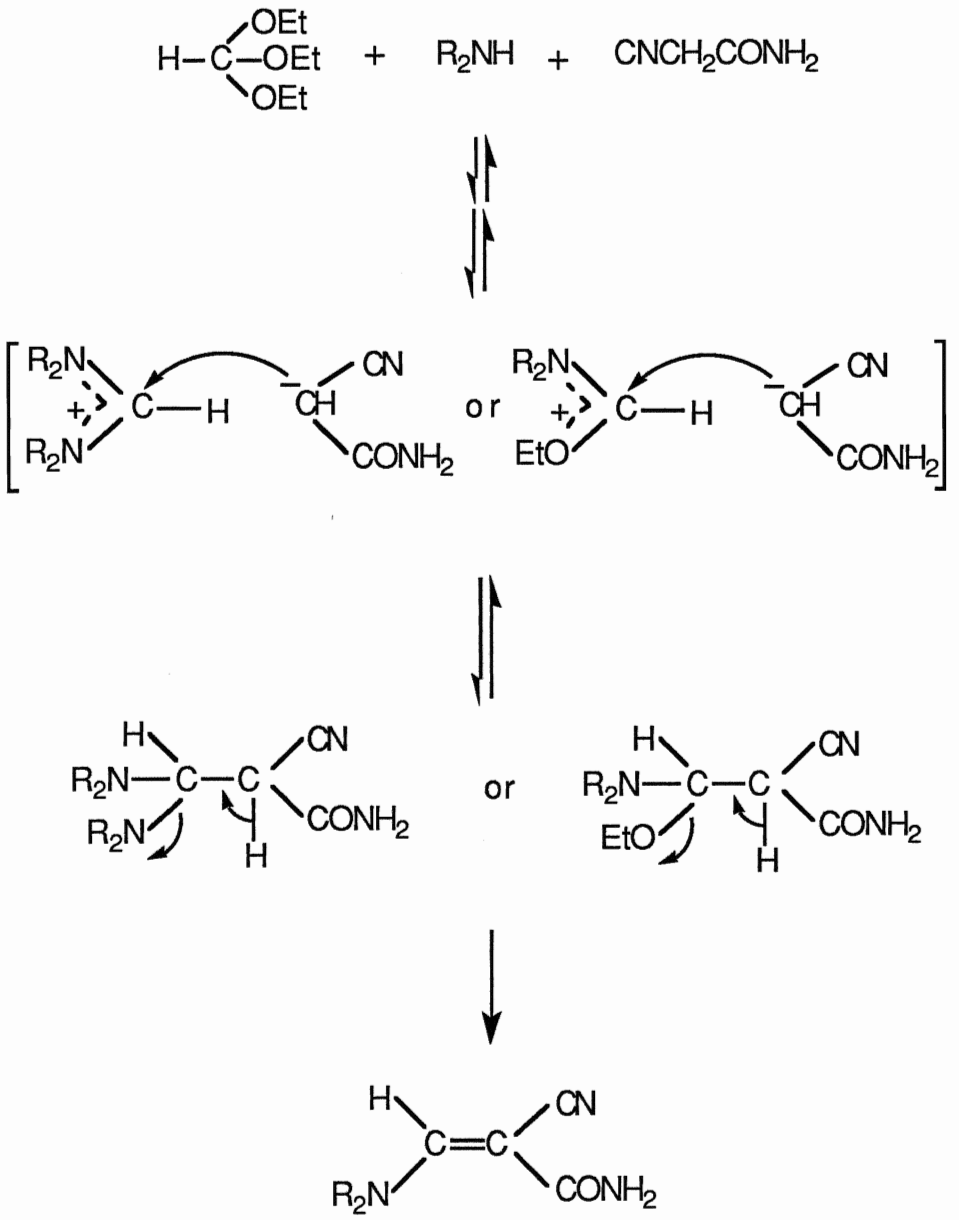


(vi) (vii) (viii)

The mechanism for formation of these substituted enamines should be different from that for the substituted enamines formed by using triethyl orthoacetate. The reason is that the absence of one of the carbon units present in triethyl orthoformate does not allow the formation of an intermediate 1,1-enediamine *in situ* .

A possible mechanism (Scheme III) could be given as; first, the reaction of morpholine with triethyl orthoformate giving one or both of the two possible cations

shown in the Scheme (III). Then the anion of cyanoacetamide presumably attacks this species losing either a molecule of amine or ethanol respectively to give the desired enamine.



Scheme (III)

The structures of the enamines (vi), (vii) and (viii) were confirmed by interpretation of $^{1}H$ NMR, $^{13}C$ NMR, IR, and mass spectra.

The proton NMR spectrum for the compound (vi) should show signals resulting from four different environments for the protons. In fact, the PMR spectrum shows a

multiplet for the morpholine ring protons (8H) at δ value 3.51-3.97 instead of separate signals. The CH signal appears at very low field at δ 7.80. The amide ($NH_2$) proton signal appears at δ 5.75, and disappears on addition of $D_2O$.

Even in the $^{13}C$ NMR spectrum the carbon signal for the CH (Cα) is at very low field (δ 155.0). This is also seen in the case of (viii) (δ155.2). But the case of pyrrolidine enamine (vii) was an anomalous one.

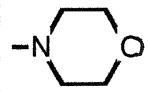
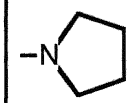
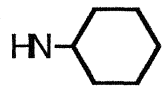
| Enamine | $NR_2$ | $C_\alpha$ | $C_\beta$ |
|---|---|---|---|
| (vi) |  | 155 | 70.3 |
| (vii) |  | 84.6 | 160.0 |
| (viii) |  | 155.2 | 69.2 |

TABLE 2

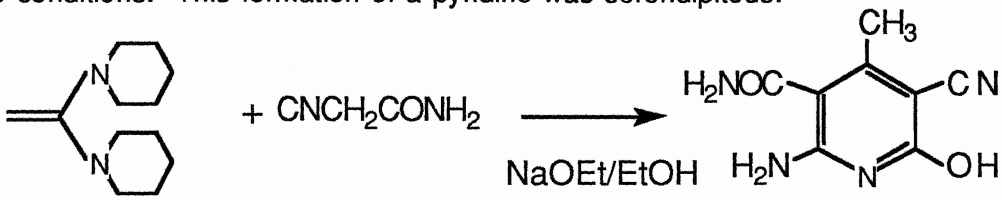
Enamine (vii) made from pyrrolidine, behaved rather differently. The $^{13}C$ NMR should show carbon signals for the Cα and Cβ in the usual pattern as observed for these types of enamines. But the chemical shift for these two carbons was reversed, i.e., the Cβ signal appeared at very low field (δ160.0)and the Cα at high field ( δ 84.6 ). This assignment of the carbon signals for the observed chemical shift was confirmed by conducting a $^{13}C$ off-resonance decoupling experiment. This showed a doublet for the Cα carbon and a singlet for the quaternary carbon Cβ , which is expected. The reason for this anomalous behaviour is unexplained.

This also made us wonder , whether the assignments for the carbon signals for the Cα and Cβ in the previous cases of compounds (iii), (iv) and (v) were correct. A similar off-resonance decoupling experiment was conducted for compound (iii). The $^{13}C$

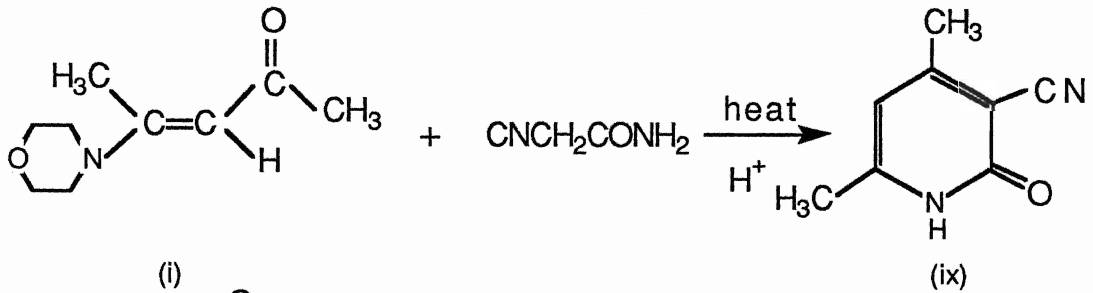
NMR showed a broad unresolved quartet for the Cα carbon which is attached to a methyl group, whereas a sharp singlet was observed at the chemical shift value for the Cβ. This broad signal may be due to a long range coupling with the methyl group. The other assignments have been made tentatively on the same assumption.

**Pyridine synthesis**

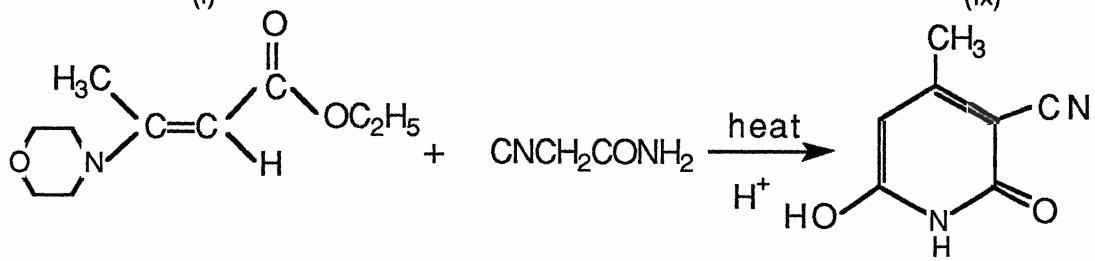
Let us recapitulate the key points from the Introduction. As already discussed in that section, Gandhi[40] examined the reaction of 1,1-dipiperidinoethene with cyanoacetamide and obtained a β-substituted enamine or a substituted pyridine depending on the conditions. This formation of a pyridine was serendipitous.




In the formation of this pyridine a β-substituted enamine was suggested to be formed as an intermediate. This gave rise to the idea that these types of enamines could be used to develop a route for pyridine synthesis. This was further explored by Ratemi[42] in our laboratory. He prepared enamines (i) and (ii) by a literature[38] method and further reacted them with a number of carbon acids. This gave rise to a number of unsymmetrically substituted pyridine derivatives. Enamines (i) and (ii) on reaction with cyanoacetamide gave pyridines (ix) and (x) respectively.



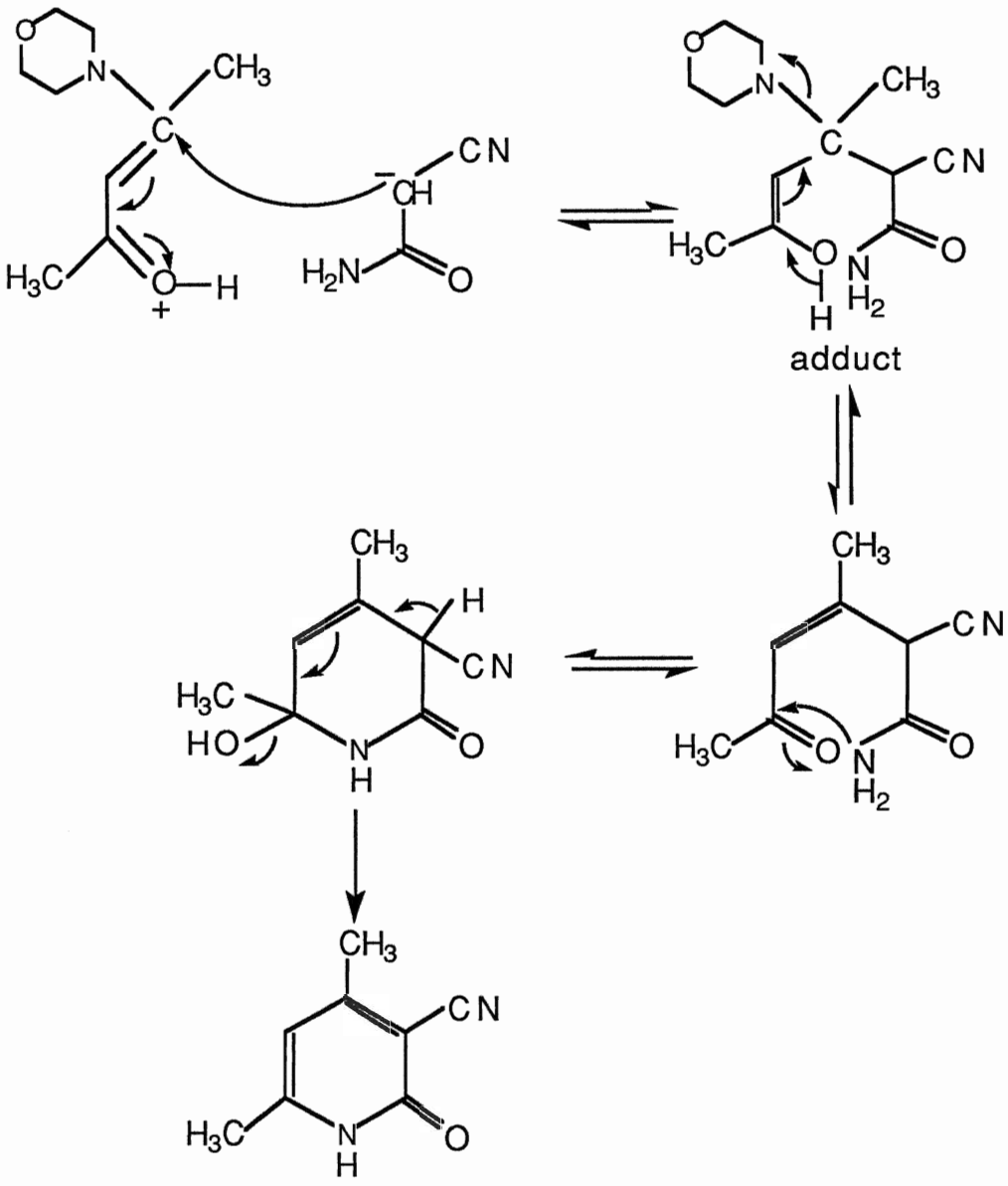

(i) (ix)




(ii) (x)

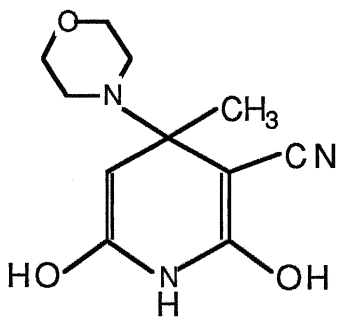
The C4 carbon in enamine (i) is electrophilic in nature and therefore susceptible

to nucleophilic attack (as discussed earlier). Proton exchange can take place between the compound (i) and the carbon acid forming a protonated species of (i) and the anion of cyanoacetamide. Ratemi[42] proposed that Michael addition of the anion to the protonated enamine species would give an adduct. Subsequent loss of the morpholine ring followed by ring closure would then give rise to the pyridine compound. A schematic representation of the mechanism is shown in Scheme (IV).




(ix) Scheme (IV)

In a similar way, formation of (x) from (ii) was also explained mechanistically. When enamine (ii) was reacted with cyanoacetamide under mild acidic conditions, a dihydropyridine compound (xi) was obtained.



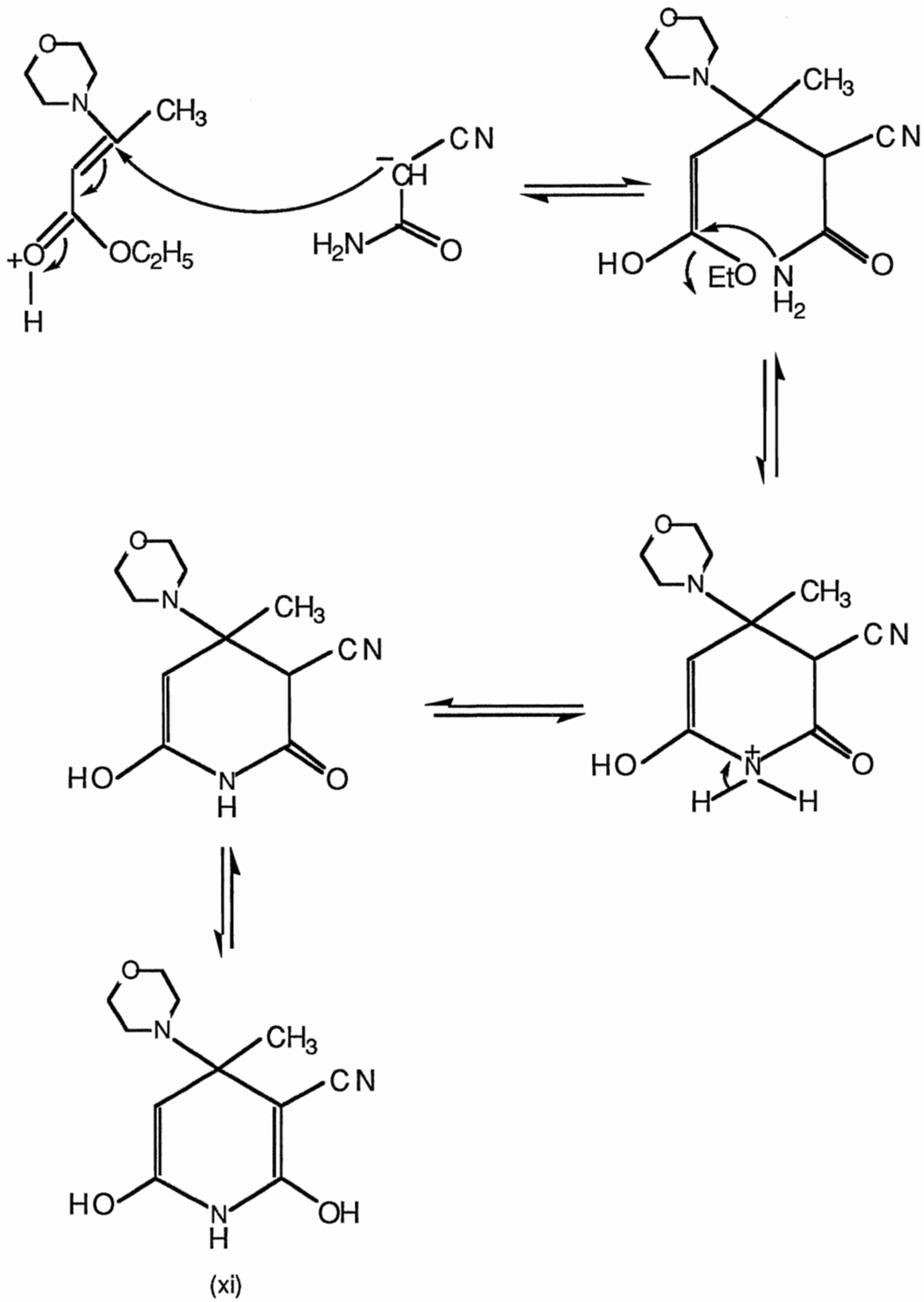

(xi)

The formation of this dihydropyridine (xi) was explained as follows (Scheme V): proton exchange between the enamine and cyanoacetamide, loss of ethanol and subsequent ring closure would give the desired compound.

Only one dihydropyridine, compound (xi), was isolated. In the case of the reaction of enamine (i), no dihydropyridine was obtained.

But the formation of (xi) raises an important question. Do dihydropyridines appear as intermediates in these pyridine syntheses? To answer this, we did a few experiments. Enamines (i) and (ii) were made as described earlier[38], and their identification was confirmed by reported spectral data. The product from the reaction of enamine (i) with cyanoacetamide under acidic conditions was found to be the pyridine (ix), 3-cyano-4,6-dimethyl-2-pyridinone. The structure was confirmed by various NMR, IR and mass spectral techniques.

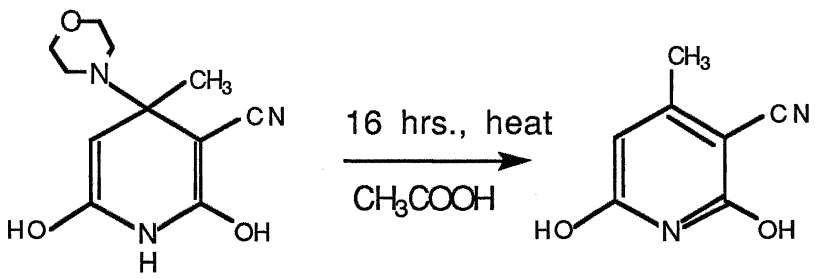
Various reaction conditions were explored in the case of enamine (i), in an attempt to isolate a dihydropyridine. All of these attempts were unsuccessful, the pyridine being obtained in each case. So the question of formation of a dihydropyridine intermediate in this case is still open.



(xi)

Scheme (V)

The other enamine (ii) was used in making the pyridine (x) and the dihydropyridine (xi) as stated earlier. Their structures were confirmed by spectral interpretation, physical properties (mp) and comparison with previously reported data[42]. The acidic conditions, mentioned in the reported synthesis of (xi) were in fact found to be non-acidic when the pH of the reaction mixture was checked. This suggests that for pyridine formation the conditions should be acidic enough. The question as asked earlier, whether a dihydropyridine is an intermediate, was brought into focus again. To find an answer for this, several experiments were designed in which the dihydropyridine (xi) already made was subjected to a series of different conditions so as to obtain the pyridine (x). One of the conditions applied was very successful. Heating the dihydropyridine (xi) in aqueous acetic acid for 16 hrs. followed by work up gave a compound which melting point determination, spectral analysis, and thin layer chromatography confirmed as 3-cyano-2,6-dihydroxy-4-methylpyridine (x).




(xi) (x)

This result does confirm, in this case, that a dihydropyridine is formed as an intermediate. Hence the mechanism for the formation of pyridine (x), and perhaps (ix), could be given via the respective dihydropyridines.

We may note in passing that when a β-substituted enamine is reacted with various carbon acids, as discussed by Gandhi and Gibson[40], two different types of pyridine can be formed, depending on the carbon acids used. The carbon acid used for the enamine formation and subsequent pyridine synthesis may be one and the same as in Gandhi's experiment[40] (and so might be done as a one pot synthesis) or may be different as in Ratemi's experiments[42].

