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Synthesis and reactions of new pyrimidines containing functionalised side chains

by

Tomás D. Duff

A thesis submitted to the University of Dublin

for the degree of Doctor of philosophy

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(signed)

Abbreviations

Ac_2O	acetic anhydride
BFIB	bis(trifluoroacetoxy)iodobenzene
br	broad
conc	concentrated
d	doublet
DCM	dichloromethane
DEPT	distortionless enhancement by polarisation transfer
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
Et	ethyl
EtOAc	Ethyl acetate
Hex	hexane
Hz	hertz
hν	irradiation
I.R.	infra red
m.p.	melting point
m	multiplet
NMR	nucleur magnetic resonance
ppm	parts per million
rot vap	rotary evaporator
s	singlet
sat'd	saturated
t	triplet
THF	tetrahydrofuran
TLC	thin layer chromatography
UV	ultra violet

Thin layer chromatography was carried out using Merck Kiesgel 60 F254 0.2 mm silica gel plates. Visualisation was by means of ultra violet light at 254 nm or by development in potassium permanganate solution. Flash chromatography was carried out using Merck Kieselgel 60 (mesh 230-400 ASTM) silica gel. 'Concentration' of solutions refers to the use of a Buchi rotary evaporator. Dry THF was obtained by first drying over potassium hydroxide pellets for 24 hours, then distilling from lithium aluminium hydride and finally distilling from sodium benzophenone ketyl.

Melting points are uncorrected and were measured in unsealed capillary tubes using either Stuart scientific SMP2 digital apparatus or Electrothermal IA9100 melting point apparatus. Infrared spectra were recorded as Nujol mulls using either Perkin-Elmer 883 or perkin-Elmer 1000 spectrometers.

Nuclear magnetic resonance spectra were recorded using Brucker WP-80, Brucker MSL 300 or Brucker DPX 400 spectrometers. Chemical shifts of ^{1}H and ^{13}C NMR spectra were measured in deuteriated chloroform, acetone or methanol relative to tetramethylsilane as internal standard or in deuteriated dimethyl sulfoxide. Coupling constants (J) are measured in Hertz. Elemental analysis were carried out at the Microanalyticl Laboratory, University College Dublin.

"Nothing in the world can take the place of persistence.
Talent will not; nothing is more common than
unsuccessful men with talent.
Genius will not; unrewarded genius is almost a proverb.
Education will not; the world is full of educated derilicts.
Persistence and determination alone are omnipotent."

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Dedicated to my late Dad, Eddie Duff R.I.P.
Sadly missed by all who knew him.

Acknowledgements

I would like to thank my supervisor Dr Peter Boyle for his numerous suggestions and advice, and for giving me the chance to do this research in the first place. I would like to thank Prof John Kelly for allowing me to use chemisty department facilities. I thank all of the technical staff, Fred, Colm, Eddie, the two Brendans, and Ciaran. Thanks to John O' Brien for all those peaks. A Very special thanks to Celine for putting up with me. I salute all of my fellow collegues in the chemistry department especially those, past and present, in lab 0.14, including, Khadja, Pat G, Eileen, Dermot, John, Pat M, Damien, Christophe, Sylvain, Partizia, Muriel, Moh, Conor, Tom, Yvonne and Ken. A special thank you to Marion and all my friends at home and abroad.

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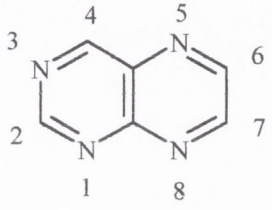
Chapter one

Introduction

1.1. Pteridines

1.1.1 Historical background

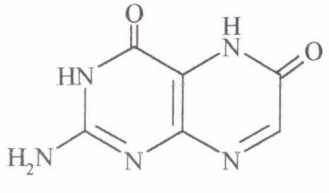
The pteridines constitute a group of naturally occurring heterocyclic compounds, which were first isolated, many years ago from butterfly wings by the English chemist Hopkins.[1]



(1)

The structure of pteridine was not elucidated until 1940 when it was shown to contain the nucleus **(1)**. Since this initial breakthrough, research into pteridine chemistry has been continuous. The pteridines are now recognised to play an extremely important role in mammalian biochemistry. For example, the vitamin co-factor folic acid is needed for DNA synthesis and is essential for one carbon metabolism. In 1963, it was discovered that the essential cofactor for phenylalanine hydroxylase (PAH) was tetrahydrobiopterin,[2] which was later shown to play a vital role in the biology of many organisms.

Many of the naturally occurring pteridines have secondary biological roles, such as the following coloured pteridines (**2**) – (**4**) isolated from common butterfly wings.[3,4,5] Other known pteridines have biological functions which are not yet known. For this reason the synthesis and study of pteridine molecules has always been an important challenge.



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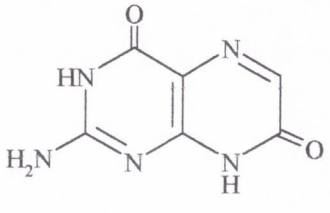

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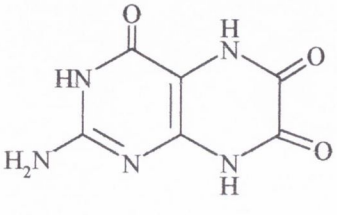
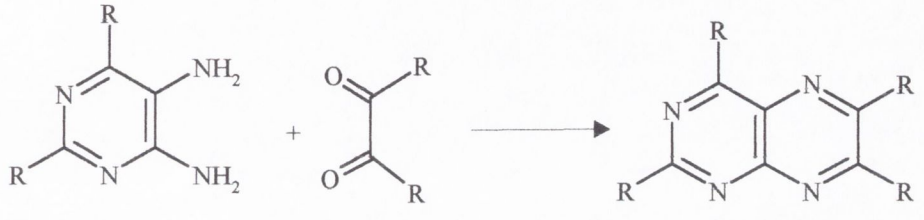


(4)

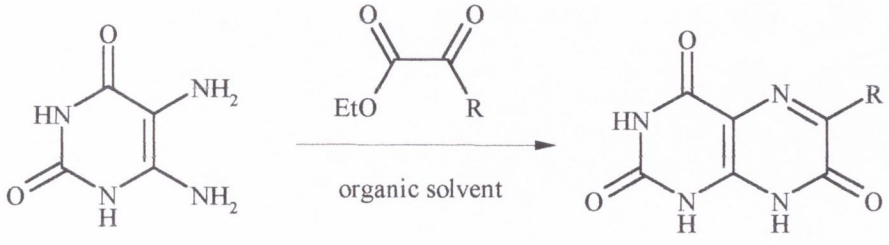
1.1.2 Synthesis of pteridines

There are several general ways in which the pteridine nucleus can be constructed. The first of these methods is to combine a 4,5-diaminopyrimidine (**5**) with a two carbon fragment such as (**6**) to produce (**7**) in what is generally known as the Gabriel-Isay reaction.[6,7,8.]



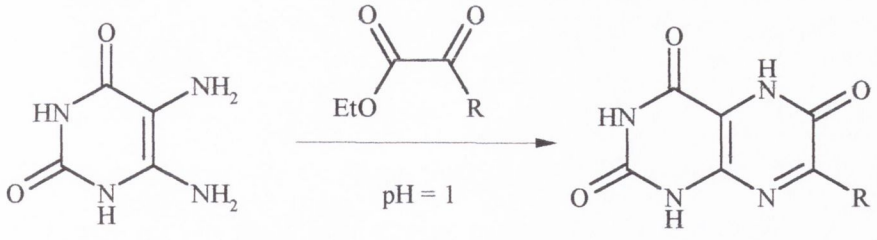
(5) **(6)** **(7)**

This method is applicable to all symmetrical 1,2-diketo compounds. However, unsymmetrical reagents such as alpha keto aldehydes or acids, give rise to mixtures of substituted pteridines isomeric at the 6 and 7-positions. This selectivity problem can be overcome, somewhat, by applying the principle of pH dependent condensation,[9] in which, by altering the pH of the reaction, one can influence it's orientation. For example, condensation of the 5,6-diaminouracil (**8**) with α-ketoacids or α-ketoesters, in neutral or weakly acidic media, as well as in organic solvents, favours the formation of pteridin-7-ones (**9**). Thus in neutral solution the more basic 5-amino group preferentially attacks the keto group. In strongly acidic media, protonation of the more basic 5-amino group leads to the opposite orientation of the substituents to give pteridin-6-ones (**10**).[10,11,12,13.]



(8)

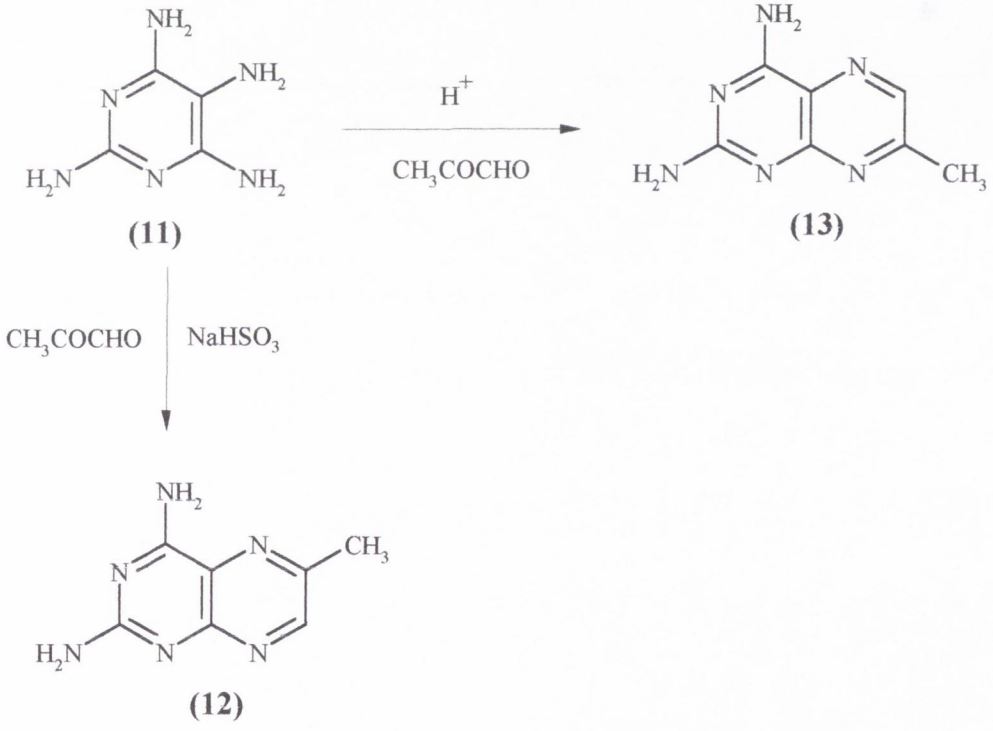
Pteridin-7-one **(9)**



(8)

Pteridin-6-one **(10)**

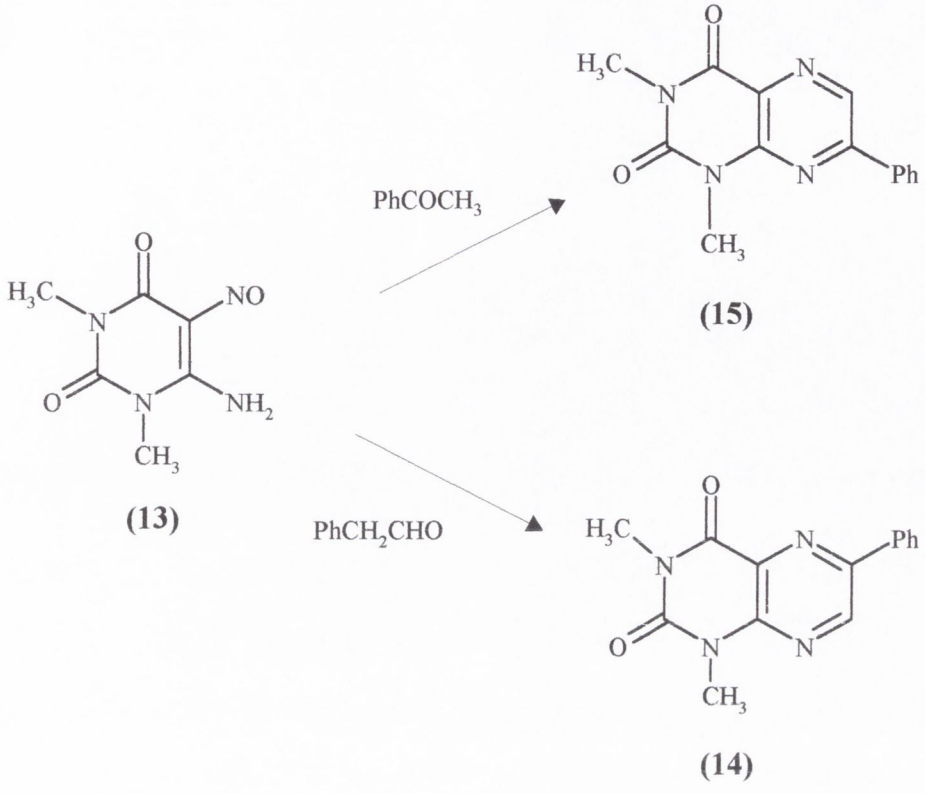
The selectivity problem has also been tackled using aldehyde and ketone binding reagents such as hydrazine and sodium hydrogen sulphide, which tend to direct an alkyl group unto the 6-position, as in the preparation of the 6-methylpterin (**12**) from (**11**). In the presence of acid, the same reagents combine to give the 7-methylpterin (**13**).[14] In general the presence of acid causes protonation of the 5-position and thus alkylation at the 7-position.



(11) **(13)**

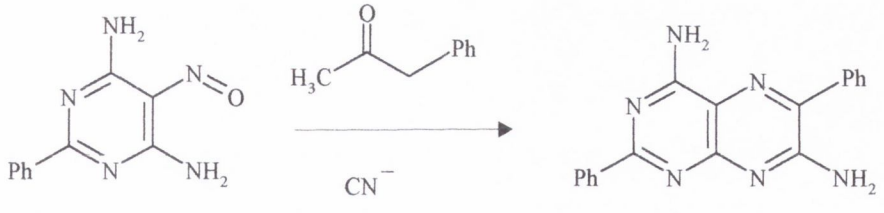
(12)

Another closely related reaction to the Gabriel method is the Timmis reaction. In this reaction a 4-amino-5-nitrosopyrimidine is used as the main building block. The reaction is applicable to aldehydes, ketones, esters, nitriles and acyl halides possessing an active methylene group adjacent to these groups. The active methylene group is attacked by the nitroso group thereby giving selectively either a 6- (**14**) or a 7-substituted pteridine (**15**) depending on the two carbon fragment used.[15,16.]