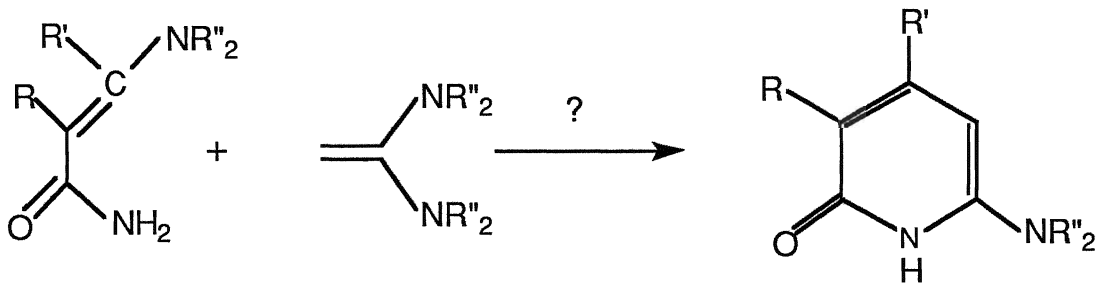
The instance where the carbon acid used is the same in both cases, is similar to the classical Hantzsch[49] synthesis, which also uses two moles of the same carbon acid.

The use of two different carbon acids in sequence (i.e. isolate the enamine and proceed to the second step) would result in a different pyridine. This synthesis thus has advantages over the Hantzsch synthesis. This matter is of current interest. Svetlik and co-workers[50] have recently reported a modified Hantzsch type synthesis for 2-pyridinones and tetrahydropyridines.

**An alternative pyridine synthesis**

As discussed earlier, in β -substituted enamines the carbon atom α -to the amino group is electrophilic in nature, due to the extended conjugation, and can evidently undergo nucleophilic addition. In previous sections we have noted the reactions of some enamines of this type with cyanoacetamide as nucleophile. If these react with one type of nucleophile, then what about other nucleophiles and particularly the 1,1-enediamines? Expressed differently, this raises the question of whether 1,1-enediamines can act as a Michael donor to the β -substituted enamines and, if so, then how and under what conditions can this reaction give rise to pyridines?

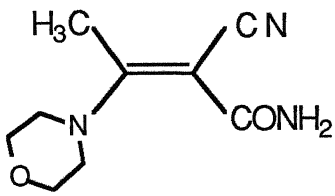
This idea can be formulated as follows:



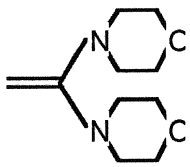

Is such a reaction possible? To explore this, we designed three different ways in which various β -substituted enamines with 1,1-enediamines might be induced to react. So, for simplification, this section is divided into three different subsections.

**( 1 ) Reactions of a β -substituted enamine with a 1,1-enediamine**

This subsection deals with the reaction of enamine (xii) (made from using Gandhi and Gibson's method[40]) with 1,1-enediamine (xiii) (Baganz and Domaschke's method[3]). The plan was to make these two separately and then react them together under appropriate conditions.



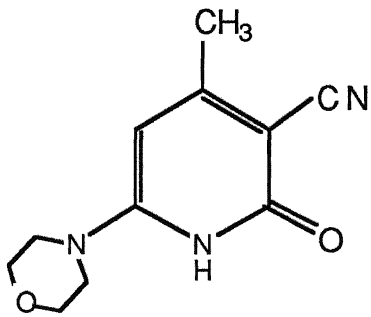

(xii)




(xiii)

The enamine (xii) was made by refluxing a mixture of freshly prepared 1,1-dimorpholinoethene (xiii) with cyanoacetamide, in ethereal medium. After the work-up, a brown solid was obtained which was identified as 2-cyano-3-morpholinocrotonamide (xii). The yield obtained (30%) was a little less than that reported[40](33%). The crotonamide (xii) and excess of 1,1-dimorpholinoethene were mixed together and refluxed for 2 hrs. After cooling, a brownish solid was obtained which on purification gave a light colored compound. Unfortunately, the yield was low.

This light colored solid was identified on the basis of spectral data as 3-cyano-4-methyl-6-(1-morpholino)-2-pyridinone (xiv).

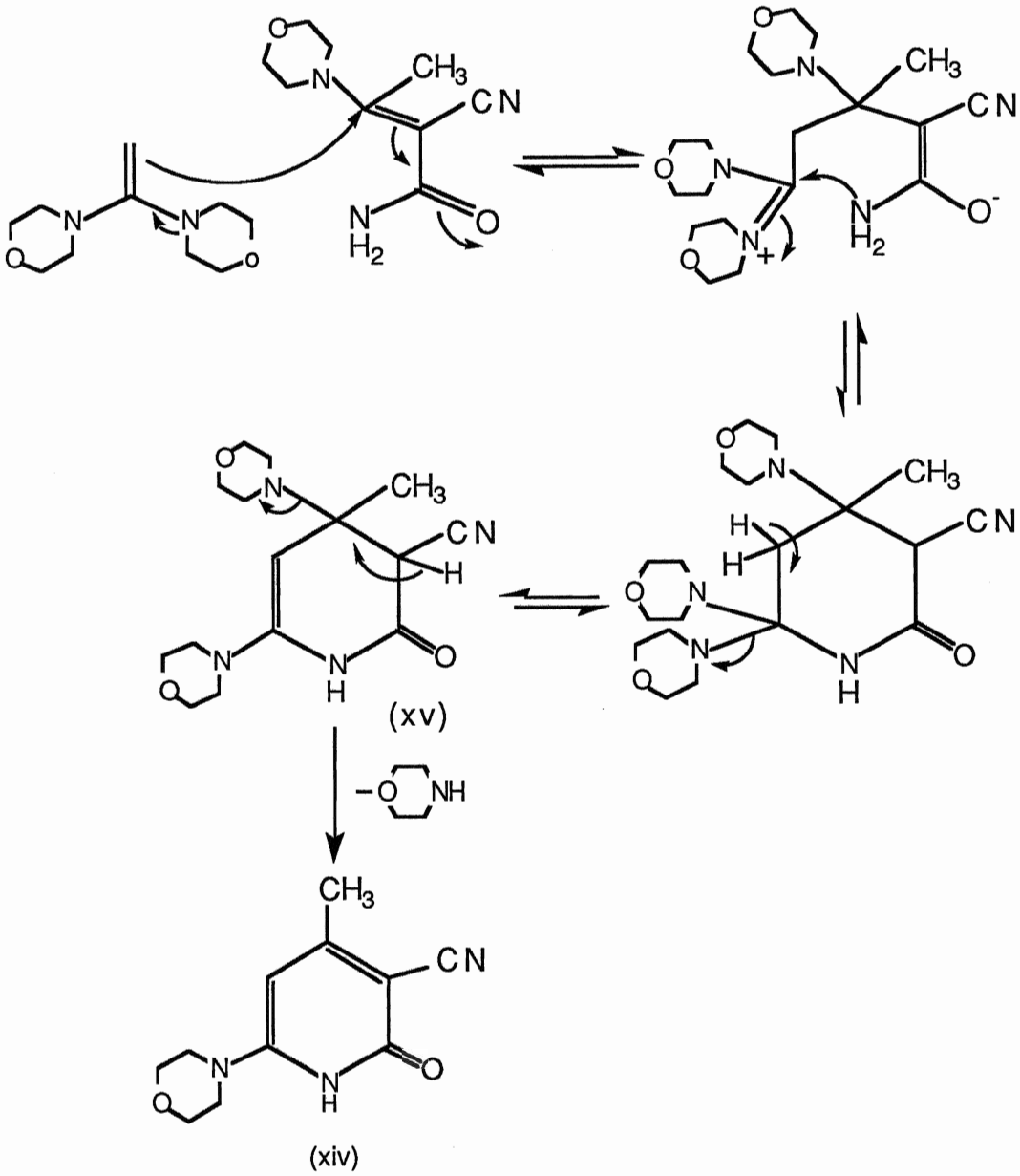



(xiv)

Thus, the solid obtained gave the expected $^1$H NMR spectrum for the compound having structure (xiv). There was a singlet at δ 2.08 integrating for methyl protons, a multiplet at δ 3.34-3.54 for the morpholine protons (8H), a singlet for the pyridine

ring CH at δ 5.81, and a broad singlet downfield at a chemical shift of δ 11.3 integrating for the NH of the pyridine ring.

The mass spectrum showed the molecular ion at the expected m/z value. The $^{13}C$ NMR spectrum exhibited nine different signals in accordance with the structure of (xiv). The infra red spectrum confirmed the presence of C=O, CN, and NH groups. The formation of (xiv) can be explained with a plausible mechanism as in Scheme (VI). The pair of electrons from the π system of the 1,1-enediamine attack the C3 electrophilic centre of the enamine (xii). The mechanism may be developed via the formation of a dihydropyridine type intermediate (xv) which then loses one morpholine unit to give the desired pyridine (xiv).




Scheme (VI)

The compound (xiv) is present in the lactam form and not in the hydroxy form, which can be confirmed by the presence of carbonyl group stretch (1647cm$^{-1}$) in the infrared spectrum.

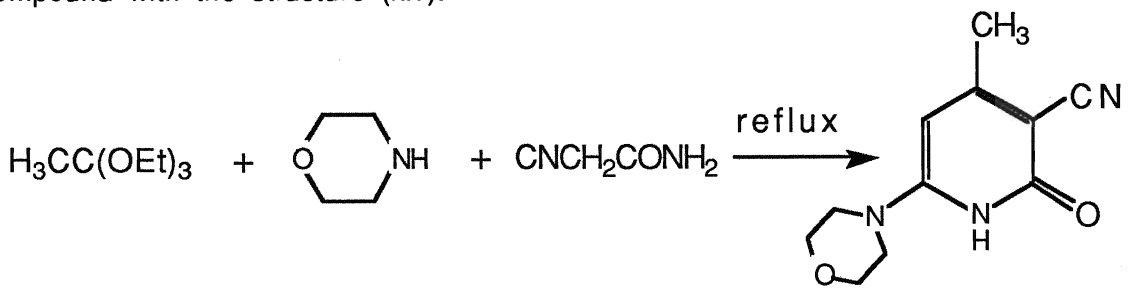
The individual yields of the enamine (xii) and the pyridinone (xiv), and the complications from the presence of the hydrolysis products of the 1,1-enediamine prompted us to think that the reaction might with advantage be done without handling

them individually. This raised the possibility of a "one pot synthesis", as was earlier adopted in case of the β -substituted enamines (Discussion p-28). This is discussed in the next subsection.

**(2) The One-pot synthesis**

The yield and the reactivity problem of the 1,1-enediamine led to this idea. Keeping this in mind a number of experiments were done which are described in this subsection.

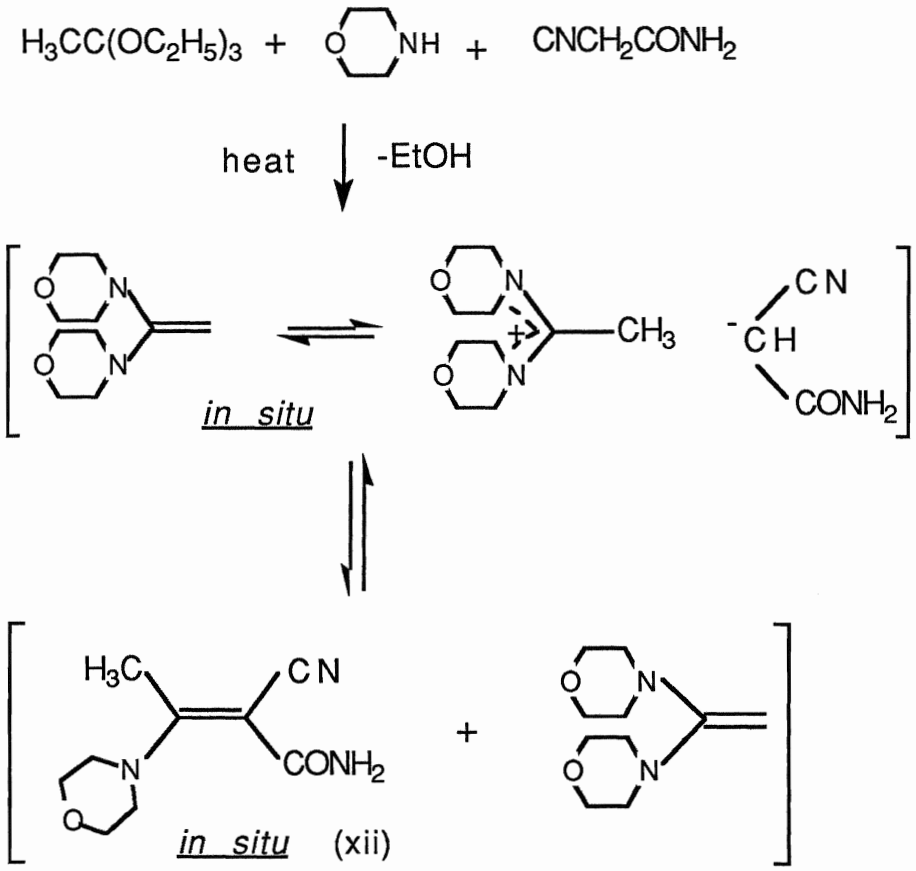
Triethyl orthoacetate and morpholine were mixed in equimolar proportions and to this cyanoacetamide (half the mole proportion of the other reactants) was added.The mixture was refluxed under a Vigreux column, through which the ethanol produced in the reaction was distilled out. Spectral analysis of the resulting product pointed to a compound with the structure (xiv).



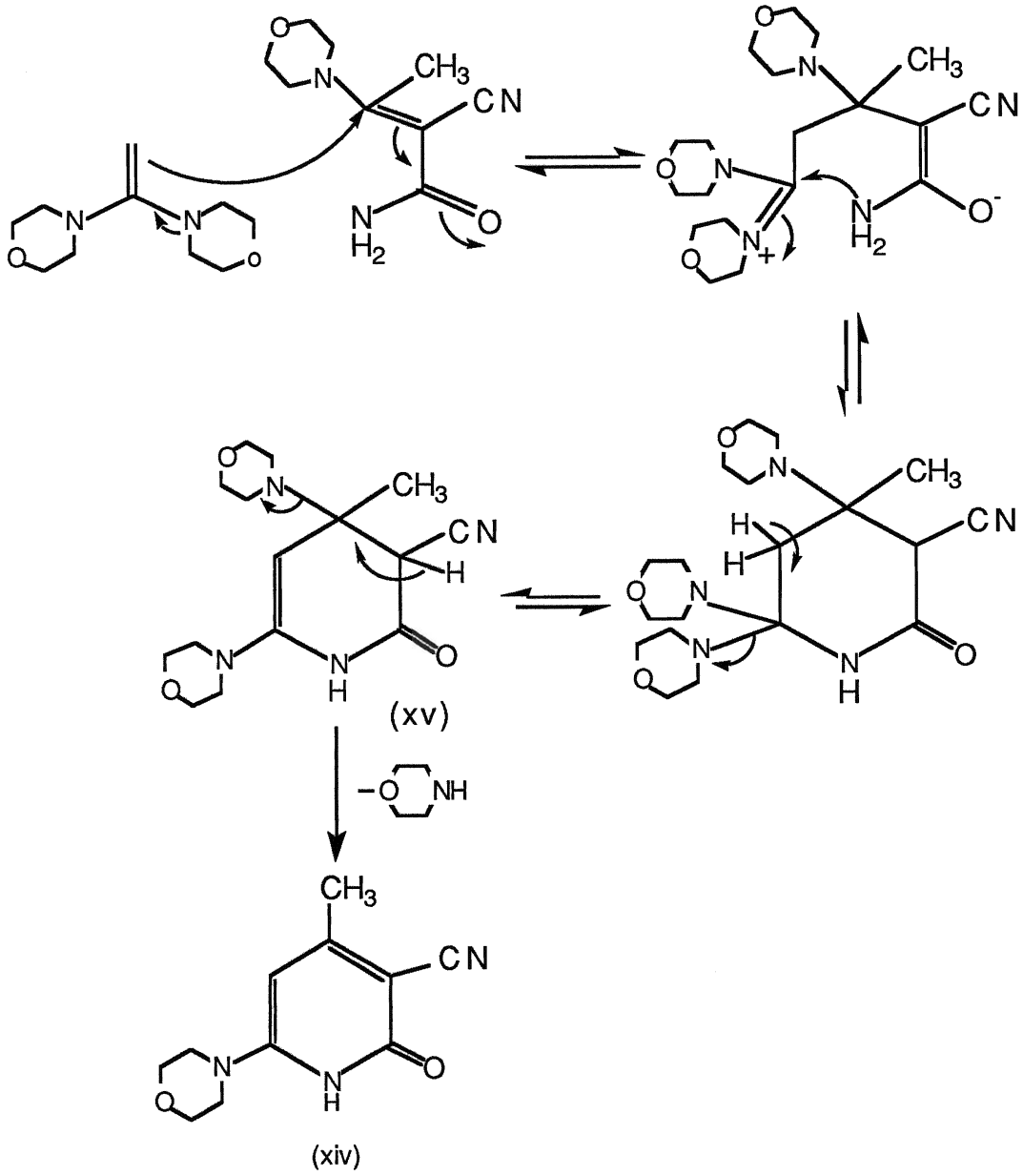

(xiv)

The $^{1}H$ NMR, $^{13}C$ nmr, IR and mass spectra gave data which were in accordance with that seen for compound (xiv) obtained in the earlier section.

The formation of (xiv) from this 'one pot synthesis' can be explained mechanistically as follows (Scheme VII): one way to explain would be by first the formation of the 1,1-dimorpholinoethene, *in situ,* by the reacton of triethyl orthoacetate and morpholine. This then probably undergoes a proton exchange with the cyanoacetamide also present in the reaction mixture, to form the amidinium ion and anion of cyanoacetamide. Addition of this anion to the amidinium ion would then give the enamine intermediate (xii), again *in situ* . Then Michael addition of the 1,1-enediamine, and not cyanoacetamide as noted earlier, to the enamine gives the desired pyridinone (xiv).



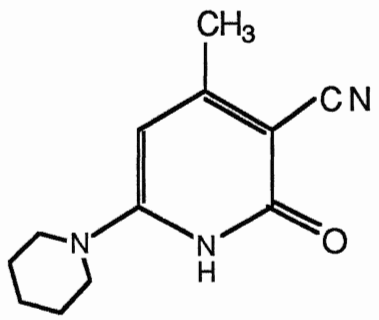

Scheme VII (contd. on next page)



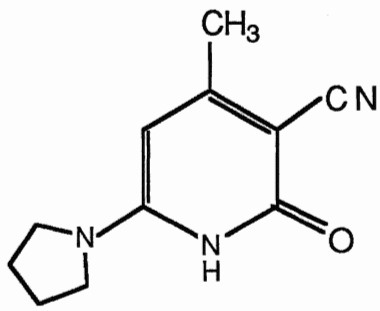

Scheme (VII)

We do not know the sequence for introduction of the amine group in this reaction, i.e., whether it takes part earlier, as described before, to form the enediamine or it enters the reaction at a later stage. This can be checked and confirmed if the reaction is interrupted at an intermediate stage and and the carbon acid is then added. This interrupted reaction would also confirm whether the enediamine could be formed or not.

Two other pyridinones, (xvi) and (xvii), were also made by substituting morpholine with piperidine and pyrrolidine respectively.




(xvi)




(xvii)

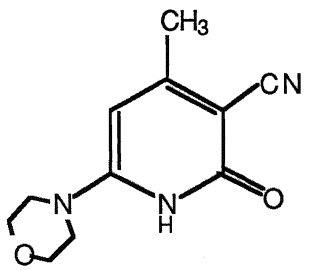
The mechanism for formation of these two pyridinones could be explained in a similar way to that for (xiv). The structures of (xvi) and (xvii) were assigned and identified through spectral interpretation.

This one pot synthesis avoids all of the problems encountered in the previous route. Since the reaction is not open to air (exclusion of moisture), the problem of hydrolysis of the 1,1-enediamine is solved. The yield (50%, for compound xiv) is also better than that obtained for the first route.

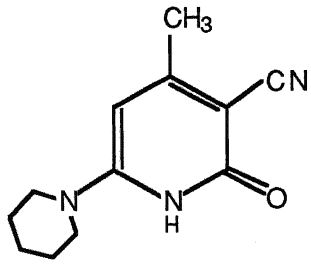
The formation of (xiv), (xvi), and (xvii) was also achieved by a slightly modified procedure which we call 'the interrupted one pot synthesis' and is discussed in the next subsection.

**(3) The interrupted one pot synthesis**

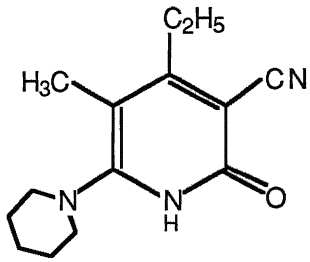
It was decided to explore a modification of the one pot synthesis, where the 1,1-enediamine is thought to be formed *in situ*. The basis of this idea was to interrupt the reaction at the stage where the enediamine had been formed *in situ*, and then to add the carbon acid ( the enediamine is not isolated and purified, but used as such). This proved to be a convenient way to prepare the following pyridinones.