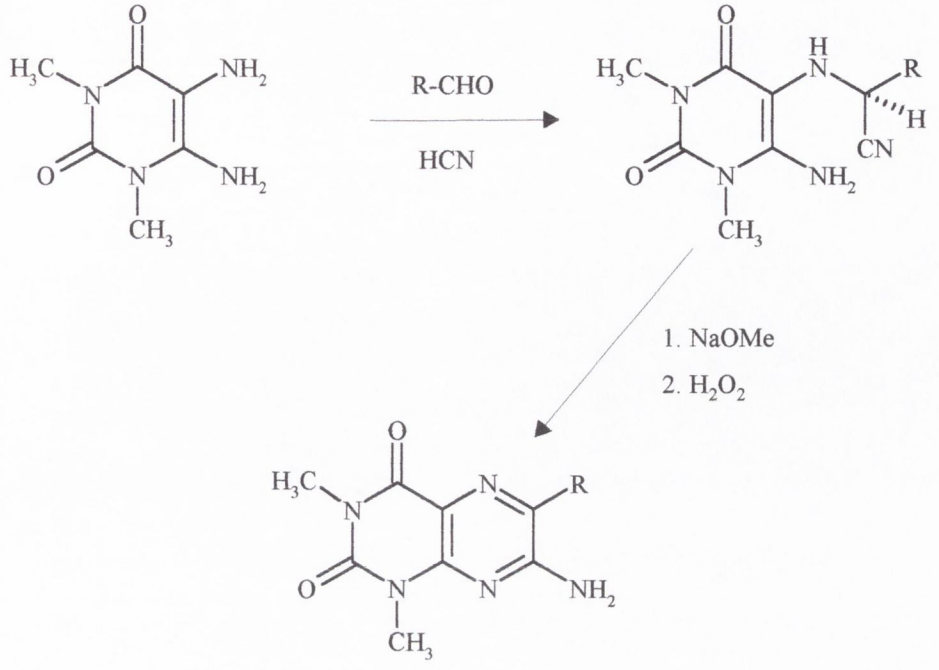
(13) **(15)** **(14)**

Another useful reaction for the synthesis of pteridines is the Pachter reaction,[17] which is a modification of the Timmis reaction. This reaction involves the addition of cyanide ion, which results in 7-amino-6-substituted pteridines (**17**), as in this example.



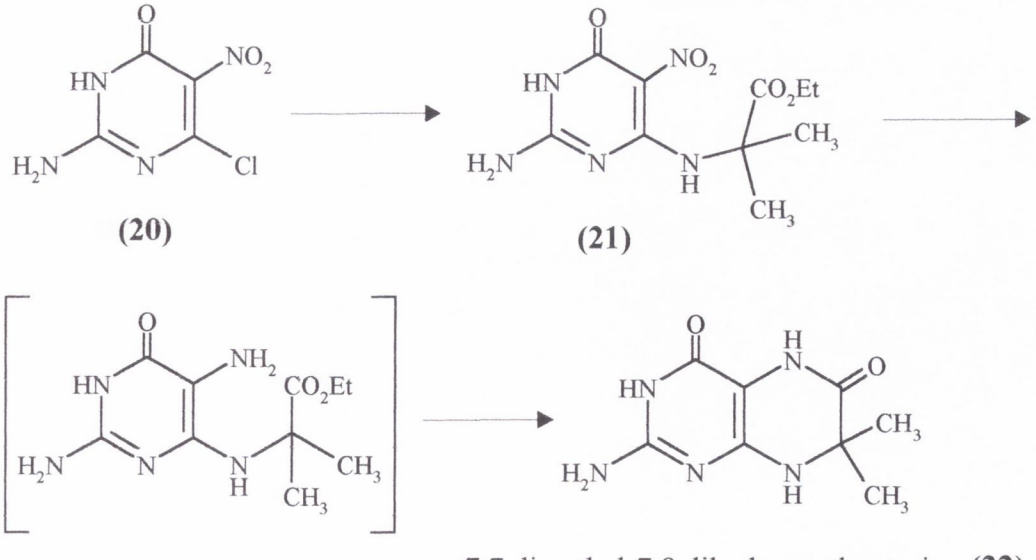
(16) **(17)**

A further modification of this reaction known as the Blicke-Pachter reaction,[18,19] involves the formation of amino nitriles from 5,6-diaminopyrimidines, aldehydes and hydrogen cyanide followed by base catalysed cyclisation with sodium methoxide and oxidation with H_2O_2 to produce 7-amino pteridines, as shown below to give (**18**).



(18)

Another approach to pteridine synthesis, especially those substituted in the 7 position, is known as the Polonovski-Boon reaction,[20, 21] and produces these pteridines *via* the nucleophilic substitution of 4-chloro-5-nitropyrimidines with an alpha amino carbonyl compound Thus treatment of (**20**) with α-aminoisobutyrate gave the intermediate (**21**), which upon catalytic reduction and cyclisation gave (**22**).[22]

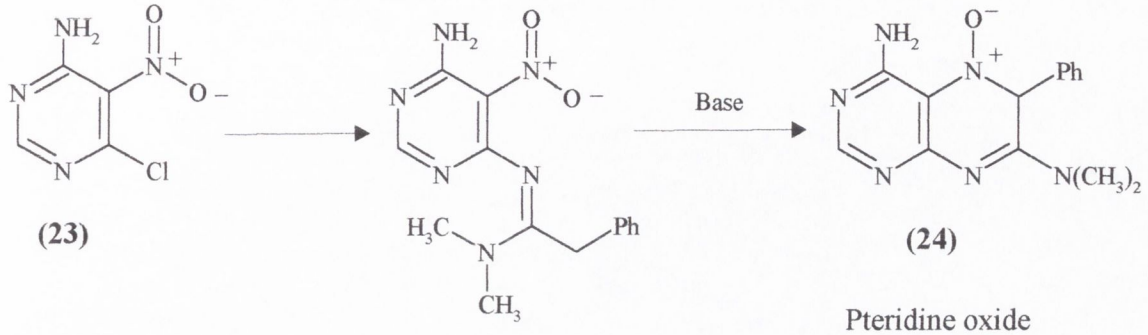


(20) **(21)**

7,7 dimethyl-7,8,dihydroxanthopterin **(22)**

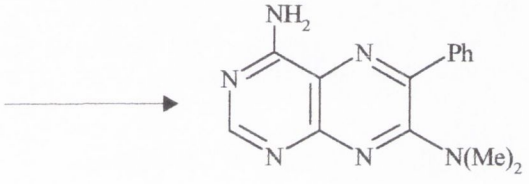
Various modifications of the Boon synthesis exist, such as the reaction of 6-chloro-5-nitropyrimidines (**23**), with alpha phenyl substituted amidines followed by

base catalysed cyclization to pteridine 5-oxides (**24**). The latter can be reduced with sodium dithionate to the heteroaromatic analogues (**25**).[23]



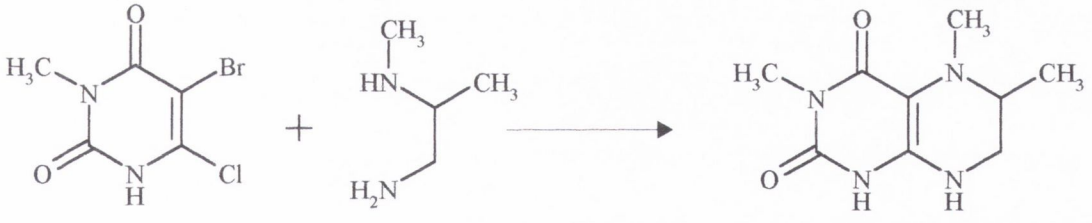
(23) **(24)**

Pteridine oxide



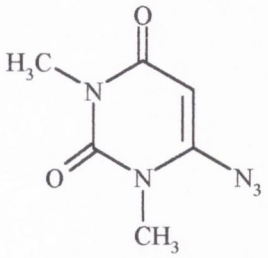
(25)

Also used, is the reaction of a 5,6-dihalopyrimidine (**26**) with ethylenediamine derivatives (**27**), as in the following example for the preparation of (**28**).[24]



(26) **(27)** **(28)**

An unusual approach to the lumazine nucleus was found in the photochemical transformation of 6-azido-1,3-dimethyluracil (**29**) with for example, α-amino acid esters to give 7-substituted 7,8-dihydrolumazin-6-ones (**30**), or with α-amino ketones to give 6-substituted 7,8-dihydrolumazines (**31**).[25]



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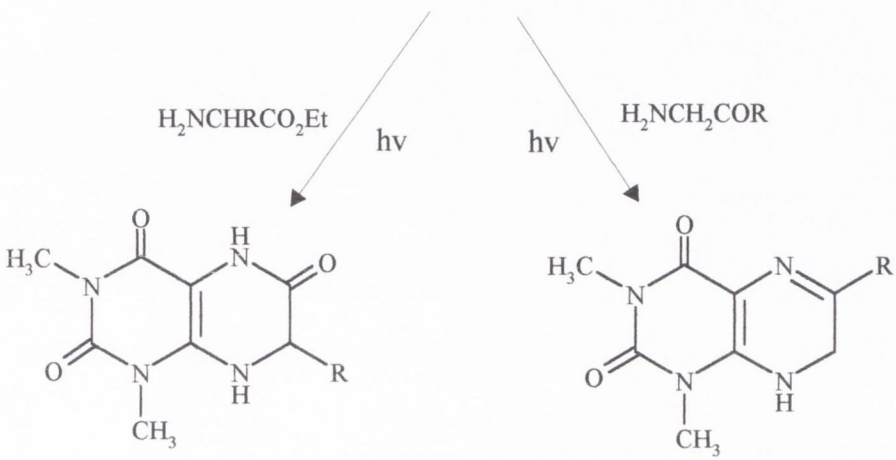
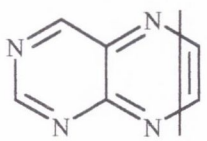
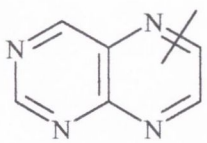
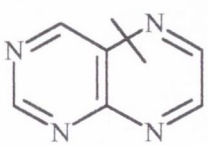


(30) **(31)**

A summary of the synthetic strategies currently available for preparing pteridines from pyrimidine precursors is given in the following scheme. The last approach, however, involving an intramolecular cyclisation onto the 5-position of a pyrimidine ring, using a suitably substituted 4-aminopyrimidine, is one which has not been achieved as yet. This thesis describes new experiments designed to test the feasibility of this approach.

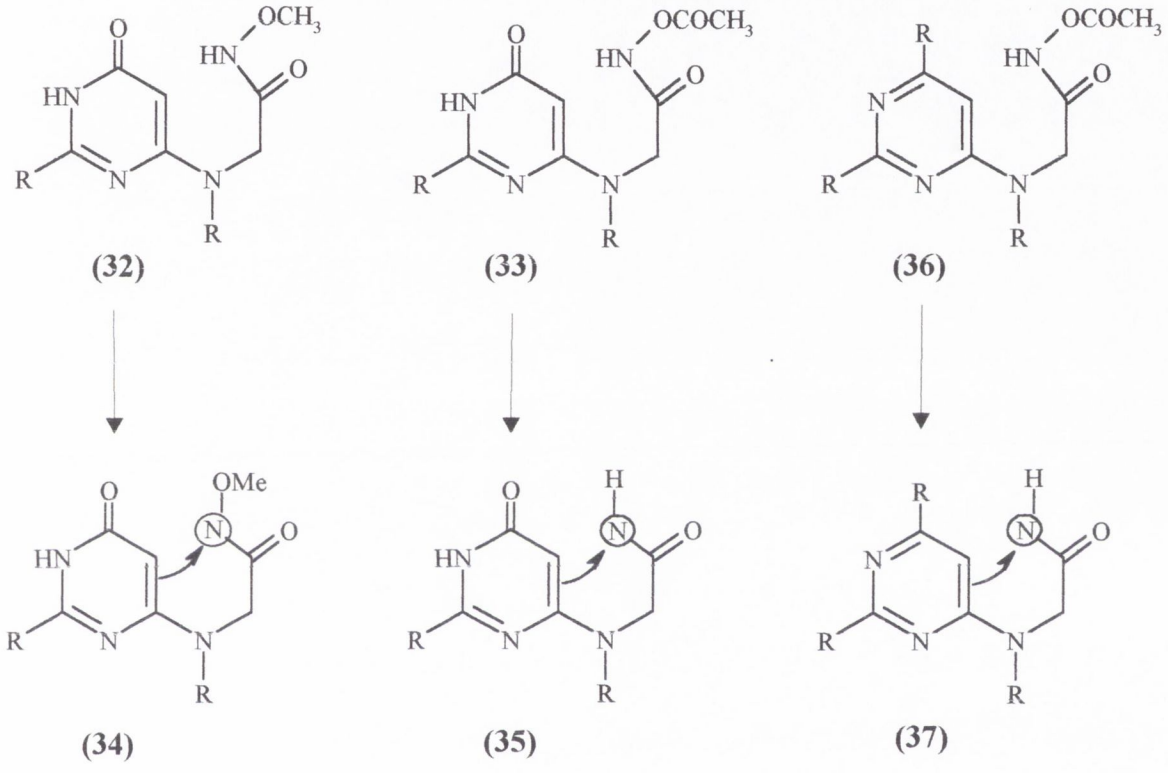
Gabriel-Isay 

Boon 

Unknown 

The experiments described involved the preparation, and attempted preparation, of pyrimidine substrates having a suitable side chain at the 4 or 6 positions. This side

chain would be capable of supporting an electrophilic nitrogen species, which could substitute onto the nucleophilic 5-position of the pyrimidine ring. Intramolecular cyclisations of this type onto a benzene ring have already been achieved [26,27,28] and it was hoped to extend these types of reactions to the pyrimidine area, in order to prepare pteridines. The possible implementation of this strategy is illustrated in **(32)-(37)** below



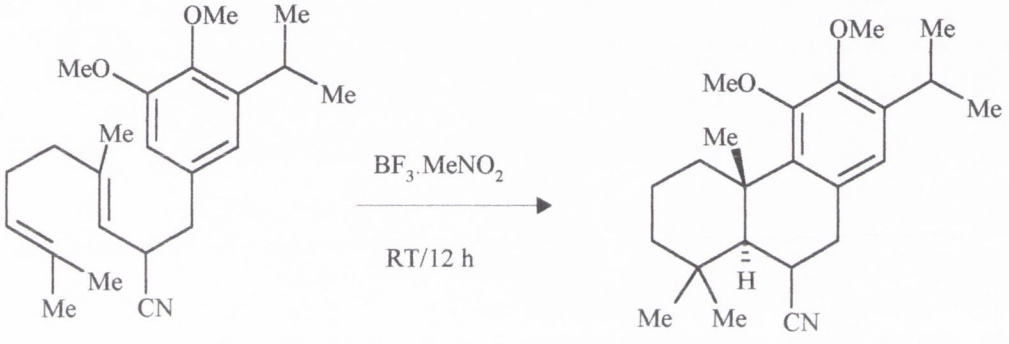
Where Ⓝ = an electrophilic nitrogen species