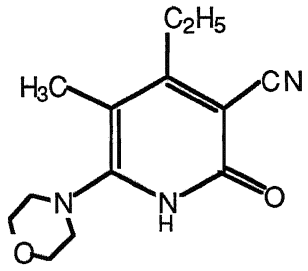

(xiv)




(xvi)




(xviii)




(xix)

Compounds (xiv) and (xvi) were prepared by refluxing the mixture of the respective secondary amine and triethyl orthoacetate under the conditions of Baganz's method[3]. After removal of ethanol produced through the Vigreux column, refluxing was stopped, the carbon acid, cyanoacetamide in this case, was added, and heating was then resumed. In case of (xiv) a yellow solid was separated which on purification gave the desired product in 50% yield; examination of spectral data confirmed the product as (xiv). The yield was the same in this method as that obtained in the last method. When piperidine was used, the solid obtained after the work-up was very pure even though not crystallised. Melting point determination and spectral analysis of this compound

confirmed it to be 3-cyano-4-methyl-6-piperidino-2-pyridinone (xvi).

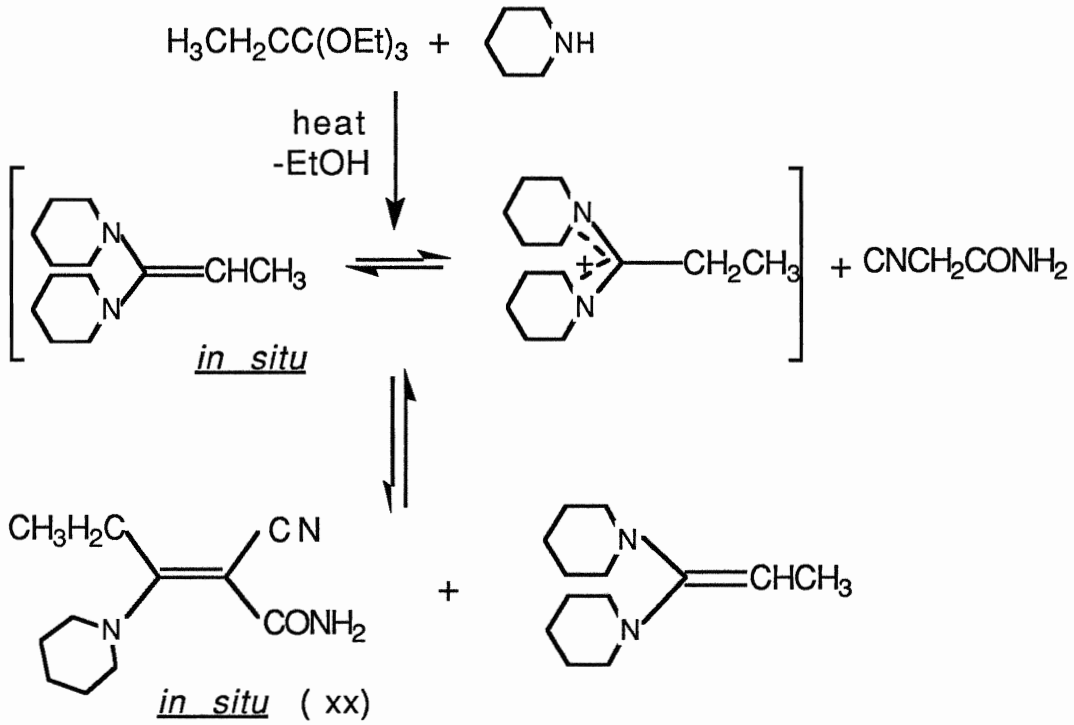
The yield (41%) was greatly improved in this method, when compared with that in the one pot synthesis (yield 14%).

A plausible mechanism for formation of (xiv) and (xvi) by this method could be given as that already outlined in Scheme (VII)(p. 50-51) for the one pot synthesis.

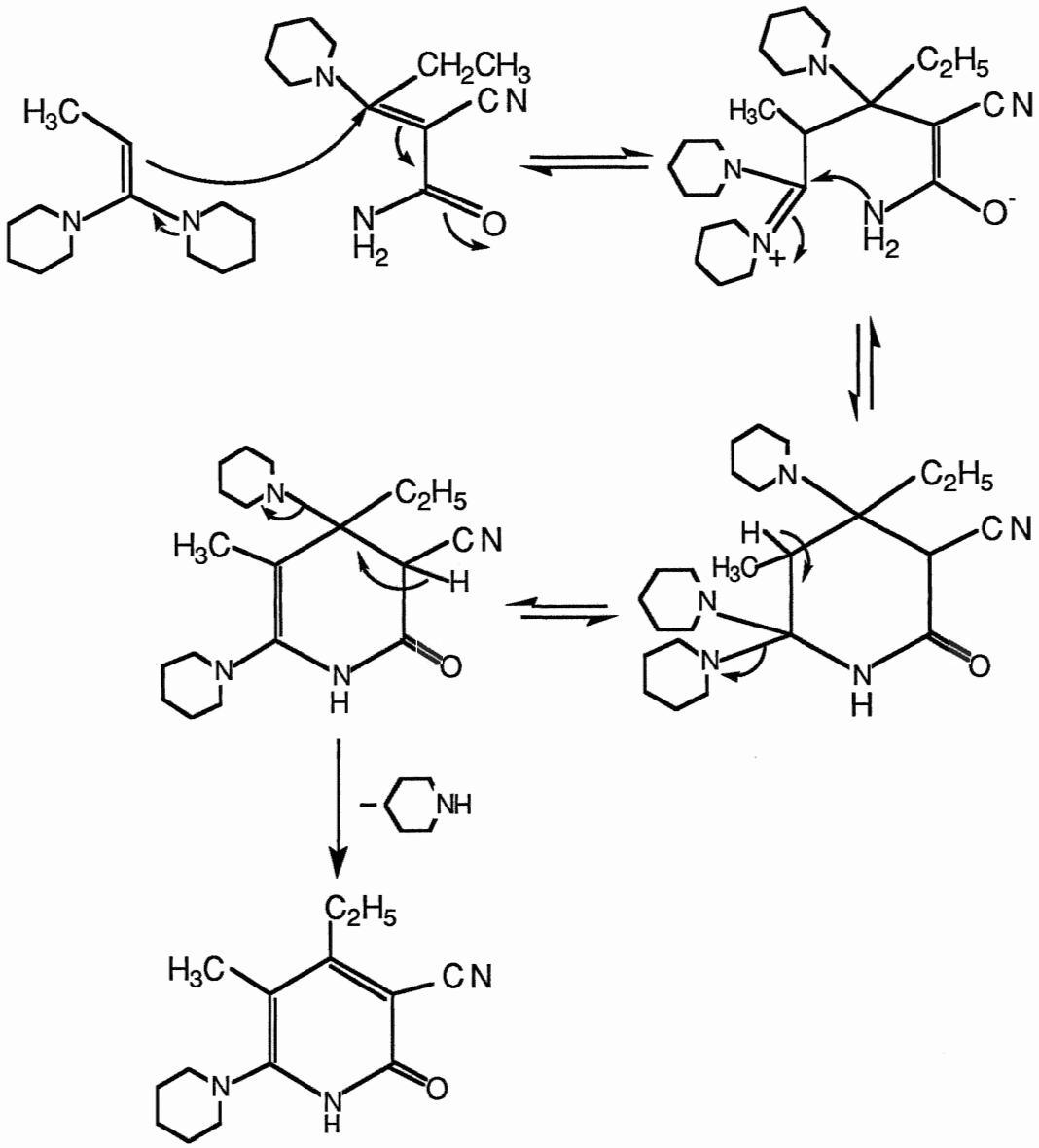
The compounds (xviii) and (xix) were produced when triethyl orthopropionate was used instead of triethyl orthoacetate. The reaction conditions were similar to those for the pyridinones (xiv) and (xvi).

The reaction of piperidine and triethyl orthopropionate with cyanoacetamide in an extension of this synthetic route yielded a shiny light colored solid. This crude material on TLC (acetone) showed only one spot ($R_f$ 0.82), as observed in the case of (xvi) discussed earlier. Consideration of various spectra confirmed it to be 3-cyano-4-ethyl-5-methyl-6-piperidino-2-pyridinone, (xviii). The $^1H$ nmr spectrum of (xviii) showed 6 different signals. A distinct triplet and a quartet for the ethyl group were observed at $\delta$ 1.21 and 2.58 respectively.The methyl group on C5 was observed at $\delta$ 1.99, the six protons for the piperidine methylenes remote from nitrogen were observed at $\delta$ 1.69, and the remaining four protons of the piperidine ring were seen at $\delta$ 3.38. The NH signal of the pyridinone ring was observed very much downfield at $\delta$ 12.4, and this signal disappeared upon addition of $D_2O$. The EI mass spectrum showed the molecular ion at m/z value 245, as expected.

We think that the likely mechanism (see Scheme VIII) for the formation of (xviii) first involves formation of 1,1-dipiperidinopropene *in situ* (this enediamine was also synthesised by Baganz and Domaschke[3]). When cyanoacetamide is added, the positively charged species from this enediamine and the anion of cyanoacetamide would be formed reversibly and then react to form the appropriate enamine intermediate (xx). This enamine then presumably reacts with the remaining 1,1-dipiperidinopropene to give, the highly substituted pyridinone as in the less substituted cases previously observed and discussed.




Scheme (VIII) contd. on next page



(xviii)

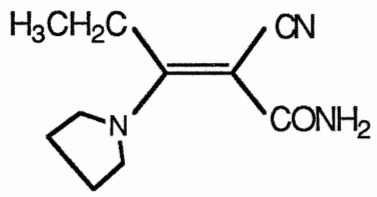
Scheme (VIII)

Pyridinone (xix) was prepared in a similar way by using morpholine instead of piperidine. The assignment of these two structures was confirmed by using proton and carbon NMR, IR, and EI mass spectral techniques.

Both compounds (xviii) and (xix) were found to be in the lactam form and not the hydroxy forms. This was confirmed by the C=O group absorption in their IR specta (1636 and 1641 $cm^{-1}$ respectively) and signals at δ 168 and 167 respectively in

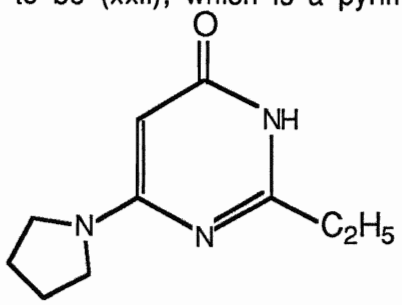
their $^{13}C$ nmr spectra. The presence of an NH stretch was also noted in the IR spectra (3124 and 3250$cm^{-1}$ respectively).

When pyrrolidine was used as the other secondary amine, no pyridinone was observed. The isolated compound showed a parent ion signal at m/z 193 in the EI mass spectrum. Initially, we thought that the enamine (xxi) must be formed in this case, since the molecular ion for this particular enamine (which could be formed from the orthopropionate, pyrrolidine and cyanoacetamide) would also be observed at the same m/z value. However, the study of $^{13}C$ NMR and IR spectra revealed that there was no CN group present in the compound obtained. This was very strange, but was sufficient to rule out the formation of the enamine (xxi).




(xxi)

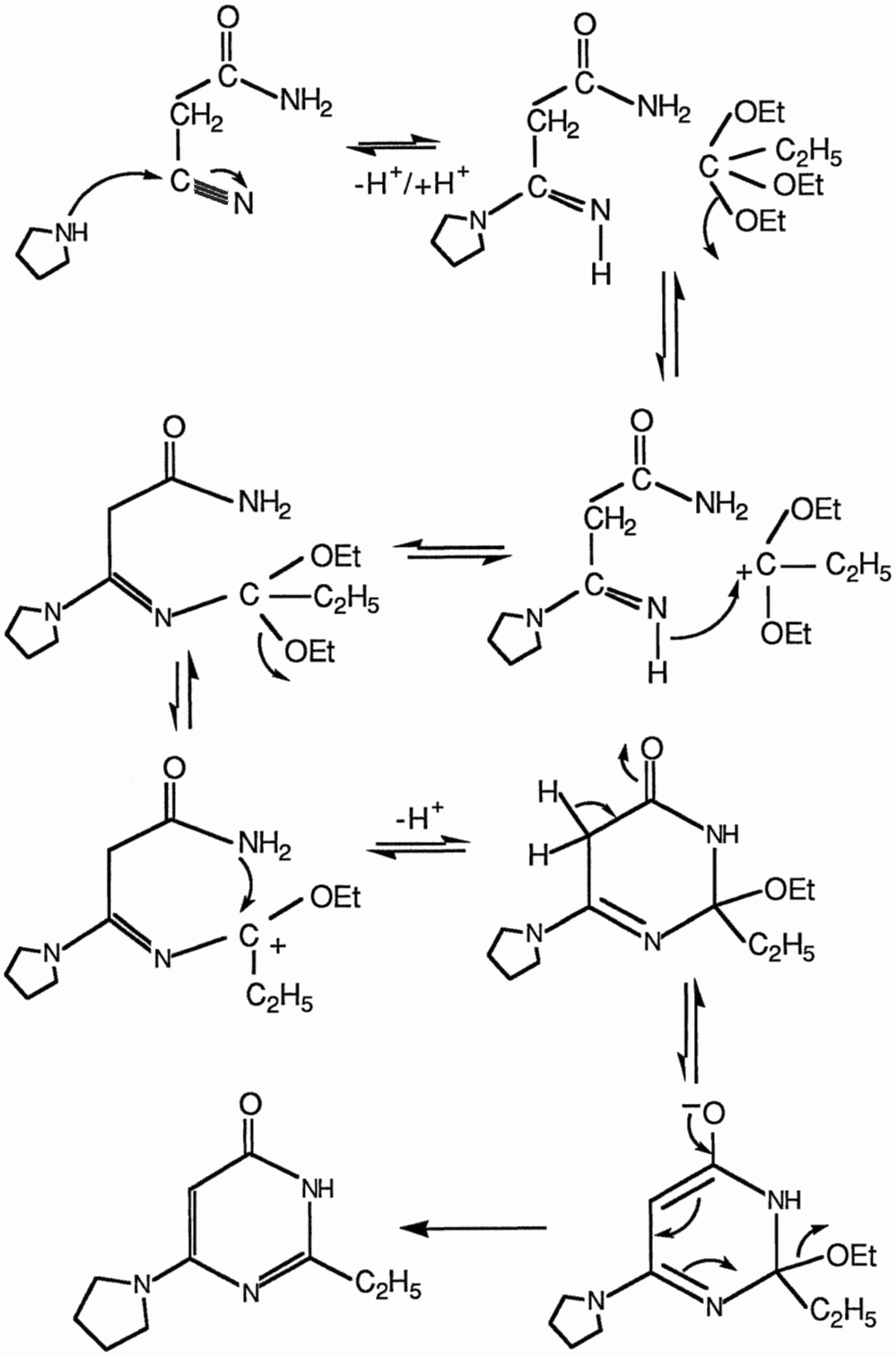
The proton NMR spectrum showed the presence of an ethyl group, a CH, a pyrrolidine ring and an NH group. In the $^{13}C$ NMR spectrum there were in total eight carbon signals, one at the chemical shift for $CH_3$, for $CH_2$, for methylene signals from the pyrrolidine ring, for a CH signal, and for three quaternary signals which were quite downfield. A close study of the isotopic mass peak at m/z 194 in the EI mass spectrum revealed that there should be 10 or possibly 11 carbon atoms present in the molecule, 10 being more probable. All the spectral data indicated a structure which would have the same groups as in (xxi), but with a CH group replacing the CN group. The most likely structure seems to be (xxii), which is a pyrimidinone.




(xxii)

This pyrimidinone (xxii) correlates with all the spectral data obtained. The

formation of this pyrimidinone could be explained by disconnecting the molecule to provide three synthons, the reagents for these synthons being the triethyl orthoester, pyrrolidine, and cyanoacetamide. A mechanism based on this is represented in Scheme (IX).



(xxii) Scheme (IX)

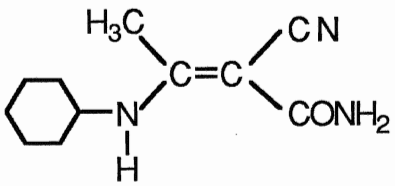
The mechanism outlined above involves the attack of the lone pair of electrons of the amine nitrogen on the cyano carbon of cyanoacetamide to give an amidine adduct. This adduct then acts as a compound with two nucleophilic ends, one end of which adds to the electrophilic carbon of the orthoester. Subsequent loss of ethanol, ring closure and the loss of a final molecule of ethanol gives (xxii).

Apart from this exception, the routes we have examined seem very successful in synthesising various substituted pyridines.

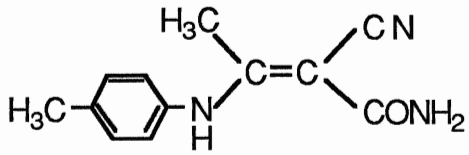
**Scope and Limitations**

When primary amines were used in this one pot synthesis of pyridines, the reaction proceeded only till the enamine stage. No pyridine was obtained.

We used triethyl orthoacetate, cyanoacetamide, and cyclohexylamine and p-toluidine separately, in two sets of reactions. The final products obtained were found to be the enamines ( iv) and (v) respectively.




(iv)




(v)

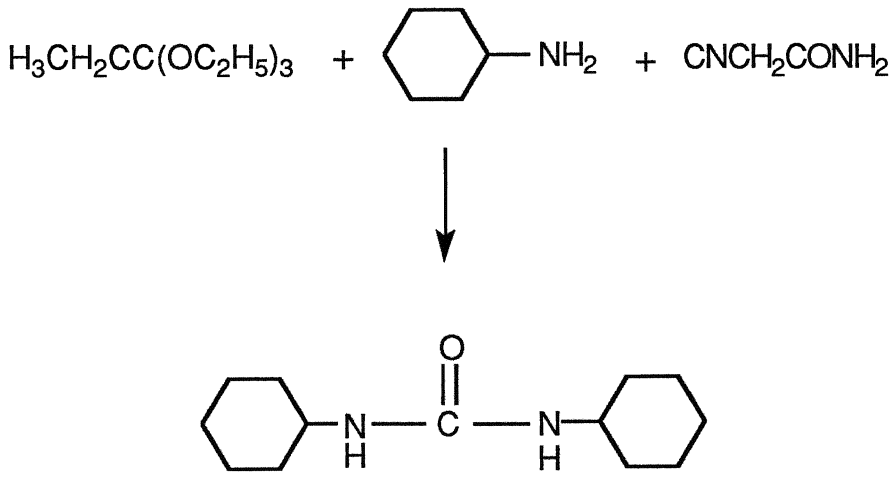
Repeated trials of the reactions were unsuccessful as far as pyridine synthesis was concerned.

**Miscellaneous Experiments :**

**( a )** A surprise was encountered when these primary amines were used in conjunction with triethyl orthopropionate instead of orthoacetate. The reaction conditions were set up so as to obtain a highly substituted pyridinone. However, this pyridinone was clearly not obtained when spectral data were examined.

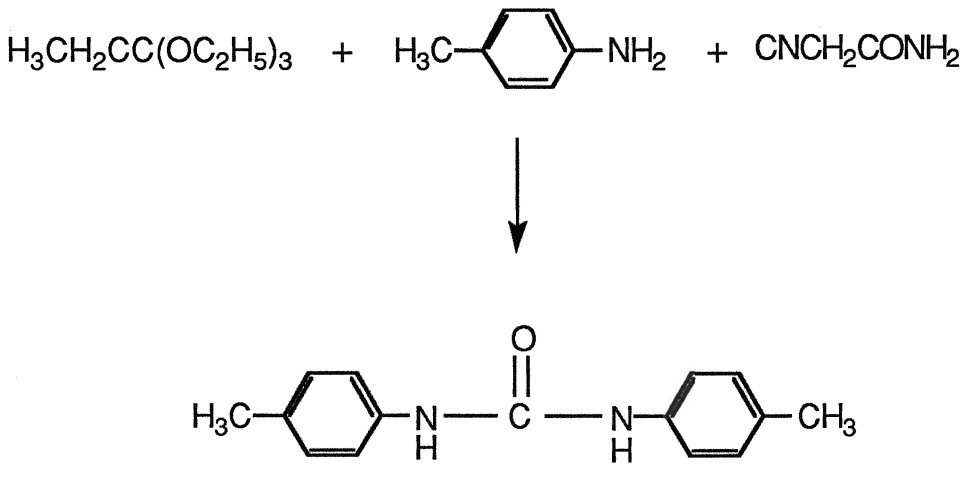
When the EI mass spectrum of the product from the reaction of cyclohexylamine and the other reactants was obtained, a parent ion peak at m/z 224 was observed. This gave no immediate clue as to the identity of the compound. But the $^{1}H$ NMR and $^{13}C$ NMR spectra were very helpful. The $^{1}H$ NMR spectrum showed only the presence of the cyclohexyl ring protons. No NH signal was visible (this may be due to the solvent used). The $^{13}C$ NMR spectrum was very simple. It exhibited signals from the cyclohexyl ring carbons and only one quaternary carbon signal which was observed far downfield in the region where the carbonyl signal appears. Furthermore, the IR spectrum showed the absence of a CN group and the presence of carbonyl (1679 $cm^{-1}$) and NH (3323-

3332 $cm^{-1}$) groups. Melting point determination and comparison with the literature value[51] then confirmed that the product obtained was N,N'-dicylohexylurea (xxiii).



(xxiii)

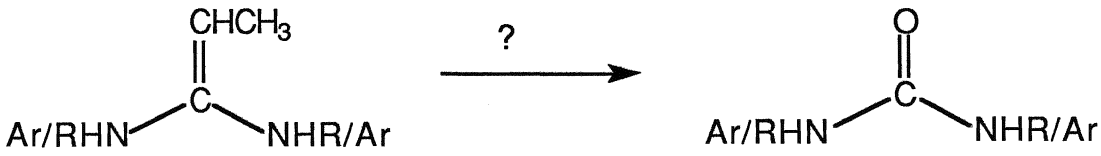
Similarly, when p-toluidine was used as the other primary amine, the reaction under similar conditions as for (xxiii) gave N,N'-di-p-tolylurea (xxiv). The structure was confirmed by melting point comparison with the literature value[52] and interpretation of the various spectral data.