The 5-position in the pyrimidine ring is the normal site for electrophilic attack. For example, nitration, nitrosation, and formylation occur at this point, particularly if electron-donating groups are present on the ring. It was hoped that the 5-position of the pyrimidine ring would be able to react with any short lived electrophilic nitrogen species, which could be generated from pyrimidines such as (**32**), (**33**) and (**36**). This would then lead to the pteridine ring system. Therefore the aim of this project, was to synthesise precursors such as (**32**), (**33**) and (**36**), and try to cyclise them to give pteridines. A brief outline of some general cyclisation methods used in synthesis, and in particular in reactions involving electrophilic nitrogen species, will be discussed in the following sections.

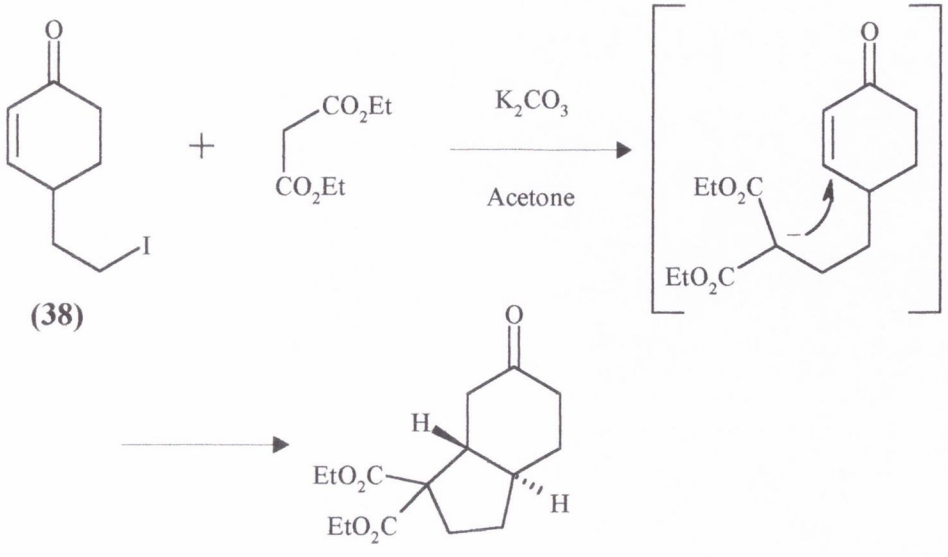
1.2 Intramolecular cyclisations in synthesis...

The fact that the molecules of nature possess cyclic components has made the cyclisation reaction one of the most important reaction types in organic synthesis. In general, cyclisation reactions may be grouped into four main types, *i.e.* those involving cationic, anionic, radical, and metal complex intermediates. A brief survey of these methods will serve to illustrate the cyclisation concept.

Cationic cyclisations include reactions, which involve carbocations, iminium ions, oxonium ions, and vinyl silanes. An example is the carbocation-olefin cyclisation shown below.[29]



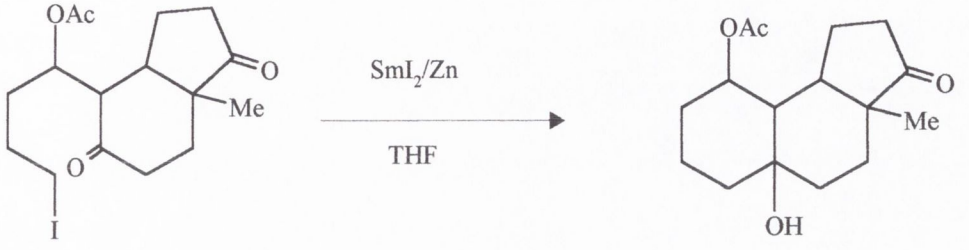
Anionic cyclisations commonly involve the intramolecular attack by anionic centres on electrophiles in simple S_N2 fashion, or Michael addition reactions. For example, in the preparation of (**39**), the starting material (**38**) underwent consecutive alkylation-Michael addition reactions to give (**39**).[30]



(38)

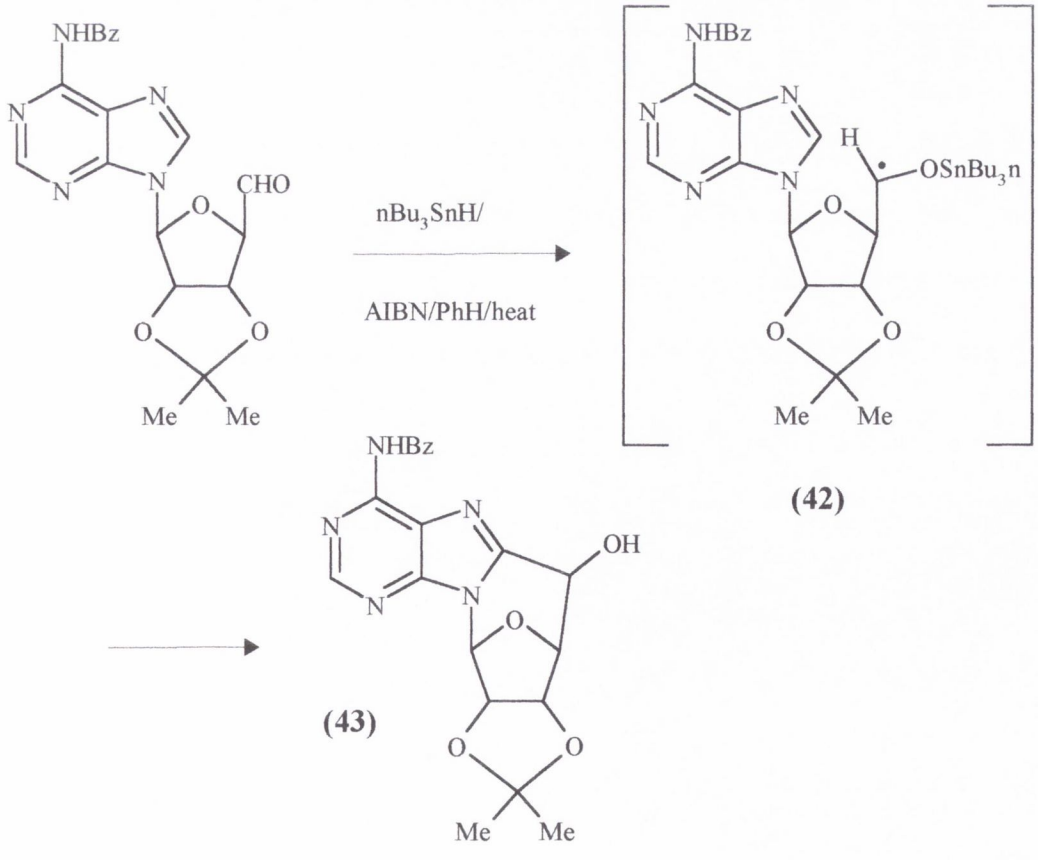
(39)