(xxiv)

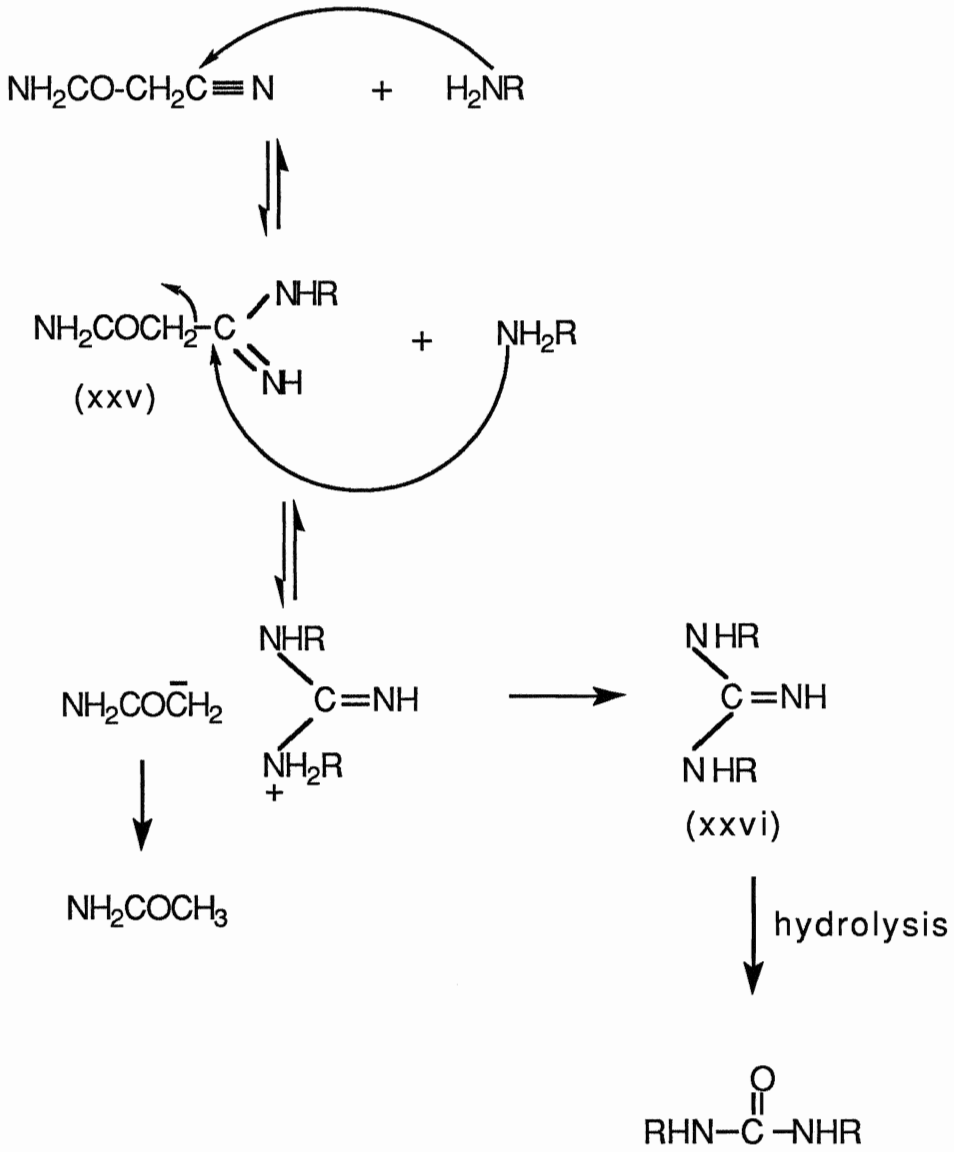
The mechanism for the formation of these urea products is not immediately clear.

At first we thought that maybe the 1,1-enediamine is formed, which then somehow gets oxidised to give the substituted urea (Scheme X).




Scheme (X)

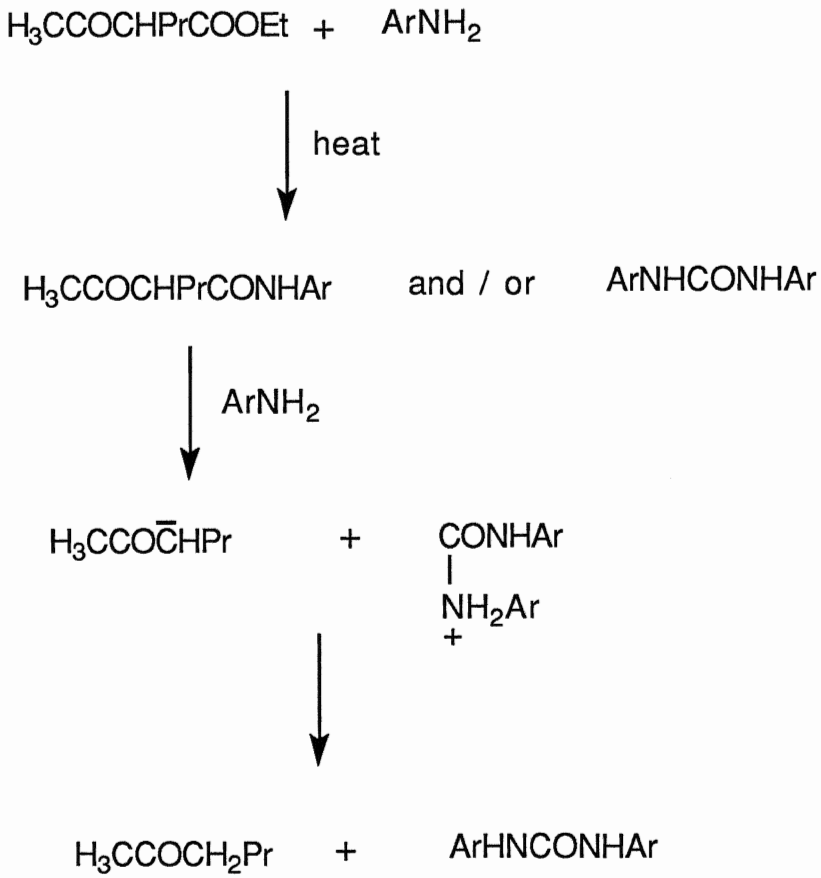
Further thought gave rise to a more plausible mechanism (Scheme XI) which involves only the primary amine used and cyanoacetamide. The lone pair of electrons on the amine nitrogen could attack the electrophilic carbon of the CN group in cyanoacetamide to give an amidine type adduct (xxv). Another molecule of amine would then react with this adduct, subsequently displacing acetamide and giving a guanidine derivative (xxvi). This guanidine derivative (xxvi) could undergo hydrolysis to give the desired urea derivative. The hydrolysis step may alternatively take place at the amidine stage. Since no water is used in the reaction, the water for hydrolysis would likely come from traces present in the amine.



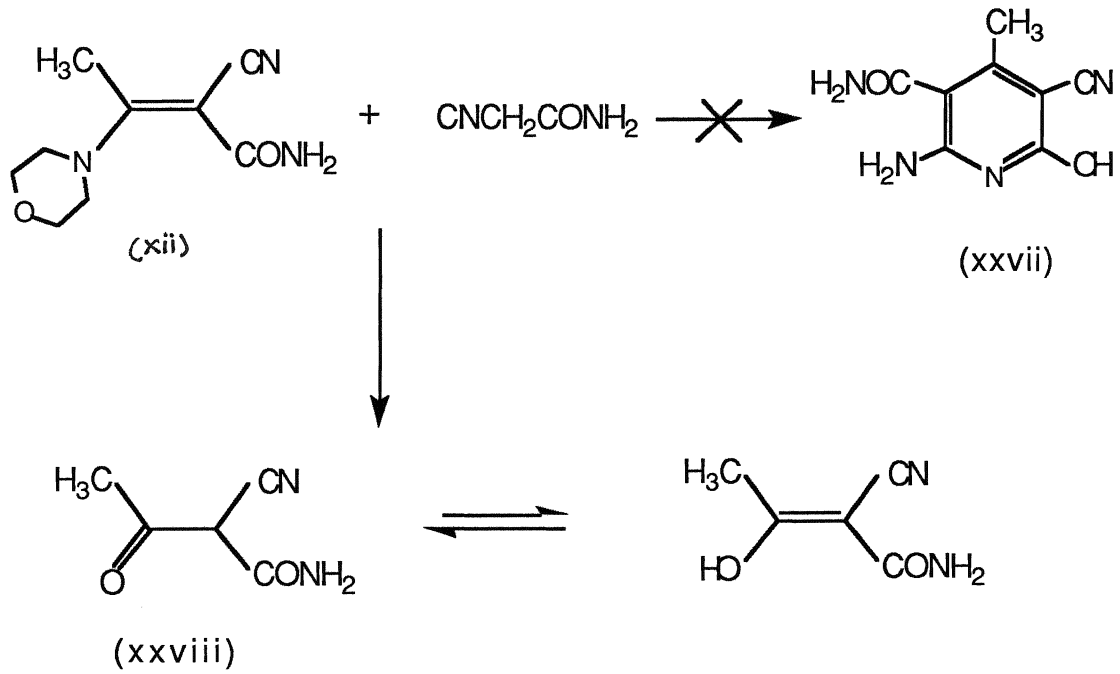

Scheme (XI)

A different mechanism can be proposed which is similar to the above in the respect that only amine and cyanoacetamide take part in the reaction. The lone pair of electrons from the amine nitrogen could attack the carbonyl carbon instead of the cyanide carbon of cyanoacetamide. We are not sure where the carbon of the carbonyl group in the urea derivatives comes from, but these reactions are very intriguing.

It is interesting to recall that Jadhav[52] noted formation of N,N'-di(p-tolyl)urea as one product of reaction of p-toluidine with a β-ketoamide. We would now interpret his reaction as follows:

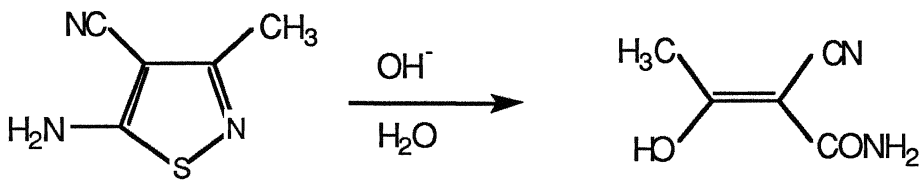



**( b )** When enamine (xii) was reacted with cyanoacetamide under the conditions specified in Gandhi's report[40], instead of obtaining a pyridine derivative ( xxvii) , the acetyl derivative of cyanoacetamide (xxviii) was obtained. This was reported as a side reaction product by Gandhi and Gibson[40]. The yield obtained in our work (51%) is an improvement on that reported in the literature by Anderson and Hsiao[53] (yield 28%).




(xxviii)

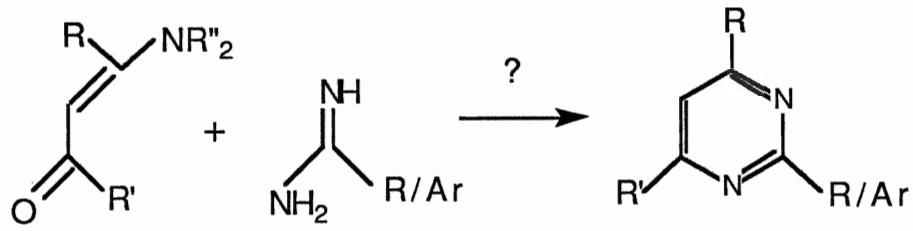
Anderson and Hsiao[53] synthesised (xxviii) by hydrolysis of 5-amino -3-methylisothiazole-4-carbonitrile with 2N NaOH.




(xxviii)

**Pyrimidine Syntheses**

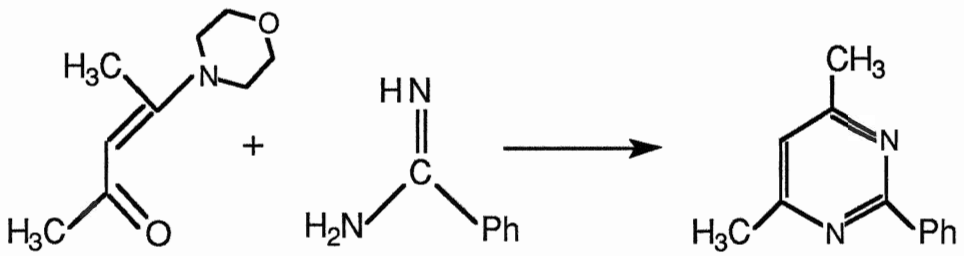
The β-substituted enamines discussed in the earlier sections of this thesis are reactive towards nucleophiles. In particular, the successful outcome of reactions with the nucleophilic 1,1-enediamines led us to consider other nucleophiles which might react with these β-substituted enamines. Possibly nucleophiles like amidines, which have two nucleophilic centres in the same molecule, would react with these enamines to give pyrimidine derivatives.




To explore the feasibility of this approach we first explored the reaction of (i) with benzamidine, an aromatic amidine.

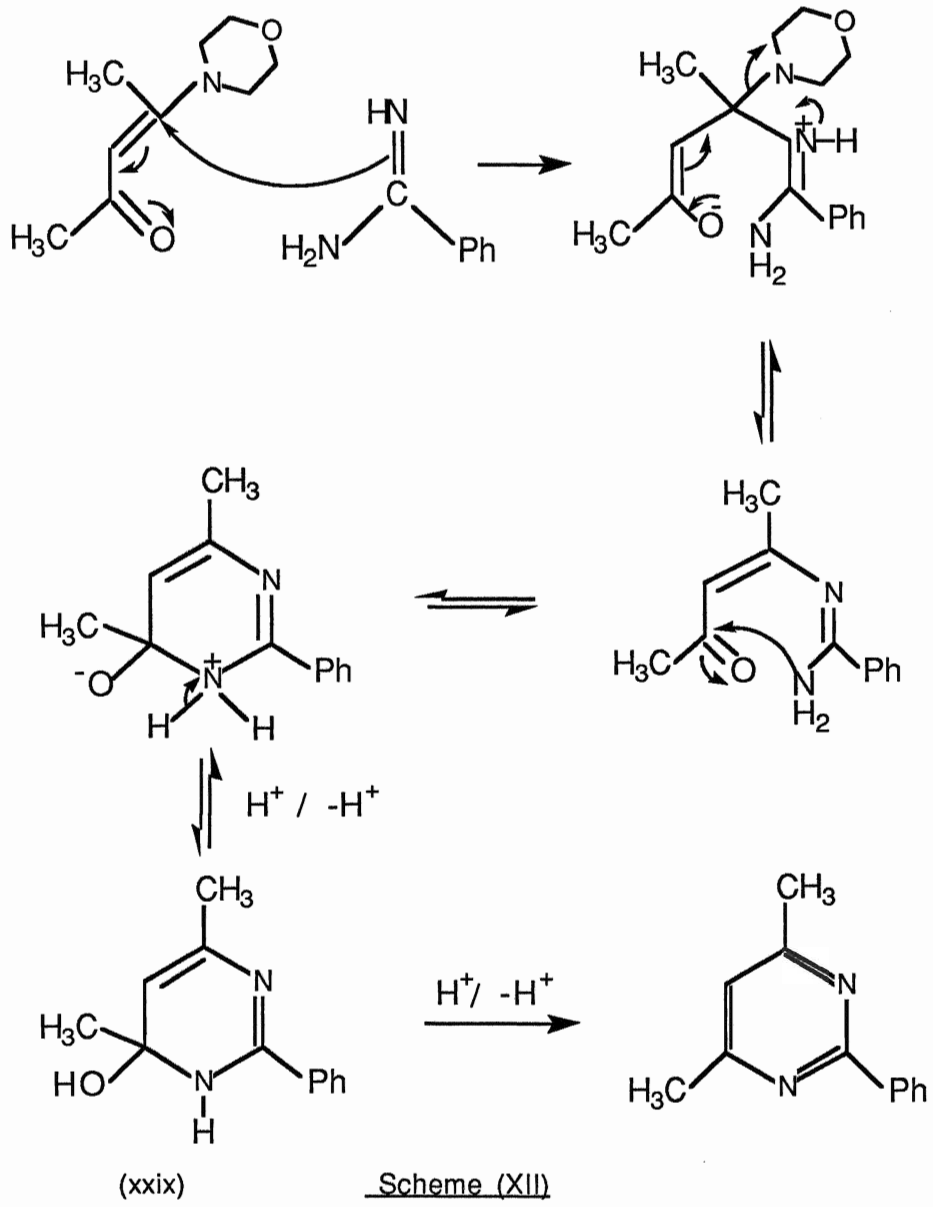
Enamine (i)[38] was taken along with benzamidine hydrochloride hydrate (in excess since the number of moles of water present in the commercial sample was not known) in acetic acid in the presence of a buffer (sodium acetate). The resulting mixture was refluxed and, after work up, a shiny white solid was obtained.

This shiny product on spectral analysis and correlation of melting point with the literature value[54] was found to be 4,6-dimethyl-2-phenylpyrimidine (xxix).




(i) (xxix)

We think that the formation of (xxix) can be explained mechanistically as shown (for one particular nitrogen atom) in Scheme ( XII).

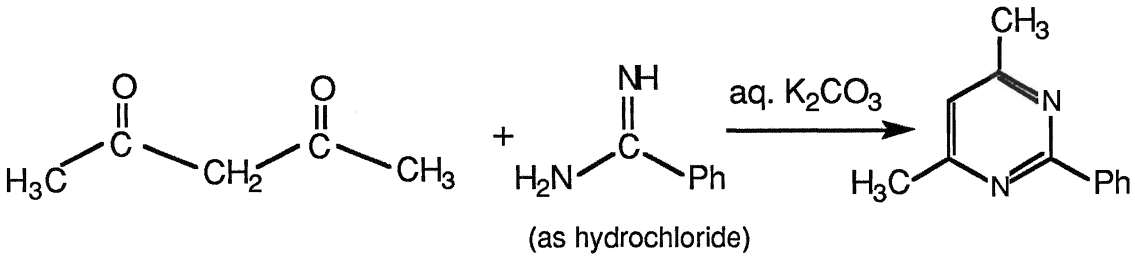


(xxix) Scheme (XII)

The mechanism involves first an attack of the lone pair of electrons of a nitrogen from the amidine on the electron deficient α-carbon centre (C4) of the enamine (i). Morpholine loss and condensation or vice versa would then give the required compound.

In the literature, the original synthesis of this compound was reported by Pinner[54]. He made (xxix) by treating acetylacetone with benzamidine hydrochloride in

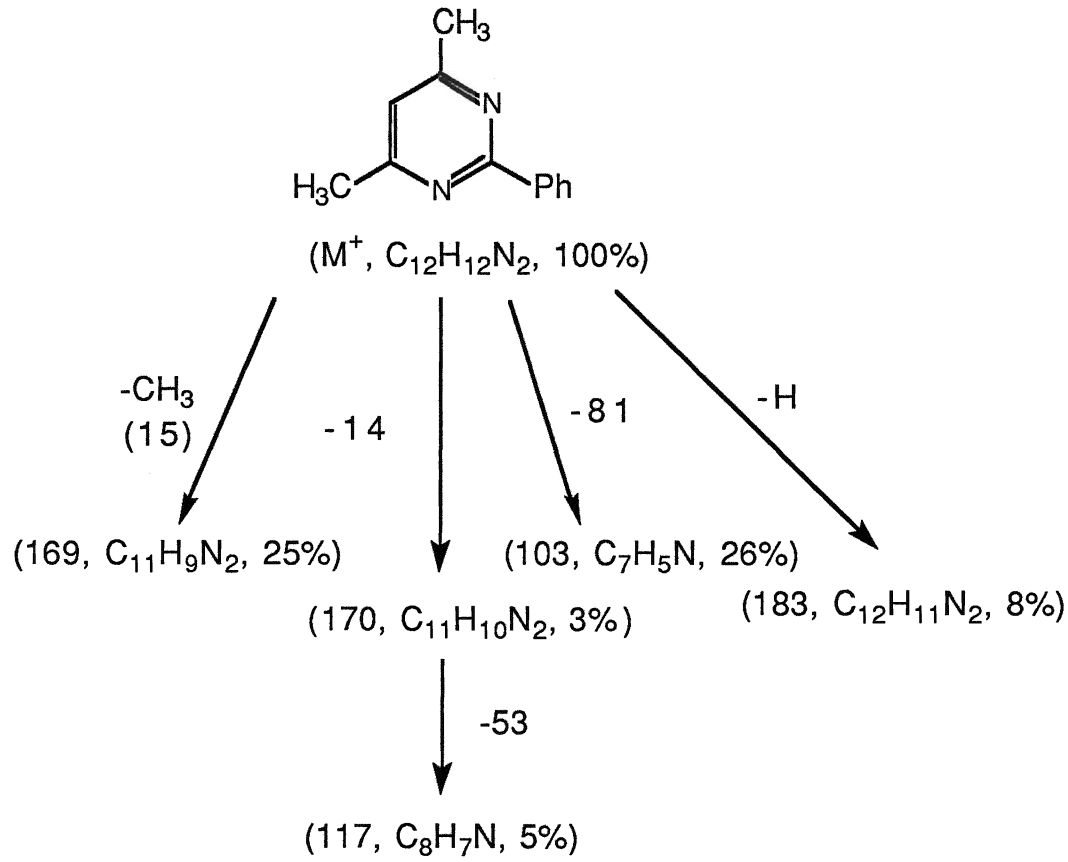
aqueous potassium carbonate solution.




(as hydrochloride)

(xxix)

The mass spectrum of (xxix) showed the molecular ion peak at the expected m/z value 184, which was also the base peak. The fragmentation pattern (Scheme XIII) confirms the structure of (xxix)



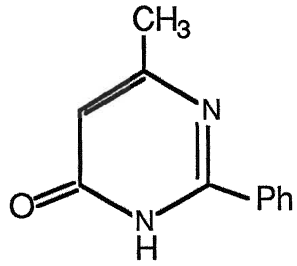

Scheme (XIII)

The $^1H$ NMR spectrum for (xxix) should show signals for 12 protons in four

different environments, and this was found to be the case. The two methyl groups on the ring are equivalent and these protons appear as one signal at δ 2.52; the pyrimidine ring CH came at δ 6.91, and the rest as multiplets at δ 7.44 and 8.41 integrating for 3H and 2H of the phenyl ring.