Many cyclisation reactions are known to be catalysed by metals and examples include cyclisations catalysed by palladium, cobalt, silver, metal carbenes, and more recently, samarium iodide. The use of the latter reagent is illustrated in the Barbier reaction in which a halo ketone (**40**) is cyclised to give (**41**) using SmI_2.[31]

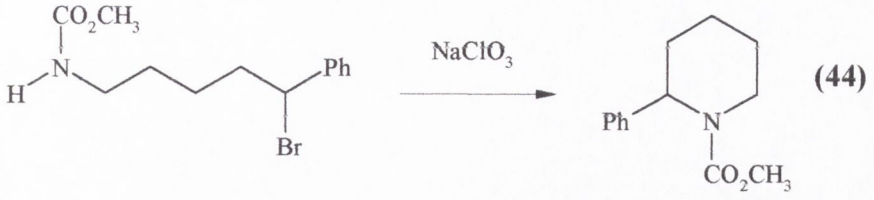


(40) **(41)** 68 %

Cyclisation reactions can often be brought about by the use of reagents such as tributyl tin hydride and tris(trimethylsilyl)silane, which are capable of generating radicals, which undergo cyclisations. For example, the preparation of (**43**) results from cyclisation of the initially formed radical (**42**).[32]

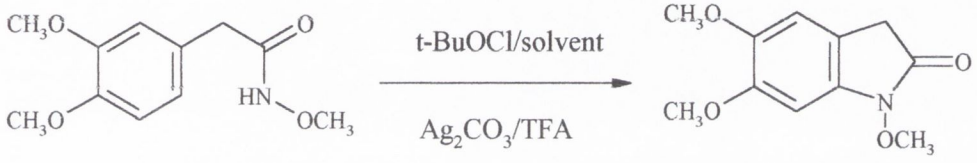


A carbamyl radical was proposed as an intermediate in the following synthesis of **(44)**.[33]



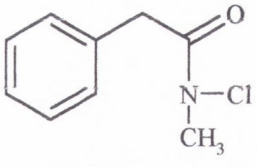
(44)

Some cyclisations involve charged reactive species, such as the nitrenium ion, believed[34] to have been formed by silver catalysed dechlorination of an *N*-chloro-*N*-methoxyamide, giving (**45**). These kinds of experiments will be discussed in more detail in section **1.3.3**.(page 15)



(45)

An interesting aspect of these results, was the observation that the substrates (**46**)-(**49**) failed to give cyclised products under the same conditions. This is evidence for the theory that an electron donating methoxy group and a withdrawing carbonyl group are vital to the formation and/or stability of nitrenium ions.



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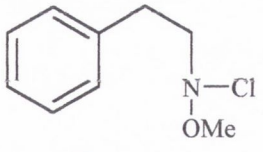

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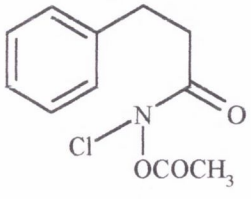

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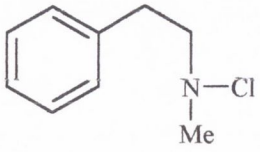


(49)

1.3 Electrophilic Nitrogen intermediates

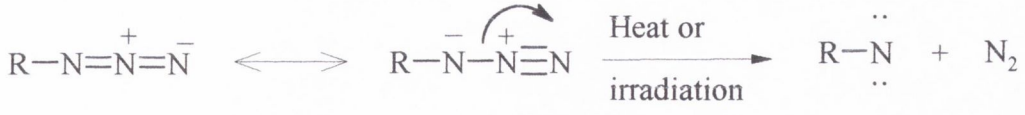
1.3.1. Nitrenes

Nitrenes are reactive intermediates in which nitrogen is attached to one R group and has either two lone pairs (singlet) or has one lone pair and two unpaired electrons (triplet). They are the nitrogen analogues of carbenes in which the triplet state is usually the ground state, but either species can be involved in reactions

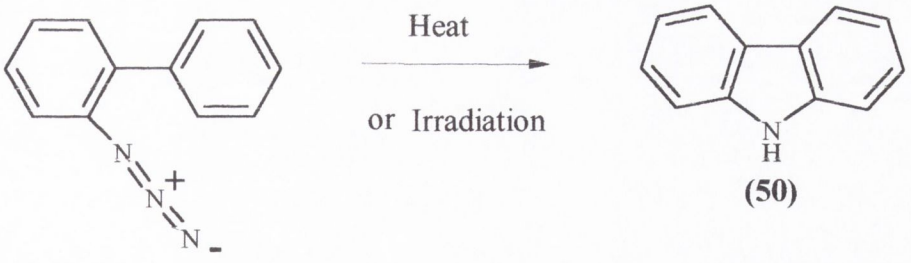
(singlet) (triplet)

Nitrenes can be generated in two ways, (1) elimination and (2) breakdown of certain double bonds. In the first method, base is used to abstract a proton from a nitrogen atom, which also contains a good leaving group as in the case of sulphonamides.

An example of the second method is the thermal degradation of an azide. The loss of molecular nitrogen from organic azides results in uncharged monovalent nitrogen intermediates variously called nitrenes.[35]



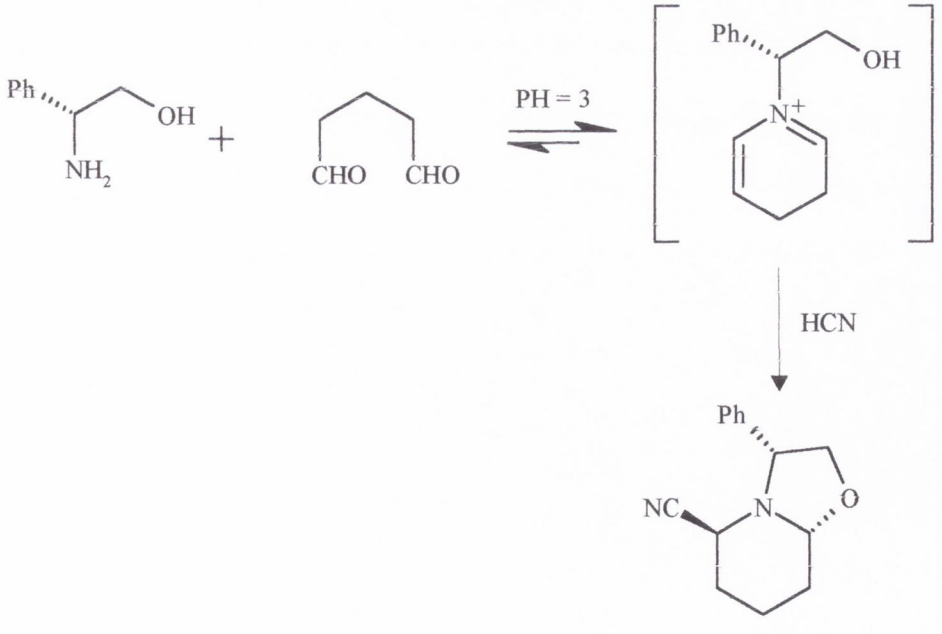
The types of azides, which have been used for generation of nitrenes, include alkyl,[36] aryl,[37] acyl,[38] and sulfonyl derivatives.[39] A few intramolecular insertion reactions, especially in aromatic systems, occur in good yield as in the preparation of (**50**).[40]



(50)