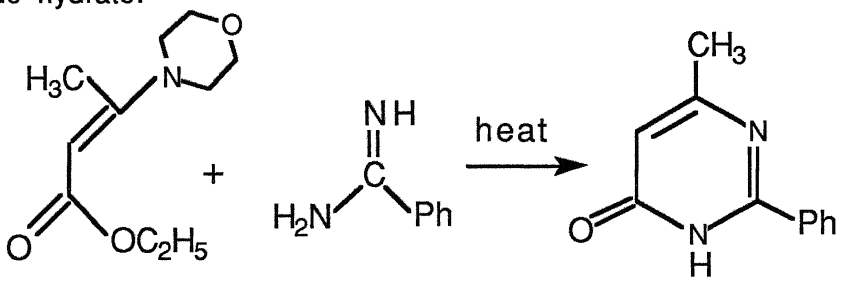
The $^{13}C$ NMR spectrum exhibited 8 different types of carbon signals. The carbon signal for the two methyl group carbons (which are equivalent since the molecule is symmetrical) appeared at the expected chemical shift value.

The other compound which was made from the reaction of a β- substituted enamine and an amidine was (xxx).



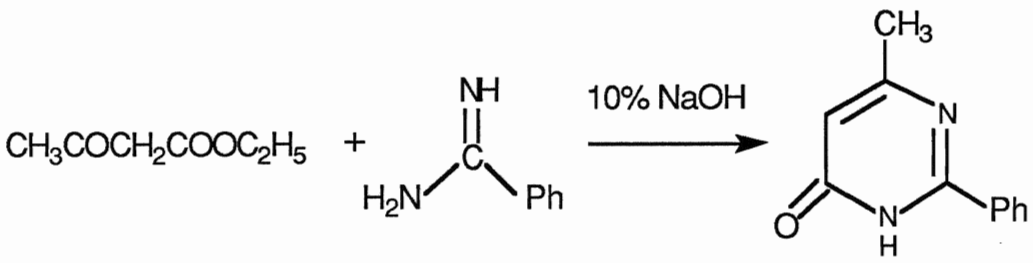
(xxx)

This compound was made by treating enamine (ii)[38] with benzamidine hydrochloride hydrate.



(ii) (xxx)

Pinner[55] also reported a synthesis for compound (xxx). In his work, the reaction between ethyl acetoacetate and benzamidine hydrochloride in 10% aqueous sodium hydroxide was used to make the required compound.



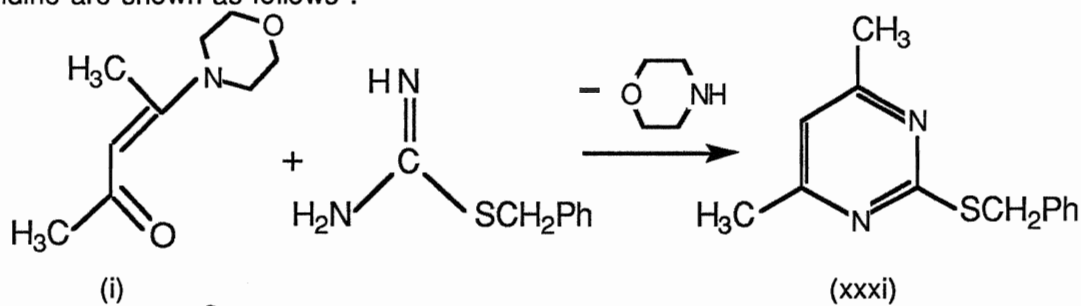

(as hydrochloride) (xxx)

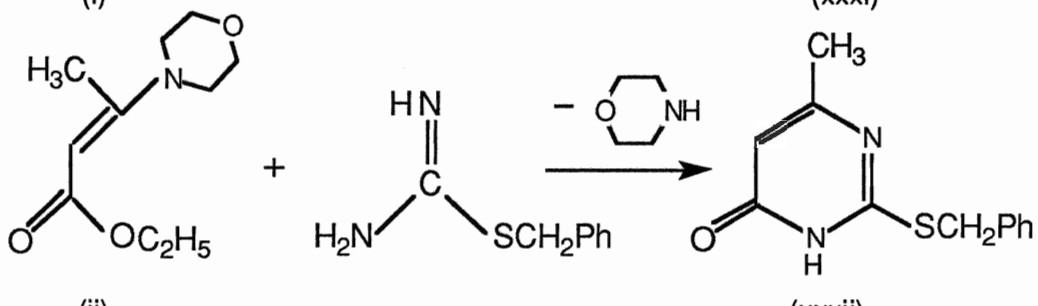
The formation of (xxx) from an enamine (ii) and the amidine could be explained, mechanistically, in a similar way to that for (xxix).

The $^{1}H$ NMR spectrum of (xxx) showed all of the expected proton signals. The signal for NH appeared at low field (chemical shift: δ 10.1), and disappeared after $D_2O$ exchange.

The compound exists in the carbonyl form and not in the hydroxy form. This was confirmed by the presence of a carbonyl carbon signal in the $^{13}C$ NMR spectrum (δ value 165) and by a carbonyl absorption band in the IR spectrum (1674 $cm^{-1}$).

Enamines (i) and (ii) were also reacted with another amidine. 2-Benzyl-2-thiopseudourea hydrochloride was used as the source of this nucleophile for the formation of the pyrimidine ring system. The planned reactions of (i) and (ii) with this amidine are shown as follows :

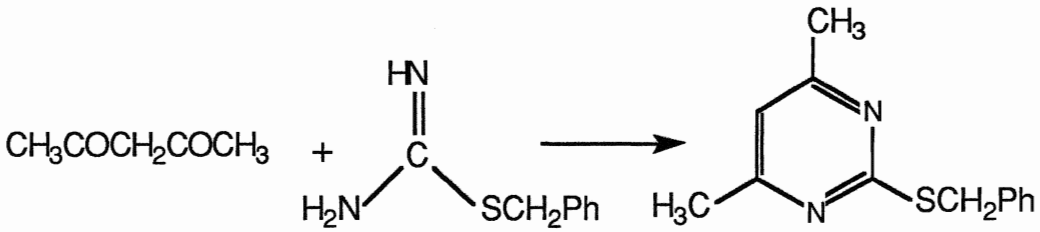


Enamine (i) and 2-benzyl-2-thiopseudourea hydrochloride were mixed and melted together. The solution obtained was refluxed, and after cooling gave a solid. This solid on correlation of physical properties and spectral data with the literature data[56] was identified as 4,6-dimethyl-2-mercaptobenzylpyrimidine (xxxi).

The proton NMR, $^{13}C$ NMR, IR and mass spectra all conform with the structure of (xxxi). The proton NMR spectrum showed very distinct signals for the methyl, methylene, CH and the phenyl protons. The carbon NMR spectrum exhibited nine different carbon signals. The signals for the $CH_3$, $CH_2$, pyrimidine ring CH, phenyl CH's and quaternary carbons were easily assigned. Since the molecule is symmetrical, the signals for the pyrimidine quaternary carbons, C4 and C6, appear as only one. The pyrimidine ring carbon, C2, was tentatively assigned a chemical shift which was the farthest downfield. This was based on the argument that the carbon attached to two nitrogen atoms would be shifted to a greater down field chemical shift than the carbon atom attached to only one nitrogen atom. The assignment of this chemical shift could in principle be confirmed by conducting an off-resonance decoupling experiment, which would cause a splitting in the signal for the carbons attached to the methyl group due to long range coupling. A first attempt to resolve this question was inconclusive.

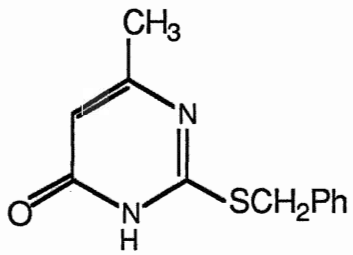
This compound (xxxi) was first made by Cranham and co-workers[56] by reacting a 2-halogeno-4,6-dimethylpyrimidine with benzyl mercaptan. Later, Brokke[57] also gave a synthesis which was based on Pinner's method[54]. He used acetylacetone and the chloride of 2-benzyl-2-thiopseudourea to obtain the desired compound (xxxi). This compound was found to have antiviral activity.




(as hydrochloride) (xxxi)

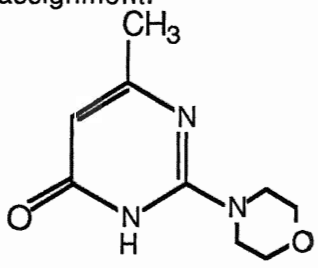
The mechanism for the formation of (xxxi) from the enamine (i) could be explained in a similar way to that of compound (xxix).

The second enamine (ii) on reaction with the thiopseudourea derivative gave a solid whose melting point was found to be $240^0$C. The $^1$H NMR spectrum of this solid showed the presence of the expected methyl and the ring CH protons, but it also exhibited morpholine protons and a distinct absence of the benzyl group protons. This was also confirmed by the absence of aromatic carbon signals in the $^{13}$C NMR spectrum. This was very surprising. The EI mass spectrum showed a peak at m/z value 195, which was 37 mass units less than the expected value for the pyrimidinone (xxxii).




(xxxii)

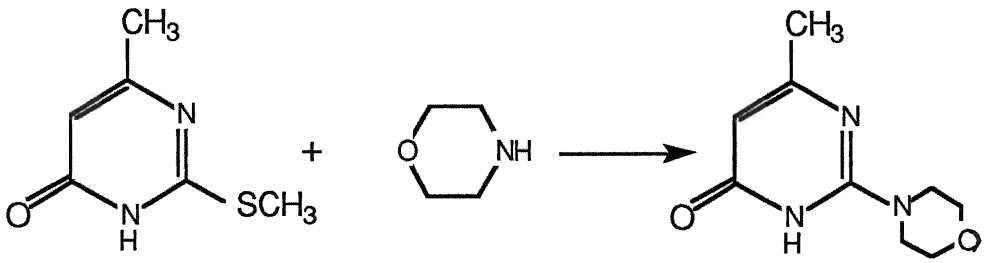
Further considerations of the spectra led to the tentative assignment of structure (xxxiii) to this compound. Later, comparison of the mp and spectra with that reported in the literature[58], confirmed our assignment.




(xxxiii)

A plausible mechanism which can explain this reaction is quite interesting. We think that the enamine (ii) reacts with the thiopseudourea derivative to give first a compound with structure (xxxii). Since in this reaction morpholine is liberated, but is not distilled out, it is able to displace the mercaptobenzyl group from (xxxii) and give the morpholine derivative (xxxiii).

In 1963, Roth and Schloemer[58] had made this compound (xxxiii) by heating 6-methyl-2-(S-methyl)-4-pyrimidinone with morpholine.

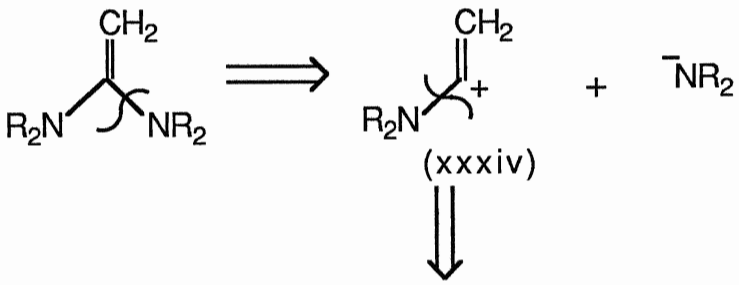



(xxxiii)

**Quinazolone and Benzothiadiazine Syntheses**

This section deals with reactions of 1,1-enediamines when used as an equivalent to the synthon $H_2C{=}C^{+2}$. This approach was designed to give two different but related ring systems.

A 1,1-enediamine can be disconnected as follows:




Scheme (XIV)

The first disconnection of the 1,1-enediamine gives the synthon (xxxiv) with one positive charge, and this synthon, on further disconnection affords the synthon with two positive charges (xxxv). This led us to the idea of making use of 1,1-enediamines as an equivalent to these two synthons.

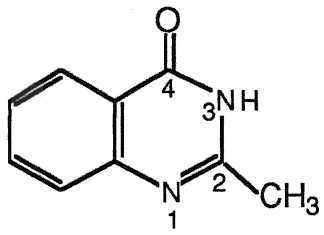
The first question is: what sort of applications could be suggested by these two synthons? We have already seen in the previous sections on β-substituted enamines and pyridine synthesis that the reagent for synthon (xxxiv) can be used in a one pot synthesis.

This leaves the synthon (xxxv), which also represents an electrophile. The second question is: what sort of target compounds might be amenable to an approach using this synthon?

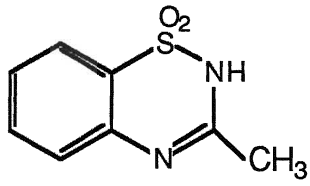
The first possibility would be to couple (xxxv) with two different nucleophiles. The second choice would be to couple it with a compound having two nucleophilic centres.

Out of various ideas the second possibility led us to consider making simple

derivatives of the quinazolone and benzothiadiazine ring systems.

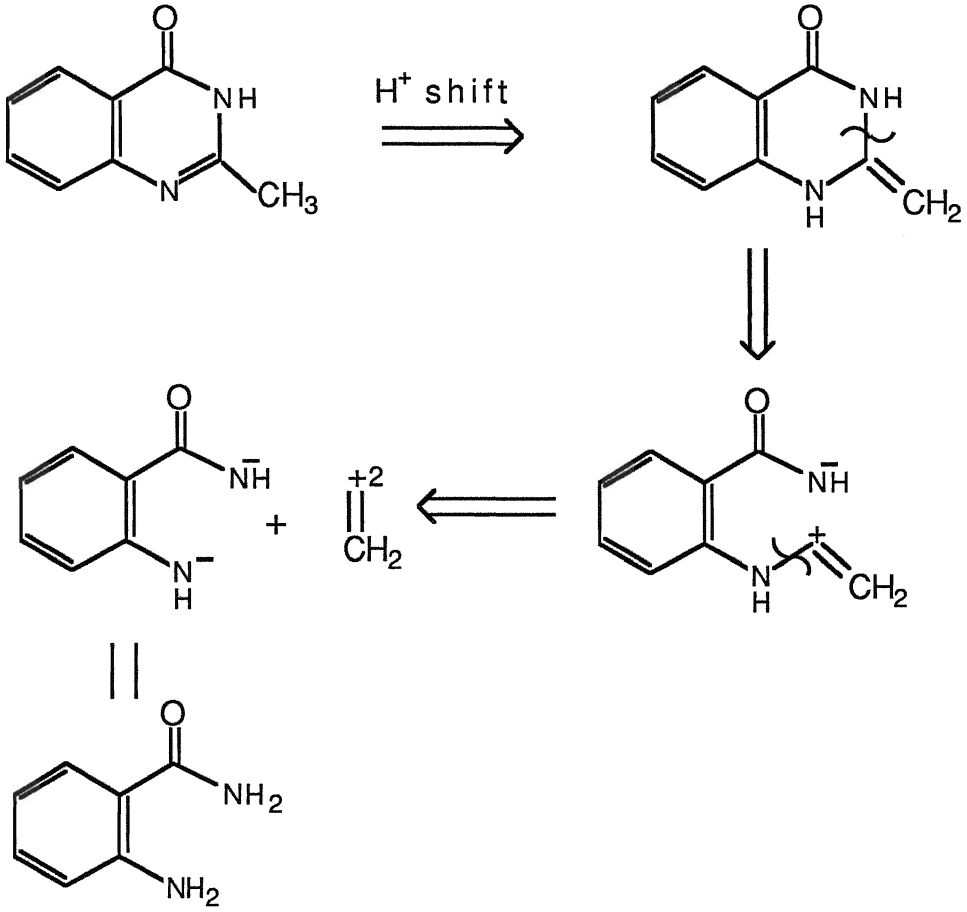


(xxxvi)

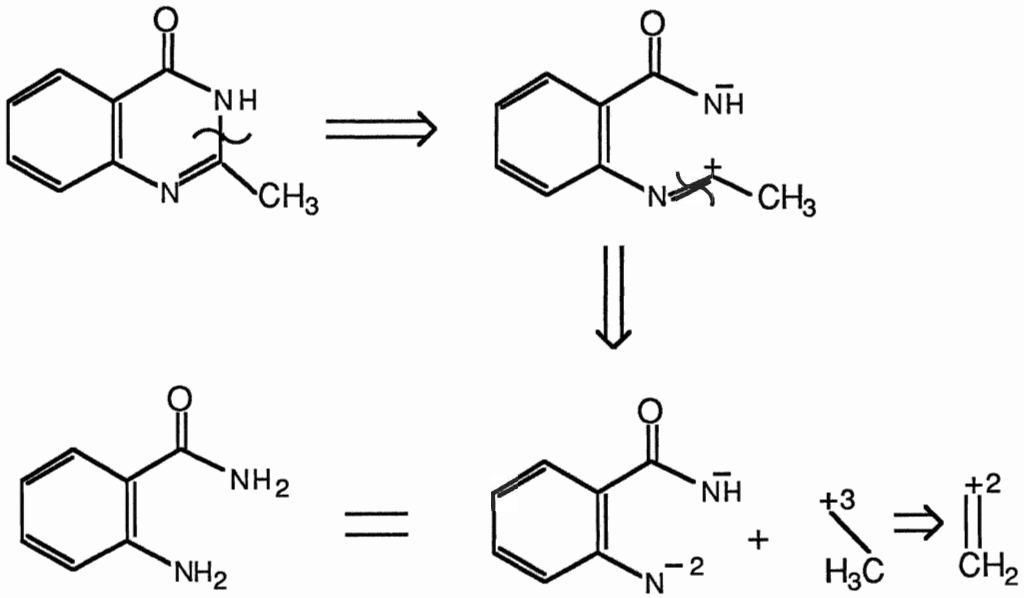


(xxxvii)

A series of disconnections of (xxxvi) (Scheme XV-a or XV-b ) leads to anthranilamide as the reagent to use.



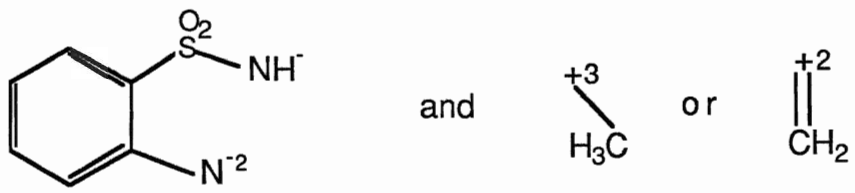

Scheme (XV-a)



synthetic reagent (xxxviii) (xxxv)

Scheme (XV-b)

In a similar way, retrosynthetic analysis of (xxxiv) gives the synthons,



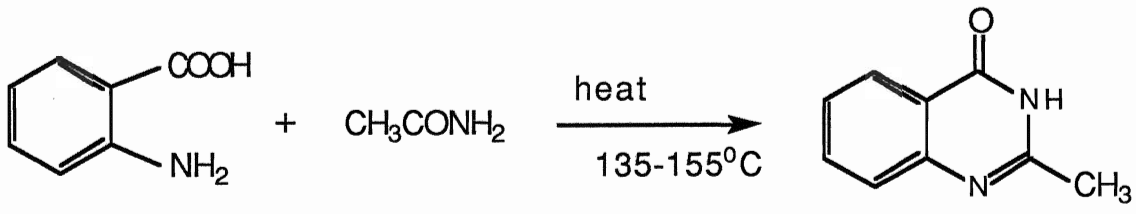
The analysis is in accordance with our thinking that (xxxv) could be used in devising syntheses of systems like (xxxvi) and (xxxvii).

As seen in the analysis, the synthetic equivalent for the synthon (xxxviii) could be anthranilamide; N-substituted derivatives of anthranilamide might also be useful for more substituted products. For synthons (xxxiv) and (xxxv), as seen in Scheme (XIV) , a 1,1-enediamine could be used as a synthetic equivalent.

We prepared (xxxvi) by refluxing anthranilamide with 1,1-dimorpholinoethene (in excess) under nitrogen.

The yield (83%) obtained was more than in early literature methods. Niementowski[59] first made (xxxvi) by heating anthranilic acid with acetamide in an

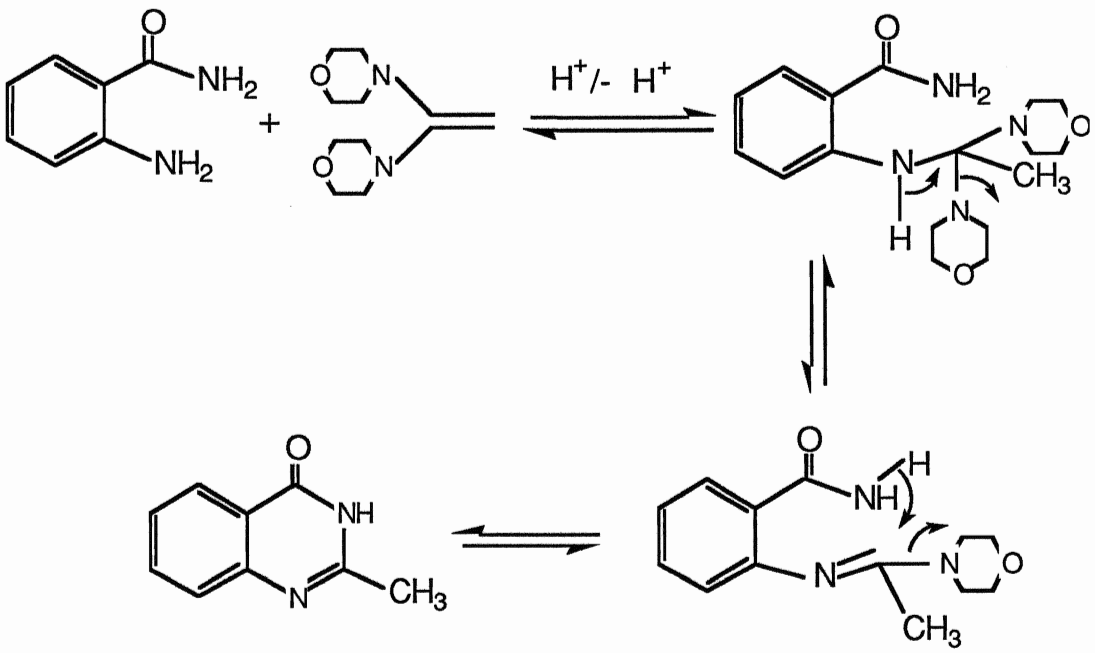
open flask at 135-155$^0$C.




(xxxvi)

Bischler and Burkart[60] reported another synthesis by heating the ammonium salt of N-acetylanthranilic acid.

A probable mechanism for our synthesis of (xxxvi) is shown in Scheme ((XVI).




(xxxvi) Scheme (XVI)

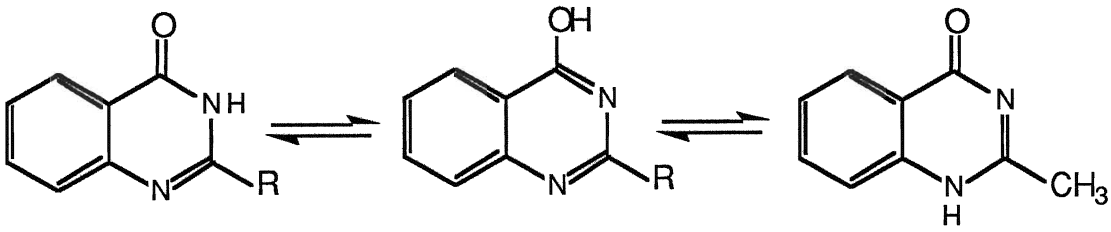
After the internal proton transfer which provides an amidinium ion, the lone pair of electrons of the free amine group of anthranilamide attack the first carbon (electron deficient centre) of the protonated 1,1-enediamine. Internal proton transfer, ring closure and subsequent loss of both morpholine units gives (xxxvi).

The mass spectrum of compound (xxxvi) gave a strong molecular ion peak at the

expected m/z value. The fragmentation of the molecular ion corresponds with that for the structure of (xxxvi).

The $^1H$ NMR spectrum of (xxxvi) showed a singlet at δ 2.60 integrating for 3H for the methyl group, a multiplet at δ 7.44-8.31 for the aromatic protons and a broad singlet at δ 11.7 for the NH which is exchangeable with $D_2O$. The $^{13}C$ NMR spectrum also shows the relevant carbon signals for the compound (xxxvi).

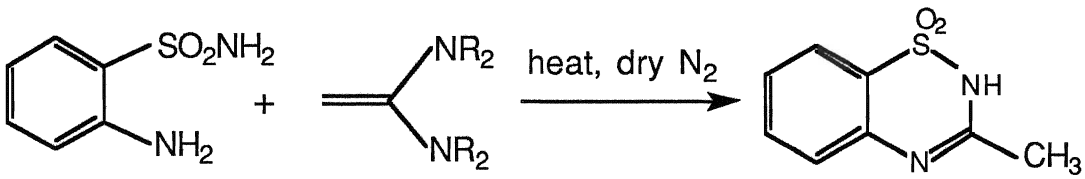
Compound (xxxvi) belongs to the 4-quinazolone group of compounds. The 4-quinazolones are tautomeric with the 4-hydroxy forms; 1H and 3H tautomers are also possible, as shown below.



(a) (b) (c)

Comparisons of the ultra violet spectra of 4-hydroxyquinazoline and 4-quinazolone derivatives have shown that structure (c) is least favoured for compounds in this series[61]. Based on our data and literature data, the position of NH would seem to be favoured at the 3 position in compound (xxxvi). This is consistent with the IR data (C=O stretch at 1682 $cm^{-1}$) and with the $^{13}C$ NMR spectrum which shows a signal at δ 153 (C=O).

Compound (xxxvii) was made in a similar procedure as for (xxxvi), but in place of anthranilamide, 2-aminobenzenesulphonamide was used.



(xxxvii)

Ekbom[62] reported the original synthesis from 2-acetamido benzenesulphonamide, which was heated at 200$^0$C for 2 hrs. to give 3-methyl-1,2,4-

benzothiadiazine-1,1-dioxide.

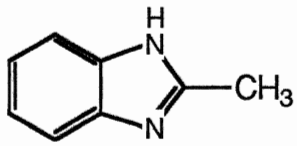
The $^1H$ NMR spectrum of (xxxvii) in $CDCl_3$+DMSO-$d_6$ showed a singlet at δ 2.34 for the methyl group, with a multiplet at δ 7.19-7.87 for the aromatic protons; the NH signal was observed at low field (δ 11.4), and disappeared on $D_2O$ exchange.

The presence of the $SO_2$ group was confirmed by the $SO_2$ (sulphonamide) stretch in the IR spectrum at 1157-1134 and 1380 $cm^{-1}$.

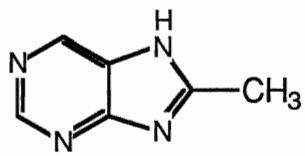
The mechanism for formation of (xxxvii) could be explained in a similar way to that for the compound (xxxvi).

The position of the NH in (xxxvii) has been arbitrarily assigned to be the 2 position, i.e., as (2H). On the basis of studies conducted on similar types of compounds in solution, Jacobsen and Treppendahl[63] have provided evidence for equilibrium between (2H)- and (4H)- forms.

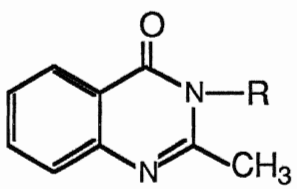
The synthesis of these two compounds raises other possibilities for the use of 1,1-enediamines. They could be used in synthesis of other systems like five-membered rings fused with a benzene ring, e.g.,



or purine type ring systems, e.g.,



These (1,1-enediamines) could also be used for syntheses of substituted quinazoline or benzothiadiazine ring systems, such as those containing alkyl groups on one or both of the nitrogen atoms, e.g.,



as well as those containing substituents in the benzene ring.

# CONCLUSIONS

The one pot synthesis approach to the synthesis of β-substituted enamines (push-pull olefine type) and various substituted pyridines was very successful.

In general, the pyridine syntheses are very versatile. A different group of carbon acids could also be used which would give different substituents in the ring. The only difficulty with this synthesis is that enamines derived from primary amines do not give rise to pyridines. The mass spectrum of one particular enamine (v) suggests the possibility of use in quinoline syntheses. Further studies in that area might be useful. The formation of pyrimidinone (xxii) under the conditions for this pyridine synthesis shows that this reaction needs more close observation and study.

The pyrimidine syntheses from β-substituted enamines and the amidines looks very useful. Additional nucleophiles could be used, for example, O-alkylpseudourea(s), urea and thiourea. An attempt was made to make pyrimidines from urea and these enamines which was not rewarding, but different conditions would be worth exploring. The replacement of the S-benzyl group by the morpholine ring to give (xxxiii) suggests that under different conditions differently substituted pyrimidines might be obtained.

As noted already, the approach to quinazolone synthesis might be expanded into purine and other ring systems.

# EXPERIMENTAL

## GENERAL ASPECTS

Melting Points

All of the melting points were measured on an Electrothermal electrical apparatus or a Koffler hot stage apparatus, and are uncorrected.

Thin Layer Chromatography

This was done using TLC plastic sheets coated with silica gel (fluorescence sensitive) from E.Merck.

Solvents

All of the solvents used were from stock or ordered as may be the case. In some cases dry toluene, ether and benzene were used. These were dried over sodium. Absolute ethanol was dried by using $Mg/I_2$.

Chemicals

All of the chemicals used for the reactions were ordered from the Aldrich Chemical Co. and were of commercial grade.

N.M.R. Spectra

The spectra were obtained on a Bruker AC 200 NMR spectrophotometer. The proton NMR spectra were obtained at 200 MHz ( using tetramethylsilane as the reference) whereas the $^{13}C$ NMR spectra were obtained at 50 MHz.

Infra Red Spectra

IR spectra of the compounds were obtained using potassium bromide discs on a Analect FX 6260 FTIR spectrophotometer.

Mass Spectra

Kratos Concept 1S double focussing mass spectrometer was used for the mass spectral analysis. Glycerol or m-NBA was used as FAB matrix.

# SYNTHESES

## Preparation of (E)-4-(1-Morpholino)-3-pentenone (i)

This was prepared by the method of Hickmott and Sheppard[38].

Acetylacetone (24 g, 0.24 mole) was mixed with morpholine (32 ml, ca 0.36mole) in a 250 ml round bottomed flask containing dry benzene (80 ml). To this solution 100 mg of p-toluenesulphonic acid was added and the resulting solution was refluxed under a Dean - Stark separator to remove water formed during the reaction. The quantity of water collected was 8.6 mls, which is more than expected (4.7 ml). This may be due to the presence of water in the benzene, acetylacetone or morpholine used. The solution was refluxed till no more water separated (reaction time 17-18 hrs.). After the solution had cooled to room temperature, 100 mg of anhydrous sodium carbonate was added to remove p-toluenesulphonic acid. The mixture was filtered under suction and the solvent was evaporated using a rotary evaporator. After standing in the fume hood for a few days, the crude oily product deposited yellowish crystals, mp $32^0$C (lit[38] mp 46-$47^0$C). The crystals were filtered off and washed with hexane. Thin layer chromatography in absolute ethanol showed that traces of morpholine were present in addition to the expected compound.

$^1$H NMR $\delta$ ($CDCl_3$): 2.04 (s, 3H, $CH_3$-CO), 2.41 (s, 3H, $CH_3C$=), 3.25 (t, 4H, -$N(CH_2)_2$), 3.67 (t, 4H, $O(CH_2)_2$), 5.18 (s, 1H, =CH); $^{13}$C NMR(JMOD) $\delta$ ($CDCl_3$): 15.3 (C5), 31.9 (C1), 46.1 (methylene carbons attached to nitrogen atom in morpholine ring), 66.2 (methylene carbons attached to the oxygen atom), 97.2 (C3), 160.7 (C4), 195.6 (C2); EI mass spectrum: m/z 169 ($M^+$, $C_9H_{15}NO_2$, 43), 154 ($C_8H_{12}NO_2$, 50), 126 ($C_7H_{12}NO$, 65), 111 ($C_6H_9NO$, 16), 96 (73) and 69 (59%); high resolution mass spectrometry: measured mass: 169.1130; calculated mass: 169.1102.

**Preparation of Ethyl (E)-3-(1-morpholino)crotonate (ii)**

This was also prepared by the method of Hickmott and Sheppard[38].

A solution of ethyl acetoacetate (43.3 g, 0.33 mole), morpholine (34.8 g, 0.40 mole) and formic acid (1ml) in dry benzene (150ml) was refluxed for 8 hrs. The water formed in the reaction was removed using a Dean-Stark separator. The solvent was then removed under vacuum using a rotary evaporator, and the oily crude product (70.0 ml) was then used for further reactions. Thin layer chromatography showed traces of morpholine were present in the product.

$^1$H NMR δ ($CDCl_3$): 1.22 (t, 3H, $-CH_3$), 2.39 (s, 3H, $CH_3C=$), 3.19 (t, 4H, $N(CH_2)_2$), 3.66 (t, 4H, $O(CH_2)_2$), 4.04 (q, 2H, $-CH_2$), 4.77 (s, 1H, =CH), 7.33 (benzene protons as impurity); EI mass spectrum: m/z 199 ($M^+$, $C_{10}H_{17}NO_3$, 47), 170 ($C_8H_{12}NO_3$, 15), 154 ($C_8H_{12}NO_2$, 52) and 126 ($C_7H_{12}NO$, 100%); measured mass: 199.1254; calculated mass: 199.1208.

**Preparation of (E)-2-Cyano-3-(1-pyrrolidino)crotonamide (iii)**

A mixture of triethyl orthoacetate (4.05 g, 0.025 mole), pyrrolidine (1.78 g, 0.025 mole) and cyanoacetamide (2.10 g, 0.025 mole) was heated under a Vigreux column and the volatile reaction product (presumed to be ethanol) was distilled out. A solid started to appear after 2 hrs. The dark brown mixture was cooled and absolute ethanol was added to it. After filtration and drying, the yield of the solid obtained was 0.600 g. Crystallization from methanol gave 2-cyano-3-(1-pyrrolidino)crotonamide as a light brown solid (0.500 g, 83.3%), mp 197$^0$C.

$^1$H NMR δ ($CDCl_3$+DMSO-$d_6$): 1.00-1.61 (m, 8H, pyrrolidine protons),2.41 (s, 3H, $CH_3$), 5.51 (d, 2H, $NH_2$; disappears on $D_2O$ exchange); $^{13}$C NMR (JMOD) δ ($CDCl_3$+DMSO-$d_6$): 19.1 (C4), 24.6 (C3'), 51.0 (C2'), 51.7 (C2), 121.6 (CN), 166.8 (C3), 167.6 (CO); IR (KBr) $cm^{-1}$: 1635 (C=O), 2174 (CN) and 3290 (N-H); EI mass spectrum: m/z 179 ($M^+$, $C_9H_{13}N_3O$, 93), 162 (loss of $NH_3$, 96),135

($C_8H_{11}N_2$, 100), 134 ($C_8H_{10}N_2$, 84) and 107 ( $C_7H_9N$, 31%); high resolution mass spectrometry: measured mass: 179.1064; calculated mass: 179.1058.

**Preparation of (Z)-2-Cyano-3-(1-cyclohexylamino)crotonamide (iv)**

A mixture of triethyl orthoacetate (4.05 g, 0.025 mole), cyclohexylamine (2.47 g, 0.025 mole) and cyanoacetamide (2.10 g, 0.025 mole) was refluxed under a Vigreux column. The volatile reaction product (ethanol) was distilled off and collected. Heating was continued until a solid started to appear (a little more than 2hrs.). The off white solid, yield 1.52 g (30%), after addition of absolute ethanol was filtered off, dried, and crystalized from chloroform/hexane to yield 2-cyano-3-(1-cyclohexylamino)crotonamide (0.900 g, 60%), mp 197$^0$C.

$^1$H NMR δ ($CDCl_3$): 1.27-2.04 (m, 11H, cyclohexyl protons), 2.16 (s, 3H, $CH_3$), 5.51 (br s, 2H, $NH_2$ exchangeable with $D_2O$),10.8 (br s, 1H, NH; disappears after $D_2O$ exchange); $^{13}$C NMR (JMOD) δ ($CDCl_3$): 17.4 (C4), 24.2 (C4'), 25.0 (C3'), 33.3 (C2'), 52.6 (C1'), 70.3 (C2), 121.3 (CN), 166.7 (C3), 170.6 (CO); IR (KBr) cm$^{-1}$: 1687 (C=O), 2186 (CN), and 3050 (N-H), 3270-3370 ($NH_2$); EI mass spectrum: m/z 207 ($M^+$, $C_{11}H_{17}N_3O$, 83), 190 ($C_{11}H_{14}N_2O$, 8), 164 ($C_{10}H_{17}N_3$, 20), 109 ($C_7H_{12}N$, 37), 108 ($C_7H_{11}N$, 36), 86 ($C_6H_{11}$, 55) and 55 ($C_4H_7/C_2H_2NO$, 100%); high resolution mass spectrometry: measured mass: 207.1377; calculated mass: 207.1371.

**Synthesis of (Z)-2-Cyano-3-p-toluidinocrotonamide (v)**

Triethyl orthoacetate ( 8.1g, 0.05 mole) and p-toluidine (5.35 g, 0.05 mole) were mixed together and to this mixture 2-cyanoacetamide (4.2 g, 0.05 mole) was added. The reaction mixture was then heated under reflux under a Vigreux column. The heating was continued for 2-2.5 hrs. Ethanol produced as a reaction product was distilled off and collected. After cooling, the desired product was obtained as a semi-solid mass. To this residue, absolute ethanol was added and the resulting solid was filtered off

and dried; yield 1.3 g (24%). After various recrystallisations from isopropanol and benzene, a pure product was finally obtained. TLC showed only one spot. The shiny white crystals obtained weighed 0.900 g (70%), and had mp 189-190$^0$C.

$^1$H NMR δ ($CDCl_3$): 2.20 (s, 3H, $CH_3$), 2.36 (s, 3H, $CH_3$), 5.60 (br s, 2H, $NH_2$; disappears on $D_2O$ exchange), 7.02-7.36 (AA'BB' pattern, 4H, aromatic protons), 12.2 (s,1H, NH; signal disappears on $D_2O$ exchange);$^{13}$C NMR (JMOD) δ ($CDCl_3$): 18.8 ($CH_3$), 20.9 ($CH_3$), 72.8 (C2), 120.3 (CN), 125.5 (C3'), 130 (C2'),134.5 (C4'),137.4 (C1'),167.6 (C3), 170.0 (CO);IR (KBr) cm$^{-1}$: 1600 (aromatic C=C), 1643 (C=O), 2193 (CN), 3196-3389 (N-H); EI mass spectrum: m/z 215 ($M^+$, $C_{12}H_{13}N_3O$, 87), 198 (loss of $NH_3$, 85), 171 ($C_{11}H_{11}N_2$, 26), 156 ($C_{10}H_8N_2$, 16), 132 (100), 107 ($C_7H_9N$, 24) and 91 ($C_7H_7$, 49%); high resolution mass spectrometry: measured mass: 215.1054; calculated mass: 215.1058.

**Preparation of (E)-2-Cyano-3-(1-morpholino)propenamide (vi)**

Triethyl orthoformate (7.40 g, 0.05 mole) and morpholine (4.35 g, 0.05 mole) were mixed in a round bottomed flask, and to this cyanoacetamide (4.20 g, 0.05 mole) was added. This reaction mixture was refluxed under a Vigreux column for 3 hrs. and the ethanol produced was distilled off. After cooling, a solid separated, which was filtered off and dried. Crystallization from absolute ethanol gave 2-cyano-3-(1-morpholino)propenamide as shiny yellow crystals, yield 3.2 g (36%), m p 175$^0$C.

$^1$H NMR δ ($CDCl_3$) : 3.51-3.97 (m, 8H, morpholine protons), 5.75 (br s, 2H, $NH_2$ exchangable with $D_2O$ ), 7.80 (s, 1H, CH ) ;$^{13}$C NMR (JMOD) δ ($CDCl_3$): 65.8 and 66.8 (morpholine $CH_2$'s ), 70.3 (C2), 119.3 (CN), 155 (C3), 166.5 (CO); IR (KBr)cm-$^1$: 1680 (C=O), 2195 (CN) and 3350 ($NH_2$); EI mass spectrum: m/z 181 ($M^+$, $C_8H_{11}N_3O_2$, 100), 164 ($C_8H_8N_2O_2$, 54), 137 ($C_7H_7NO_2$, 23), 123 (20) and 107 (40%); high resolution mass spectrometry: measured mass: 181.0844, calculated mass: 181.0851.

**Preparation of (E)-2-Cyano-3-(1-pyrrolidino)propenamide (vii)**

A mixture of triethyl orthoformate (3.70 g, 0.025 mole), pyrrolidine (1.78 g, 0.025 mole) and cyanoacetamide (2.10 g, 0.025 mole) was heated under reflux conditions under a Vigreux column. After distilling off the volatile reaction product formed (presumably ethanol), a solid started to appear (ca 2hrs.). The reaction was stopped and the mixture was cooled. Absolute ethanol was added to the residue in the flask and the solid was filtered off and dried (yield 0.900g, 22%). Crystallization from chloroform/hexane gave 2-cyano-3-(1-pyrrolidino)propenamide as a light brown solid, mp $210^0$C.

$^1$H NMR δ ($CDCl_3$+DMSO-$d_6$): 1.96 (s, 4H, $CH_2$-$CH_2$ from pyrrolidine), 3.25 (s, 1H, CH), 3.35 (s, 4H, $CH_2$-N-$CH_2$ from pyrrolidine), 11.4 (br s, 2H, $NH_2$; exchangeable with $D_2O$); $^{13}$C NMR (JMOD): δ ($CDCl_3$+DMSO-$d_6$): 24.5 (C3'), 45.9 (C2'), 84.6 (C3), 147.7 (CN), 160.0 (C2), 161.8 (CO); IR(KBr) $cm^{-1}$: 1685 (C=O), 2201 (CN), 3290 (N-H); EI mass spectrum: m/z 165 ($M^+$, $C_8H_{11}N_3O$, 91), 136 (93), 109 (19), and 70 (100%); high resolution mass spectrometry: measured mass: 165.0902: calculated mass: 165.0902.

**Synthesis of 2-Cyano-3-cyclohexylaminopropenamide (viii)**

Triethyl orthoformate (3.75 ml., ca 0.025 mole), cyclohexylamine (2.47 g, 0.025 mole) and cyanoacetamide (2.10 g, 0.025 mole) were mixed together in a round bottomed flask and the mixture was refluxed under a Vigreux column for 2.75 hrs. During this period ethanol and excess cyclohexylamine were distilled off. After cooling, a solid appeared and was collected. This solid was first crystalized from aqueous ethanol. At this stage the mass spectrum showed peaks at m/z 193 and 222. This material was extracted with hot benzene, and the insoluble solid was collected. Its mass spectrum now showed the molecular ion at m/z 193 enabling the material to be identified as 2-cyano-3-cyclohexylaminopropenamide. The buff granular crystals ( 0.500g, 11%), mp $157^0$C, gave the following spectral data.