1.3.2. Iminium ions

An iminium ion is an *N,N*-disubstituted imine and thus contains a positively charged nitrogen atom. As mentioned previously, these ions can be induced to undergo cyclisation reactions, by delocalisation of the iminium π-electrons, rendering the alpha carbon atom electrophilic. For example, the stereospecific product (**51**) was prepared by reaction of the *in situ* generated iminium ion with an internal oxygen nucleophile, followed by addition across the double bond of HCN.[41]



(51) 50 %

1.3.3. Nitrenium ions

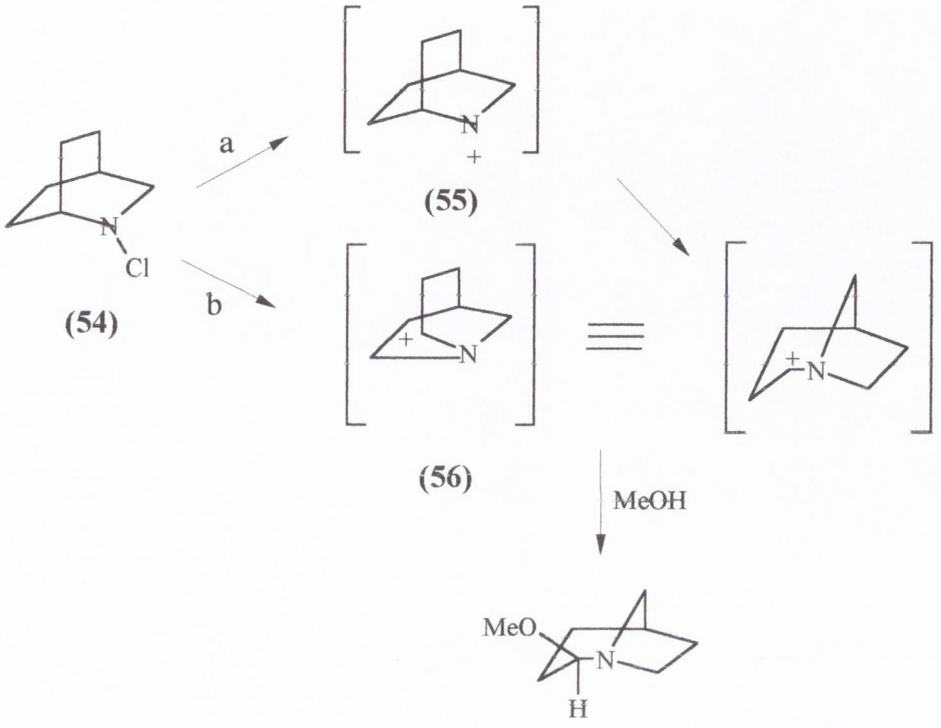
Nitrenium ions can be thought of as nitrogen analogues of carbocations, namely divalent positively charged nitrogen species.[42] They are of two general types. In one, nitrogen is bonded to two atoms as in (**52**) below, and in the other it is bound to only one other atom as in (**53**). It should be remembered that nitrenium ions contain a lone pair of electrons as well as possessing a formal positive charge.

(**52**) (**53**)

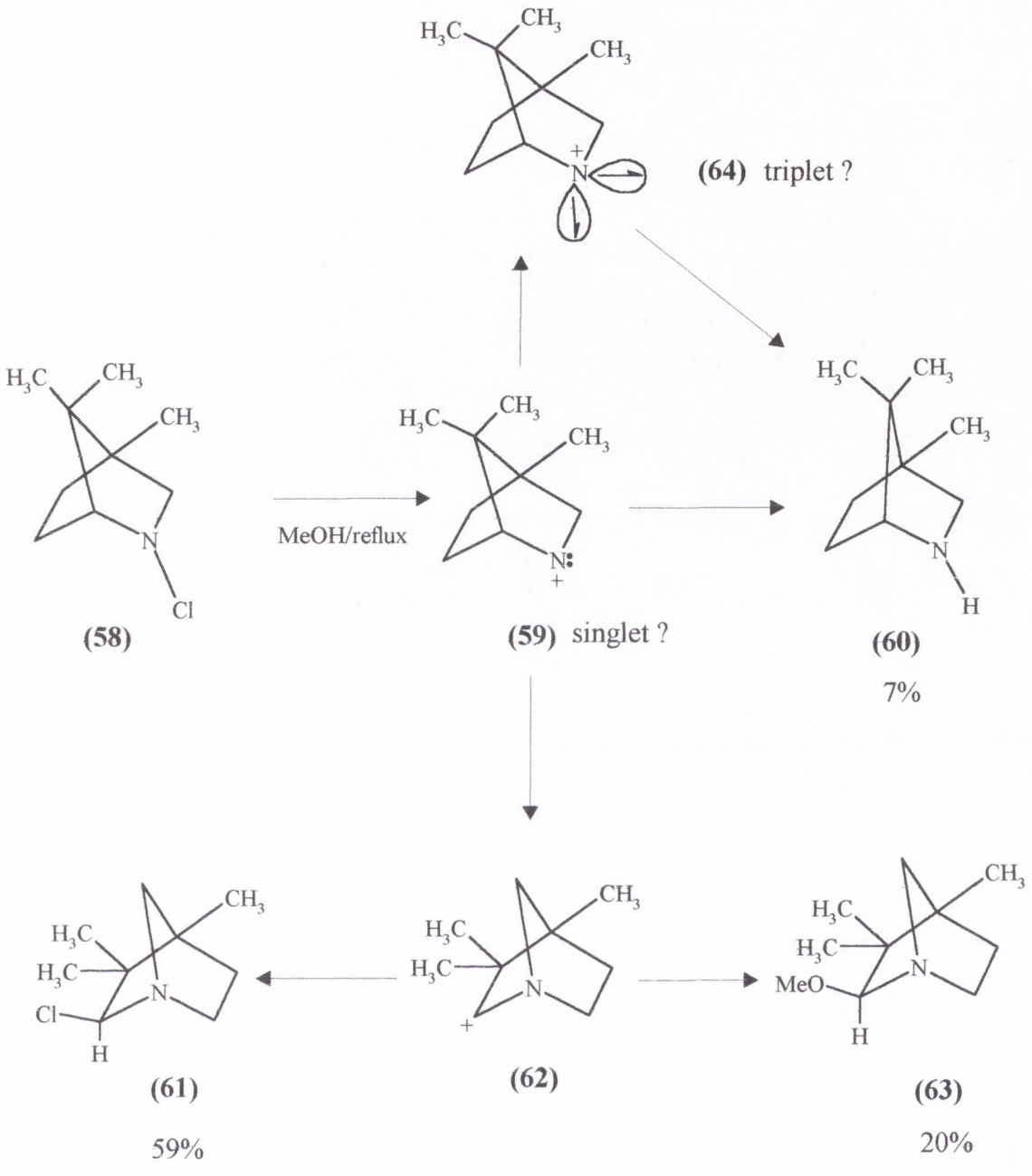
In this respect a nitrenium ion can also be viewed as a protonated nitrene.[43] Nitrenium ions are believed to be extremely carcinogenic *in vivo*. For example, sulphate or acetate esters of hydroxamic acids, are believed to be metabolically converted into acylarylnitrenium ions, which are the ultimate electrophilic carcinogens in the body.[44]

In 1970 Gassmann published a review of nitrenium ion chemistry and gave evidence for their existence through kinetic and reaction studies.[43] Nitrenium ions resemble carbonium ions in many ways and therefore rearrangements are common, *e.g.* the products obtained by Gassmann gave evidence for alkyl migration rearrangements of the Wagner Meerwein type, *via* an electron deficient nitrogen species. The example given below illustrates the type of starting material and mechanism involved. The starting materials for the reactions under study were *N*-chloroamines, which were treated with silver salts in methanol. Thus, refluxing (**54**) in a methanolic solution of $AgNO_3$ gave (**57**). The formation of (**57**) from (**54**) can occur by either of two routes. **Path a** involves the removal of a chloride anion by cationic silver to yield the nitrenium ion (**55**) as a discrete intermediate, which *via* alkyl migration would produce the carbocation (**56**). Nucleophilic addition to (**56**) would then give the observed product (**57**). **Path b** would involve concerted loss of chlorine from (**54**) and migration of the alkyl group with its pair of bonding electrons to give (**56**) directly, followed by addition of solvent as before. Regardless of whether **path a** or **path b** was followed, the alkyl group must have migrated with its electron pair, and thus an electron deficient nitrogen species must have been involved.