$^1$H NMR δ ($CDCl_3$+DMSO-$d_6$): 1.25-1.91 (m, 11H, cyclohexyl protons), 3.24 (s,

1H, HC= ), 6.23 (br s, 2H $NH_2$; signal disappears on $D_2O$ exchange ), 9.70 (br s, 1H, NH; also exchangeable with $D_2O$); $^{13}C$ NMR (JMOD) δ ($CDCl_3$+DMSO-$d_6$): 23.2 (C4'), 23.9 (C3'), 32.4 (C2'), 56.5 (CH of cyclohexyl ring), 69.2 (C2), 119.5 (CN), 155.2 (C3), 168.6 (CO); IR (KBr) $cm^{-1}$: 1659 (C=O), 2198 (CN), 3400-3200 (N-H); EI mass spectrum: m/z 193 ($M^+$, $C_{10}H_{15}N_3O$, 77). 150 ($C_9H_{14}N_2$, 71), 149 ($C_9H_{13}N_2$, 12), 112 ($C_7H_{14}N$, 16), 111 ( $C_7H_{13}N$, 32), 99 ($C_6H_{13}N$, 8 ), 83 ($C_6H_{11}$, 70) and 55 ($C_4H_7$, 100%); high resolution mass spectrometry : measured mass: 193.1211; calculated mass: 193.1215.

**Preparation of 3-Cyano-4,6-dimethyl-2-pyridinone (ix)**

(E)-4-(1-Morpholino)-3-pentenone (1.69 g, 0.01 mole) was dissolved in aqueous acetic acid (0.1ml glacial acetic acid in 4ml water), and cyanoacetamide (0.84 g, 0.01 mole) was added to the resulting solution. This was stirred for five minutes, and then the reaction mixture was refluxed for 3 hrs. A large amount of brown solid separated. When cool, the mixture was neutralised with 0.1 M NaOH and the solid was collected by suction filtration. This solid was washed with methanol, and dried (1.03g, 70%). Crystallisation from ethylene glycol gave needle shaped crystals (0.900 g, 61%), mp 287-288$^0$C with decomposition (lit.[42] m p 288-290$^0$C).

$^1H$ NMR δ (DMSO-$d_6$): 2.22 (s, 3H, $CH_3$), 2.30 (s, 3H, $CH_3$), 6.12 (s,1H, CH). 12.3 (s, 1H, NH; signal disappears on $D_2O$ exchange); $^{13}C$ NMR (JMOD) δ (DMSO-$d_6$): 18 ($CH_3$ on C4), 21 ($CH_3$ on C6), 99 (C4), 106 (C5), 115 (CN), 151 (C3), 159 (C6) and 160 (C2); IR(KBr) $cm^{-1}$: 1624 (C=C), 1748 (C=O), 2200 (CN) and 2800 (N-H); EI mass spectrum: m/z 148 ($M^+$, $C_8H_8N_2O$, 100), 120 ($C_7H_8N_2$, 44), 119 (84), 105 (23), 93 (7), 78 (21), 65 (12) and 51 (27%).

**Preparation of 3-Cyano-2,6-dihydroxy-4-methylpyridine (x) (as tautomer/s)**

Ethyl (E)-3-(1-morpholino)crotonate (9.95 g, 0.05 mole) and cyanoacetamide (4.20 g, 0.05 mole) were dissolved in aqueous acetic acid (2ml glacial acetic acid in 20 ml water). The solution formed was then heated under reflux conditions for 4hrs. When cool, the solution was made alkaline with NaOH (1M) to pH9. The solution was then just kept at room temperature overnight. Some crystals appeared at the bottom which were filtered off and weighed ( 1.3 g, 17%), and had mp $310^0$C (lit.[42] mp 312-$315^0$C).

$^1$H NMR δ (DMSO-$d_6$): 1.94 (s, 3H, $CH_3$), 4.89 (s, 1H, CH), 9.50 (br s, 2H, 1NH and 1OH; disappears on $D_2O$ exchange); $^{13}$C NMR (JMOD) δ (DMSO-$d_6$): 21 ($CH_3$), 76 (C4), 99 (C5), 121 (CN), 153 (C3), 164 (C6), 165 (C2); IR (KBr) $cm^{-1}$: 1600 (C=C), 1700 (C=O), 2209 (CN), and 3220-3403 (O-H and N-H stretch); FAB mass spectrum: m/z 151$(M+H)^+$.

**Preparation of 3-Cyano-2,6-dihydroxy-4-methyl-4-(N-morpholino)-1,4-dihydropyridine (xi) (as tautomer/s)**

Cyanoacetamide (4.20 g, 0.05 mole) and ethyl (E)-3-(1-morpholino)crotonate (9.95 g, 0.05 mole) were dissolved in aqueous acetic acid (1 ml in 20 ml water). The solution (pH 8) was then refluxed for 16 hrs. After cooling, the pH of the solution was found to be 6 and was adjusted to pH 7 with 0.1M NaOH. After 10 minutes a precipitate started to form. This precipitate was then filtered off and dried (2.6 g, 22%). Crystallisation from absolute ethanol gave shiny white crystals (2.2 g, 19%), mp $235^0$C with decomposition (lit[42] mp 235-$238^0$C).

$^1$H NMR δ (DMSO-$d_6$): 1.94 (s, 3H, $CH_3$), 3.11 (d, 4H, $CH_2$-N-$CH_2$), 3.76 (d, 4H, $CH_2$-O-$CH_2$), 4.90 (s, 1H, CH), 8.76-10.1 (d, 3H, NH and OH which are exchangeable

with $D_2O$); $^{13}C$ NMR (JMOD) δ (DMSO-$d_6$): 20 ($CH_3$), 43 ( morpholine methylenes near N), 63 (methylenes near O), 75 (C4), 99 (C5), 121 (CN), 153 (C3), 164 (C6) and 165 (C2); IR (KBr) $cm^{-1}$: 1600 (C=C), 1650 (C=O), 2215 (CN) and 2900-3320 (NH and OH stretch); FAB mass spectrum: m/z 238 $(M+H)^+$.

**Attempted preparation of 3-Cyano-2,6-dihydroxy-4-methylpyridine (x) from dihydropyridine (xi)**

**( a )** 3-Cyano-1,4-dihydro-2,6-dihydroxy-4-methyl-4-(N-morpholino)pyridine (0.5 g, 2 mmole) was dissolved in aqueous acetic acid (0.1 ml glacial acetic acid in 4 ml of water) in a round bottomed flask and the mixture (pH 5) was refluxed for 4 hrs. After cooling the pH of the mixture was adjusted to pH 9 by adding 1M NaOH solution. The resulting mixture was then kept in the refrigerator overnight. The crystals that appeared at the bottom were filtered off and dried (yield:0.400 g). The melting point was found to be $220^0C$ with decomposition. It was difficult to identify the product from the spectral data available.

$^1H$ NMR δ (DMSO-$d_6$): 2.01 (s, 3H, $CH_3$), 3.37 (s, 8H, morpholine protons), 4.98 (s, 1H, CH), 9.71 (s, 1H, NH; signal disappears on $D_2O$ exchange); IR (KBr) $cm^{-1}$: 1601 (C=C), 2210 (CN), 3015-3390 (N-H stretch); EI mass spectrum : m/z 277, 240, 195, 181, 154, 139(all signals are of less than 1% intensity), 118 (16), 106 (11), 105 (100), 91 (9), 77 (34), and 51 (13%); FAB mass spectrum: m/z 329.

**( b )** The procedure given above was repeated but the refluxing period was extended to 16 hrs . The solid obtained was dried(yield: 0.210 g) and the melting point was found to be $300^0C$. Spectral and melting comparisons confirmed that this product was (x).

$^1H$ NMR δ (DMSO-$d_6$): 1.96 (s, 3H, $CH_3$), 4.92 (s, 1H, CH), 9.58 (s, 1H, NH; signal disappears on $D_2O$ exchange); $^{13}C$ NMR (JMOD) δ (DMSO-$d_6$): 20 (CH3),76 (C4), 99 (C5), 121(CN), 154 (C3), 165 (C6), 165.3 (C2); IR (KBr) $cm^{-1}$: 1600 (C=C), 1694 (C=O), 2190 (CN), 3287-3400 (N-H stretch); EI mass spectrum: m/z 150 ( $M^+$,$C_7H_6N_2O_2$, 100); FAB mass spectrum: m/z 151 $(M+H)^+$.

**Preparation of (E)-2-Cyano-3-(1-morpholino)crotonamide (xii)**

This was prepared by the method of Gandhi and Gibson[40].

A mixture of 1,1-dimorpholinoethene[3] (1.98 g, 0.01 mole) and cyanoacetamide (0.84 g, 0.01 mole) in dry ether was refluxed under nitrogen for about 6.5 hrs. After cooling, the residue was found to be oily in appearance. Acetone was added to this and the resulting solid (0.600g , 30%), mp 165$^0$C (lit.[40] 160-162$^0$C) was filtered off.

$^1$H NMR δ ($CDCl_3$): 2.09 (s, 3H, $CH_3$), 3.41-3.82 (m, 8H, morpholine protons), 5.58 (br s, 2H, $NH_2$; signal disappears on $D_2O$ exchange); IR(KBr) cm$^{-1}$: 1648 (C=O), 2182 (CN), 3326 and 3394 (N-H); EI mass spectrum: m/z 195 ($M^+$, $C_9H_{13}N_3O_2$, 42), 178 ($C_9H_{10}N_2O_2$, 100) and 151 ($C_8H_{11}N_2O$, 39%); high resoluton mass spectrometry: measured mass: 195.1043; calculated mass: 195.1007.

**Preparation of 1,1-Dimorpholinoethene (xiii)**

This was prepared by the method of Baganz and Domaschke[3].

A mixture of triethyl orthoacetate (16.2 g, 0.10 mole), morpholine (30.5 ml, ca 0.35 mole) and p-toluenesulphonyl chloride (0.500 g) was fractionally distilled through a Vigreux column during a period of approximately 4 hrs. to remove the ethanol produced in the reaction. The Vigreux column was then removed and excess of morpholine (15 ml) was distilled off at atmospheric pressure. The remaining dark, thick liquid was distilled under vacuum (bp 62-66$^0$C, 0.05mm ) to give 1,1-dimorpholinoethene (10.2g, 50%) as a white solid, mp 42$^0$C (lit.[3] mp 59-60$^0$C). TLC in hexane-ethyl acetate (7:3) showed one spot with a tail which may be due to the hydrolysis product.

$^1$H NMR δ ($CDCl_3$): 2.89 (m, 4H, $CH_2$-N-$CH_2$), 3.31 (s, 2H, =$CH_2$), 3.62 (m, 4H, $CH_2$-O-$CH_2$); EI mass spectrum: m/z 198 ($M^+$, $C_{10}H_{18}N_2O_2$, 69), 112 ($C_6H_{10}NO$, 66), 86 ( $C_4H_8NO$, 11) and 55 ($C_3H_5N$, 100%).

The IR spectrum showed the presence of a band at 1680 $cm^{-1}$, which may be due to the C=O stretch of the acetyl morpholine formed after the hydrolysis of the enediamine.

**Preparation of 3-Cyano-4-methyl-6-morpholino-2-pyridinone (xiv)**

**(a)** A mixture of triethyl orthoacetate (8.0 ml, ca 0.05 mole), cyanoacetamide (2.10 g, 0.025 mole) and morpholine (4.35 ml, ca 0.05 mole) was refluxed for 1 hr. under a Vigreux column, during which time ethanol and excess of morpholine were distilled off and collected. A solid started to appear in the mixture and the refluxing was stopped. The solid was filtered off, washed with absolute ethanol and dried; yield 2.8g,mp 175$^0$C. Crystallization from methanol gave the pyridinone(1.40 g, 50%) as yellow feathery crystals, mp 280$^0$C. TLC in hexane-ethyl acetate (7:3) showed one spot.

$^1$H NMR δ ($CDCl_3$+DMSO-$d_6$): 2.08 (s,3H,$CH_3$), 3.34-3.54 (m, 8H, morpholine protons), 5.81 (s, 1H,CH),11.3 (s,1H,NH which disappears on $D_2O$ exchange); $^{13}$C NMR (JMOD) δ ($CDCl_3$+DMSO-$d_6$): 18.6 ($CH_3$), 48.3 (C3'), 65.4 (C2'), 80.4 (C4), 95.5 (C5), 117.7 (CN), 148.5 (C3),162 (C6) and 163 (C2); IR (KBr) $cm^{-1}$: 1647 (C=O), 2206 (CN) and 2970(N-H);EI mass spectrum: m/z 219 ($M^+$,$C_{11}H_{13}N_2O_2$, 100),193 ($C_{10}H_{13}N_2O_2$, 26), 161 ($C_9H_9N_2O$, 76),134 ($C_7H_6N_2O$, 31) and 91 ($C_6H_5N$, 76%); FAB mass spectrum: m/z 220 ($(M+H)^+$,95%); high resolution mass spectrometry: measured mass: 219.1007; calculated mass: 219.1007.

**(b) From (E)-2-cyano-3-morpholinocrotonamide(xii) and 1,1-dimorpholinoethene (xiv)**

Crotonamide (xii) (0.300 g, 0.0015 mole) and freshly prepared 1,1-dimorpholinoethene ( approx. 1 ml.) were mixed in a round bottomed flask and the resulting mixture was refluxed for 2 hrs. After cooling, a solid separated. Absolute ethanol was added to the mixture and the solid was filtered off. After crystallisation from chloroform-hexane a light brown colored solid (100 mg., 30%) was obtained. The melting point of the solid was found to be $280^0$C.

$^1$H NMR ($CDCl_3$+DMSO-$d_6$): δ 2.23 (s, 3H, $CH_3$), 3.48-4.02 (m, 8H, morpholine protons), 5.68 (s, 1H, CH), and 10.9 (s, 1H, NH; disapears on $D_2O$ exchange); $^{13}$C NMR (JMOD) ($CDCl_3$+DMSO-$d_6$): δ19.9 ( $CH_3$), 49.5 (morpholine $CH_2$'s close to nitrogen), 66.6 (morpholine $CH_2$'s close to oxygen), 81.8 (C4), 97.2 (C5), 117.5 (CN), 149.6 (C3), 163 (C6), 165.8 (C2); IR (KBr) $cm^{-1}$: 1619 (C=C), 1655 (C=O), 2206 (CN), and 2970 (N-H); EI mass spectrum: m/z 219 ($M^+$, $C_{11}H_{13}N_2O_2$, 100), 193 ($C_{10}H_{13}N_2O_2$, 11), 161 ($C_9H_9N_2O$, 86), 134 ($C_7H_6N_2O$, 60), 91 ($C_6H_5N$, 29%) ; FAB mass spectrum: m/z 220 ($(M+H)^+$,100%); high resolution mass spectrometry: measured mass: 219.1006; calculated mass: 219.1007.

**Preparation of 3-Cyano-4-methyl-6-piperidino-2-pyridinone (xvi)**

A round bottomed flask containing a mixture of piperidine (4.25 ml, ca 0.05 mole), triethyl orthoacetate (7.2 ml, ca 0.05 mole ) and cyanoacetamide (2.10 g, 0.025 mole) was heated under a Vigreux column. After 1 hr. under reflux, the temperature was raised and the ethanol produced as a reaction product together with excess of piperidine were distilled off and collected (approximately 3 ml; total time period, 2.5 hrs.). A solid separated which was filtered off and dried; the yield of 3-cyano-4-methyl-6-piperidino-2-pyridinone was 0.800g (15%), mp 248-$250^0$C. TLC showed only one spot.

$^1H$ NMR δ ($CDCl_3$) : 1.71 (s, 6H, $CH_2$-$CH_2$-$CH_2$ of piperidine ring), 2.30 (s, 3H, $CH_3$), 3.61 (s, 4H, $CH_2$-N-$CH_2$ of piperidine ring), 5.69 (s, 1H, CH), 12.5 (s, 1H, NH; exchangeable with $D_2O$); $^{13}C$ NMR (JMOD) δ ($CDCl_3$): 19.8 ($CH_3$), 24.0 (C4'), 26.0 (C3'), 50.6 (C2'), 80.2 (C4), 97.4 (C5), 118 (CN), 148 (C3), 162 (C6), 166 (C2); IR (KBr) $cm^{-1}$: 1692 (C=O), 2201 (CN), 3197 (N-H); EI mass spectrum: m/z 217 ($M^+$, $C_{12}H_{15}N_3O$, 100), 216 ($C_{12}H_{14}N_3O$, 87), 189 (16), 188 (43), 176 (18) and 161 (14%); FAB mass spectrum: m/z 218 ($(M+H)^+$, 100%); high resolution mass spectrometry: measured mass: 217.1183; calculated mass: 217.1215.

**Synthesis of 3-Cyano-4-methyl-6-pyrrolidino-2-pyridinone (xvii)**

Triethyl orthoacetate (7.20 ml, ca 0.05 mole), pyrrolidine (3.1 ml, ca 0.05 mole) and cyanoacetamide (2.10 g, 0.025 mole) were mixed in a round bottomed flask and refluxed under a Vigreux column for 45 minutes; the ethanol produced in the reaction was then distilled off. The heating was stopped, the Vigreux column was removed, and a still head was attached. The excess of amine was distilled off during which time a solid started to appear. Absolute ethanol was added to the cooled dark-colored mixture and the solid was filtered off and dried (0.750g, 15%). It was crystalized from methanol and had mp $220^0C$.

$^1H$ NMR δ ($CDCl_3$): 2.05-2.10 (m, 4H, $CH_2$-$CH_2$ of pyrrolidine), 2.30 ( s, 3H, $CH_3$), 3.52 (s, 4H, $CH_2$-N-$CH_2$ of pyrrolidine), 5.27 (s, 1H, CH), 11.4 (br s, 1H, NH; exchangeable with $D_2O$); $^{13}C$ NMR (JMOD) δ ($CDCl_3$): 21.4 ($CH_3$), 25.2 (C3'), 47.8 (C2'), 83.2 (C4), 91.4 (C5), 117 (CN), 150.7 (C3), 158 (C6), 163 (CO); IR(KBr) cm-1: 1665 (C=O), 2197 (CN) and 3293 (N-H); EI mass spectrum: m/z 203 ($M^+$, $C_{11}H_{13}N_3O$, 75), 174 ($C_{10}H_{12}N_3$, 100), 162 ($C_9H_{10}N_2O$, 70) and 148 ($C_9H_{12}N_2$, 12%); high resolution mass spectrometry: measured mass: 203.1064; calculated mass: 203.1058.

**Synthesis of 3-Cyano-4-ethyl-5-methyl-6-piperidino-2-pyridinone (xviii)**

A mixture of triethyl orthopropionate (8.81 g, 0.05 mole) and piperidine (4.25 g, 0.05 mole) was distilled via a Vigreux column for about 1.25 hrs. During this time ethanol produced as a by product distilled off and was collected. After 1.5 hr., the heating was stopped and the reaction mixture was cooled. To this cooled mixture cyanoacetamide (2.1 g, 0.025 mole) was added and the heating was resumed without the Vigreux column. Instead, a water condenser was used. The excess of piperidine was collected by distillation during approximately 1 hr. After cooling, a solid quickly separated, which was filtered and washed with acetone. 3-Cyano-4-ethyl-5-methyl-6-piperidino-2-pyridinone was obtained as a light cream colored solid (1.4g, 23%), mp 221-225$^0$C. TLC showed only one spot (acetone, Rf value 0.82).

$^1$H NMR δ ($CDCl_3$): 1.21 (t,3H,$CH_3$), 1.69 (s, 6H, $CH_2$-$CH_2$-$CH_2$), 1.99 (s, 3H, $CH_3$), 2.58 (q, 2H, $CH_2$), 3.38 (s, 4H,$CH_2$-N-$CH_2$), 12.4 (br s, 1H, NH; which disappears when $D_2O$ is added); $^{13}$C NMR (JMOD) δ ($CDCl_3$): 12.6 ($CH_3$), 13.1 ($CH_3$), 23.8 ($CH_2$), 25.6 (C4'), 26.4 (C3'), 52.4 (C2'), 89.5 (C4), 108 (C5), 117 (CN), 152 (C3), 164 (C6), 168 (CO); IR (KBr) cm$^{-1}$: 1636 (C=O), 2214 (CN), and 3124 (N-H); EI mass spectrum: m/z 245 ($M^+$, $C_{14}H_{19}N_3O$,87), 244 (M-H, 100), 230 ($C_{13}H_{16}N_3O$, 27), 216 ($C_{12}H_{14}N_3O$, 43) and 204 ($C_{12}H_{16}N_2O$, 22%); high resolution mass spectrometry: measured mass: 245.1525; calculated mass: 245.1528.

**Preparation of 3-Cyano-4-ethyl-5-methyl-6-morpholino-2-pyridinone (xix)**

0.05 Mole each of triethyl orthopropionate (8.81 g) and morpholine (4.35 ml) were mixed together and the mixture was refluxed for 1.5 hr. through a Vigreux column. After distilling off the ethanol produced as a byproduct, the mixture was cooled, and to this 0.025 mole of cyanoacetamide (2.1 g) was added. The mixture was heated again for

1 hr. A gummy mixture containing solid particles was obtained. Petroleum ether (bp 42-45$^0$C ) was added, and the gummy mixture was kept in the refrigerator overnight. A solid (0.600 g, 10%) separated which was then filtered off and washed with acetone. This was crystalized from benzene/hexane to give the pyridinone as light colored crystals, mp 195-197$^0$C.

$^1$H NMR δ ($CDCl_3$): 1.22 (t, 3H, $CH_3$), 2.01 (s, 3H $CH_3$), 2.60 (q, 2H, $CH_2$), 3.43 (t, 4H, N-$(CH_2)_2$), 3.81 (t, 4H, $CH_2$-O-$CH_2$), 12.7(s, 1H, NH; which disappears on $D_2O$ exchange); $^{13}$C NMR (JMOD) δ ($CDCl_3$): 12.6 ($CH_3$), 13.4 ($CH_3$), 25.7 (CH2), 51.4 (C3'), 67.1 (C2'), 90 (C4), 108 (C5), 116 (CN), 154 (C3), 164 (C6), 167 (CO); Ir (KBr) cm$^{-1}$: 1641 (C=O), 2214 (CN), and 3250-3400 (N-H); EI mass spectrum:m/z 247 ($M^+$, $C_{13}H_{17}N_3O_2$, 50), 232 ($C_{12}H_{14}N_2O_2$, 5), 218 ($C_{11}H_{12}N_3O_2$, 9), 202 ($C_{10}H_8N_3O_2$, 12) and 188 ($C_{10}H_{11}N_3O$, 100%); high resolution mass spectrometry: measured mass: 247.1321; calculated mass: 247.1320.

**Attempted preparation of 3-cyano-4-ethyl-5-methyl-6-pyrrolidino-2-pyridinone; accidental preparation of 2-ethyl-6-pyrrolidino-4-pyrimidinone (xxii)**

Pyrrolidine (3.55 g, 0.05 mole) and triethyl orthopropionate (8.81 g, 0.05 mole) were mixed together and refluxed for 1 hr. under a Vigreux column. Ethanol produced (presumably as a reaction product) was distilled over and collected. When cool, cyanoacetamide (2.1 g, 0.025 mole) was added to the mixture and reflux was resumed (without a Vigreux column). After 1.25 hr., the heating was stopped and the mixture was allowed to cool. The gummy mixture obtained was kept in the refrigerator overnight. A solid separated which was filtered off via suction (yield 400 mg, 8.3%). Crystallisation from benzene-hexane mixture gave light yellow crystals (300 mg, 6.2%), mp 241-242$^0$C. Tlc (ethyl acetate) showed only one spot. Spectral analysis led to the conclusion that the yellow compound was (xxii).

$^1$H NMR δ ($CDCl_3$): 1.29 (t, 3H, $CH_3$), 1.96 (br s, 4H, pyrrolidine methylenes distant from nitrogen), 2.61 (q, 2H, $CH_2$), 3.34(br s, 4H, pyrrolidine methylenes near

nitrogen), 5.07 (s, 1H, CH), 13.02 (br s, 1H NH; exchangeable with $D_2O$); $^{13}C$ NMR (JMOD) δ ($CDCl_3$): 11.2 ($CH_3$), 25.2 ($CH_2$), 28.4 (pyrrolidine $CH_2$'s), 46.6 (pyrrolidine $CH_2$'s near nitrogen), 82.9 (C5), 161.5 (C6), 162.2 (C2), 165.8 (C4); IR(KBr)$cm^{-1}$: 1491 (C=N), 1606 (C=C), 1703 (C=O), 2806-2973 (N-H stretch); EI mass spectrum: m/z 193 ($M^+$, $C_{10}H_{15}N_3O$, 100), 164 ($C_8H_{10}N_3O$, 98), 138 ($C_7H_{10}N_3$, 14), 124 (12), 70 ( $C_4H_8N$, 81%); high resolution mass spectrometry: measured mass: 193. 1234 ; calculated mass: 193.1215.

**Preparation of N,N'-di(cyclohexyl)urea (xxiii)**

Cyclohexylamine (5.0 ml, ca 0.05 mole) and triethyl orthoproprionate (8.9 ml, ca 0.05 mole) were mixed together in a flask and heated under a Vigreux column for 1.5 hrs. Volatile material was distilled off and the mixture was allowed to cool. Cyanoacetamide (2.1 g, 0.025 mole) was added to this mixture, and it was again refluxed for 45 minutes under a still head. A solid appeared which was filtered off and washed with absolute ethanol; yield 400 mg (7.1%), mp 234$^0$C. It was identified as N,N'-di (cyclohexyl)urea (lit.[51] mp 233-235$^0$C). Crystallization from isopropanol gave off white shiny crystals (0.300 g, mp 230$^0$C).

$^1H$ NMR δ ($CDCl_3$+DMSO-$d_6$): 1.09-1.89 (m, cyclohexyl protons); no NH signal visible; $^{13}C$ NMR (JMOD) δ ($CDCl_3$+DMSO-$d_6$): 24.2 (C3'), 25 (C2'), 33 (C1'), 47 (CH), 156 (CO); IR (KBr) $cm^{-1}$: 1679 (C=O), 3323-3332 (N-H stretch); EI mass spectrum: m/z 224 ($M^+$, $C_{13}H_{24}N_2O$, 32), 99 ($C_6H_{13}N$, 37) and 56 ($C_4H_8$ or $C_2H_2NO$, 100%); high resolution mass spectrometry: measured mass: 224.1804; calculated mass: 224.1888.

**Synthesis of N,N'-di(p-tolyl)urea (xxiv)**

Triethyl orthopropionate (8.9 ml, ca 0.05 mole) and p-toluidine (5.35g, 0.05

mole) were added to a round bottomed flask and heated under reflux conditions under a Vigreux column for 1 hr. The temperature was then raised, and volatile material was distilled off; the mixture was then cooled. Cyanoacetamide (2.1g, 0.025 mole) was added and refluxing was resumed (45min-1hr.). A solid separated after cooling. Chloroform was added to this mixture and the solid (0.800 g, 13.3%), mp 265$^0$C was filtered off and identified as N,N'-di(p-tolyl)urea (lit.[52] mp 263$^0$C). TLC showed only one spot.

$^1$H NMR δ ($CDCl_3$+DMSO-$d_6$): 2.28 (s,6H,2$CH_3$), 2.98 (s, 2H, 2NH; exchangeable with $D_2O$), 7.03-7.29 (AA'BB' pattern, 8H, aromatic protons); $^{13}$C NMR (JMOD) δ ($CDCl_3$+DMSO-$d_6$): 20 ($CH_3$), 118 (aromatic CH), 129 (aromatic CH near NH), 131 (aromatic quaternary carbon attached to $CH_3$), 137 (aromatic quaternary near nitrogen atom), 153 (CO); IR (KBr) cm$^{-1}$: 1640 (C=O), 3299 ( N-H); EI mass spectrum: m/z 240 ($M^+$, $C_{15}H_{16}N_2O$, 30), 133 ($C_8H_7NO$, 13), 107 ($C_7H_9N$, 100%); FAB mass spectrum: 241 ($(M+H)^+$, 100%); high resolution mass spectrometry: measured mass: 240.1299; calculated mass: 240.1262.

**Preparation of 2-Cyano-3-hydroxycrotonamide (xxviii)**

(E)-2-cyano-3-(1-morpholino)crotonamide (0.300 g, 1.54 mmole) and cyanoacetamide (0.129 g, 1.54 mmole) were dissolved in absolute ethanol (18.3 ml) and sodium metal (0.920 g, 4.01 mmole) was then added to this. After the sodium had dissolved, the reaction mixture was refluxed for 3hrs. When cool, the residual solid was filtered off and the resulting filtrate was evaporated in vacuo. The creamish residue obtained was dissolved in water (4 ml) and the solution was then acidified to pH 3 using concentrated hydrochloric acid. Immediately a brown shiny solid started to appear. After keeping the mixture in the refrigerator overnight, the shiny plate like crystals of 2-cyano-3-hydroxycrotonamide were filtered off and dried; yield 100 mg (51%), mp 170$^0$C (lit.[53] mp 171-173$^0$C).

$^1$H NMR δ ($CDCl_3$+DMSO-$d_6$): 2.21 (s, 3H, $CH_3$), 3.76 (br s, 1H, OH; signal disappears on $D_2O$ exchange), 8.23 (br s, 2H, $NH_2$; exchangeable with $D_2O$); $^{13}$C NMR (JMOD) δ ($CDCl_3$+DMSO-$d_6$): 22 ($CH_3$), 76 (C2), 116 (CN), 171 (CO), 190 (C3);

IR (KBr) $cm^{-1}$: EI mass spectrum: m/z 126 ($M^+$, $C_5H_6N_2O_2$, 85), 111 ($C_4H_3N_2O_2$, 37), 94 ($C_4H_2N_2O$, 5), 84 ($C_3H_4N_2O$, 19) and 68 ($C_3H_2NO$, 100%); high resolution mass spectrometry: measured mass: 126.0430; calculated mass: 126.0429.

**Preparation of 4,6-Dimethyl-2-phenylpyrimidine (xxix)**

(E)-4-(1-morpholino)-3-pentenone (4.57 g, 0.025 mole) and benzamidine hydrochloride hydrate* (4.87 g) were mixed in glacial acetic acid (25 ml). Anhydrous sodium acetate ( 5.08g, 0.062 mole) was added and the mixture was refluxed for 4.5 hrs. A residue appeared on the bottom of the flask, and this was filtered off while the mixture was still hot. This solid was set aside. The filtrate on cooling deposited sharp needle like crystals, which were filtered and this filtrate obtained was also set aside. The second filtrate was neutralised to pH 7 with 1M NaOH, resulting in formation of shiny crystals. These were filtered off and were noted to be shiny and light in nature (mp $81^0C$). The sharp needles obtained in the beginning were crystalized from benzene, giving 4,6-dimethyl-2-phenylpyrimidine as shiny, light crystals, mp $80\text{-}84^0C$ (lit.[54] mp $83^0C$). TLC of this product and the product obtained after neutralization gave spots with the same Rf value. Total yield: 1.50 g (33%).

$^1H$ NMR $\delta$ ($CDCl_3$): 2.52 (s,6H, $2CH_3$), 6.91 (s, 1H, CH), 7.44 (t, 3H, aromatic CH), 8.41 (d, 2H aromatic CH); $^{13}C$ NMR (JMOD) $\delta$ ($CDCl_3$): 24 ($CH_3$), 117 (C5), 128.1,128.3, 130 (3 signals for phenyl CH's), 138 (C1'), 164 (C2), 166 (C4 and C6); IR (KBr) $cm^{-1}$: 1601 (aromatic C-H stretch); EI mass spectrum: m/z 184 ($M^+$, $C_{12}H_{12}N_2$, 100), 169 ($C_{11}H_9N_2$, 25), 117 ($C_7H_5N_2$, 3), 103 ($C_7H_5N$, 46) and 92 ($C_5H_4N_2$, 8%); high resolution mass spectrometry: measured mass: 184.1004; calculated mass: 184.1000.

**Preparation of 4-Methyl-2-phenyl-6-pyrimidinone (xxx)**

Ethyl (E)-3-(1-morpholino)crotonate ( 5.0 ml, ca 0.025 mole) and benzamidine hydrochloride hydrate* ( 3.9 g) were taken in a flask and the resulting mixture was heated on a water bath to melt the starting materials. This liquid was then heated under reflux conditions for 5.5 hrs. After cooling, a solid formed which was filtered off and dried to give a white shiny solid (700mg, 15%). Crystallization from absolute ethanol gave 4-methyl-2-phenyl-6-pyrimidinone as shiny fluffy crystals (400 mg, 8.6%), mp 220$^0$C (lit.[55] mp 223-225$^0$C).

$^1$H NMR δ ($CDCl_3$+DMSO-$d_6$): 2.38 (s, 3H, $CH_3$), 6.25 (s, 1H, CH), 7.46-8.18 (m, 5H, phenyl CH's), 10.1 (br s, 1H, NH; signal disappears on $D_2O$ exchange); $^{13}$C NMR (JMOD) δ ($CDCl_3$+DMSO-$d_6$): 24 ($CH_3$), 110 (C5), 127,128 and 131 (phenyl CH carbons), 132 (C1'), 156 (C4), 164 (C2) and 165 (C6); IR (KBr) cm$^{-1}$: 1674 (C=O stretch), 1580 (C=C and C=N stretch); EI mass spectrum: m/z 186 ($M^+$, $C_{11}H_{10}N_2O$, 100), 158 ($C_{10}H_{10}N_2$, 21), 104 (65), 83 (38) and 77 (30%); high resolution mass spectrometry: measured mass: 186.0789; calculated mass: 186.0793.

**Preparation of 4,6-Dimethyl-2-(S-benzyl)pyrimidine (xxxi)**

(E)-4-(1-Morpholino)-3-pentenone (5 ml., ca. 0.025 mole) and 2-benzyl-2-thiopseudourea hydrochloride** (5 g. ) were mixed in a flask and the resulting mixture was refluxed for about 5.5 hrs. After cooling, a vaseline like substance was observed in the flask. The supernatent liquid was separated and kept in the refrigerator for a few days. The vaseline like substance was dissolved in absolute ethanol and cooled. Some needle shaped crystals appeared which on mass and NMR studies were recognised as morpholine hydrochloride.

The supernatent solution which was kept in the refrigerator, solidified to give white needle like crystals. The melting point of the crude product was found to be 54-56$^0$C. Crystallisation from ethanol and a long period of cooling yielded a white colored solid, which was collected and dried. The yield was 1.4 g (24%) and the mp was 63$^0$C

(lit.[56,57] m.p. 64.5-65$^0$C).

$^1$H NMR ($CH_3CN$-$d_3$): δ 2.30 ( s, 6H, 2 $CH_3$), 4.32 (s, 2H, $CH_2$), 6.74 (s, 1H, CH) and 7.20-7.38 (m, 5H, phenyl protons); $^{13}$C NMR (JMOD) ($CH_3CN$-$d_3$): δ 23.8 ($CH_3$), 35.4 ($CH_2$), 116.7 (C5), 127.9, 129.3,and 130.0 (phenyl CH's), 139.7 (phenyl quaternary carbon), 168.2 (C4 and C6), and 171.0(C2); IR (KBr) cm$^{-1}$: 1620 (pyrimidine C=C and C=N stretch), 1140 and 728 (C-S stretch); EI mass spectrum: m/z 230 ($M^+$, $C_{13}H_{14}N_2S$, 100), 197 ($C_{13}H_{13}N_2$, 76), 169 ($C_{13}H_{13}$, 6), 108 ($C_6H_7N_2$, 50), and 91 ($C_7H_7$, 79%); high resolution mass spectrometry: measured mass: 230.0867; calculated mass: 230.0878.

**Preparation of 6-Methyl-2-morpholino-4-pyrimidinone (xxxiii)**

Ethyl-(E)-(1-morpholino)crotonate (5 ml., ca. 0.025 mole) was mixed with 2-benzyl-2-thiopseudourea hydrochloride** (5 g) in a round bottomed flask and the resulting mixture was then refluxed for 6 hrs. After cooling, a solid was observed to be formed in the gummy mixture. Absolute ethanol was added and the mixture was heated to dissolve the solid. A clear solution was obtained which was cooled in ice to give yellow granular crystals. The melting point of this crude product was found to be 215-225$^0$C. This yellowish solid was recrystallised from absolute ethanol again, and this resulted in a light colored solid. The melting point of this solid was more sharp than the crude, at about 240$^0$C ( lit.[58] m.p. 239-243$^0$C).

$^1$H NMR ($CDCl_3$): δ 2.20 (s, 3H, $CH_3$), 3.77 (s, 8H, morpholine protons), 5.66 (s, 1H, CH), no NH was visible, $D_2O$ exchange resulted in partial resolution of the morpholine signal into a doublet; $^{13}$C NMR (JMOD) ($CDCl_3$): δ 24.0 ($CH_3$), 45.1 (morpholine $CH_2$'s near the nitrogen atom), 66.7 (morpholine $CH_2$'s near the oxygen atom), 100.8 (C5), 153.5 (C4), 166.1 (C2), and 166.9 (C6); IR (KBr) cm$^{-1}$: 1689 (C=O stretch), 1610 (C=C and C=N stretch of pyrimidine), 3178-3320 (N-H stretch); EI mass spectrum: m/z 195 ($M^+$, $C_9H_{13}N_3O_2$, 47), 165 (25), 164 (63), 150 (35), 138 (70), 110 ($C_5H_6N_2O$, 100%); high resolution mass spectrometry: measured mass: 195.1007; calculated mass: 195.1021.

* The commercial material does not specify number of moles of water in the hydrate; the quantity used was 25% in excess of the amount computed for an anhydrous sample.

** The commercial material was a hydrochloride and was specified as hygroscopic in nature. Therefore, the quantity used was a little in excess of the amount computed for the sample.

**Preparation of 2-Methyl-4-(3H)quinazolone (xxxvi)**

A mixture of 1,1-dimorpholinoethene (4.95 g, 0.025mole) and anthranilamide (1.7 g, 0.0125 mole) in dry toluene (35 ml) was heated under reflux under dry nitrogen for 4.75 hrs (with periodic monitoring of the reaction by TLC); TLC shows the same spots after 2 hrs. and 4 hrs, so the reaction is probably completed in 2 hrs. After completion, the mixture was cooled, and the solid that had separated (1.65 g, 83%; mp $234^0$C) was filtered off and washed with toluene. This was crystalized from absolute ethanol giving yellow fluffy needles (1.2 g, 60%), mp $238^0$C (lit.[59] mp 238-$239^0$C).

$^1$H NMR δ ($CDCl_3$): 2.60 (s, 3H, $CH_3$), 7.44-8.31 (m, 4H, aromatic protons), 11.7 (br s, 1H, NH; disappears on $D_2O$ exchange); $^{13}$C NMR (JMOD) δ ($CDCl_3$): 22 ($CH_3$), 120 (C10), 126.2, 126.4, 127.0 and 134 (4 signals for aromatic CH), 149 (C9), 153 (CO), 164 (C2); IR (KBr) $cm^{-1}$: 1682 (C=O), 3034-3173 (N-H); EI mass spectrum: m/z !60($M^+$, $C_9H_8N_2O$, 100), 145 ($C_8H_5N_2O$, 10), 119 ($C_7H_5NO$, 16), 118 ($C_7H_4NO$, 12), 90 ($C_6H_4N$, 12) and 75 ($C_6H_3$, 24%); high resolution mass spectrometry: measured mass: 160.0645; calculated mass: 160.0636.

**Preparation of 3-Methyl-(2H)-1,2,4-benzothiadiazine-1,1-dioxide (xxxvii)**

A reaction mixture consisting of 1,1-dimorpholinoethene (4.95 g, 0.025 mole) and 2-aminobenzenesulphonamide (2.15 g, 0.0125 mole) in dry toluene (30 ml) was placed in a three neck flask. This mixture was refluxed under dry nitrogen for about 5 hrs. Some yellow solid started to appear on the walls of the flask. After cooling, the solid (yield 0.900 g, 37%) adhering to the walls of the flask was scraped off. Crystallization from absolute ethanol gave a yellow granular solid after cooling for a long time; yield 0.850 g (35%); mp $263^0$C (lit.[62] mp 263-$264^0$C).

$^1$H NMR δ ($CDCl_3$+DMSO-$d_6$): 2.34 (s, 3H, $CH_3$), 7.19-7.87 (m, 4H, aromatic CH's), 11.4 (br s, 1H, NH; disappears on $D_2O$ exchange); $^{13}$C NMR(JMOD) δ ($CDCl_3$+DMSO-$d_6$): 22 ($CH_3$), 116, 123, 125, and 132 (four signals for the aromatic carbons), 119 (C10), 135 (C9), 156 (C2); IR (KBr) $cm^{-1}$: 1157-1134, and 1380 ($SO_2$ stretch of sulphonamide), 3175-3277 (N-H); EI mass spectrum: m/z 196 ($M^+$, $C_8H_8N_2SO_2$, 6), 155 (8), 129 (58), 114 (23), 86 (52) and 57 (100%); high resolution mass spectrometry: measured mass: 196.0321; calculated mass: 196.0306.

**Attempted preparation of 4,6-dimethyl-2-pyrimidinone**

(E)-4-(1-Morpholino)-3-pentenone (1.69 g, 0.01 mole) was dissolved in aqueous acetic acid (0.1 ml glacial acetic acid in 4 ml of water). To this solution urea (0.60 g, 0.01 mole) was added and the resulting solution was stirred for 5 minutes. This solution was then refluxed for 3 hrs. During the reflux, oily droplets were observed to form in the solution. When cooled, the mixture was neutralised with 0.1 M NaOH and the oil formed was separated using a separatory funnel. The mass spectrum of the oil showed a parent ion signal at m/z 233, whereas the expected value was 124. Furthermore the proton and carbon NMR spectra showed the presence of many signals, including those for the starting materials. This product was not identified.

**Attempted preparation of 1,4-dihydro-4,6-dimethyl-2-hydroxy-4-(N-morpholino)pyrimidinone**

(E)-4-(1-morpholino)-3-pentenone (1.69 g, 0.01 mole) was dissolved in aqueous acetic acid (0.1 ml glacial acetic acid in 4 ml of water) and to the solution obtained urea (0.60 g, 0.01 mole) was added. The resulting solution was refluxed for 8 hrs. Fine droplets of oil were observed which were too little to separate. The yield was very poor. The mass spectrum of the oil droplets exhibited a peak at mass value 218 which was 8 mass units more than the expected m/z value. This material was not identified.

**Attempted preparation of 5-Cyano-4-methyl-2-phenyl-6-pyrimidinone**

A reaction mixture containing pyrrolidine (1.8 ml, ca 0.025 mole), triethyl orthoacetate (4.1 ml, ca 0.025 mole) and cyanoacetamide (2.1 g, 0.025 mole) was refluxed under a Vigreux column for 2 hrs. The temperature was then increased and the ethanol produced was distilled out. After an hour, the heating was stopped and the mixture was cooled. Benzamidine hydrochloride hydrate*(1.0 g) was then added to the cooled mixture and the reflux was resumed. After 1.5 hrs, some solid started to appear. When cool, absolute ethanol was added to the gummy mixture. After being kept at room temperature overnight the dark brown solid that had separated was filtered off and washed with ethanol. The mass spectrum of this solid showed m/z 203 corresponding to $M^+$ for 3-cyano -4-methyl-6-pyrrolidino-2-pyridinone and other fragment ions. This corresponds to 3-cyano-4-methyl-6-pyrrolidino-2-pyridinone and not the desired product ($M^+$ 210/211).

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