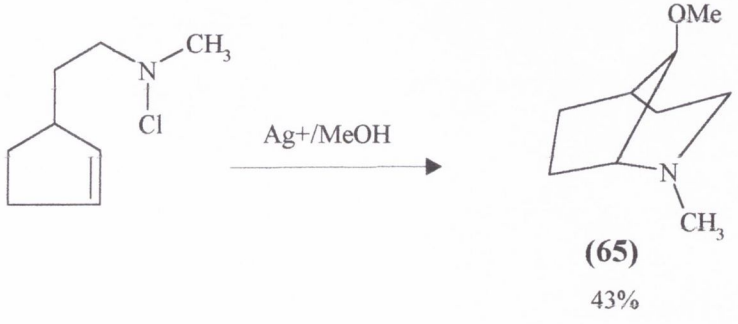
This provided Gassmann with the foundation for a general theory of the existence and reactions of divalent electron deficient nitrogen.



Additional evidence for the existence of nitrenium ions was provided by an another set of experimental results.[45] For example, refluxing the chloroamine (**58**) in methanol produced (**60**), (**61**) and (**63**) in the proportions indicated. Products (**61**) and (**63**) were formed *via* the carbonium ion (**62**), itself generated from the nitrenium ion (**59**). The mode of generation of nitrenium ions requires that (**59**) is a singlet nitrenium ion with electron spins paired. It is possible that (**59**) might undergo spin conversion to the triplet nitrenium ion (**64**). Triplet nitrenium ions should then react rapidly with a hydrogen donor such as methanol. The fact that the parent amine (**60**) was formed is evidence that triplet nitrenium ions had actually been formed. This theory of spin conversion was given greater credibility when additional experiments were carried out using a 50/50 mixture of methanol and bromoform. The only product isolated in this case was (**60**). Since it has been established that heavy atom solvents can catalyse spin conversion,[46] then (**60**) was formed from the triplet nitrenium ion (**64**). Thus Gassmann had successfully demonstrated experimentally, that nitrenium ions could be generated easily and existed as discrete entities with positive charge on nitrogen.

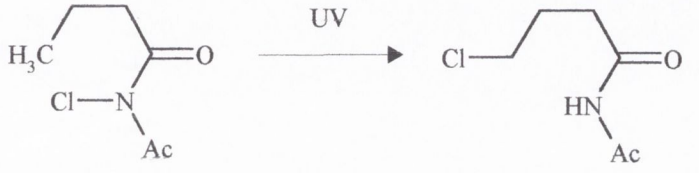


A synthetic application of the nitrenium ion theory was in the intramolecular addition to double bonds to give nitrogen-containing heterocyclics such as (**65**).[43]



Prior to Gassmann's review, Patterson had suggested the existence of reactive nitrogen intermediates, but postulated radical based species rather than nitrenium ions. For example, Patterson[47] has shown how *N*-chloro-*N*-acetylamides (**66**) could be dechlorinated and give rearranged products when irradiated with UV light.

A year later, Barton and Beckwith[48] showed how some *N*-iodoamides could be cyclised *via* an electrophilic intermediate involving nitrogen. Mokotoff [49] also suggested a nitrenium ion as an intermediate in the preparation of (**68**).



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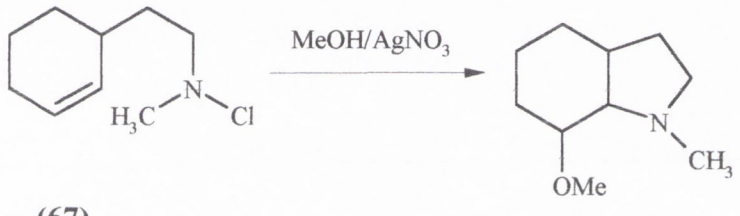
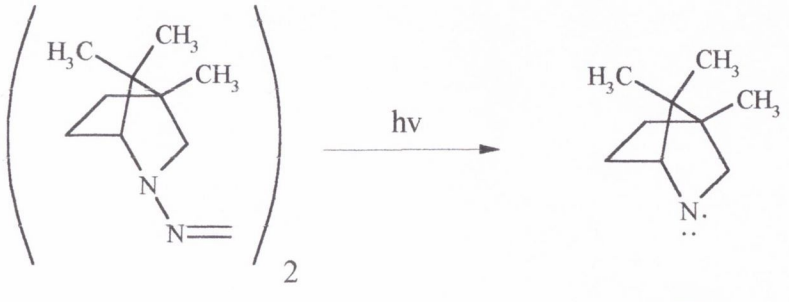


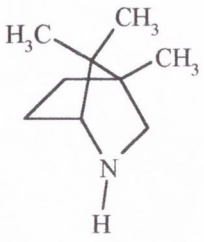
(67) **(68)** 75%

In 1972, Edwards[50] published a paper entitled "Reactions of chloramines with Ag(0) and Ag(I) states", in which he stated, that "Nitrenium ions are not generated from simple secondary chloramines in the presence of silver ions at room temperature". However, Gassmann *et al*[51] disagreed with this statement and prepared the amino radical (**70**) to compare the products derived from it with those derived from solvolytic reactions previously studied[43]. In order to generate the radical (**70**), Gassmann used tetrazene (**69**) as the precursor. Tetrazenes are well established sources of nitrogen radicals.[51]



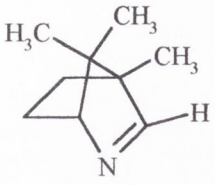
(69) **(70)**

When (**69**) was irradiated in methanol only (**71**) and (**72**) were obtained and no products derived from skeletal rearrangements could be detected.



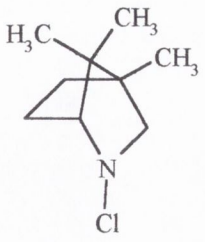
(71)

63 %

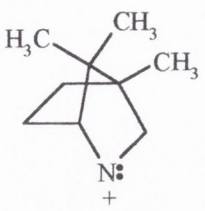


(72)

34%



(58)



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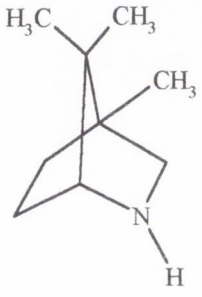
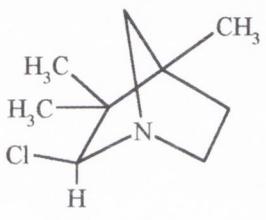
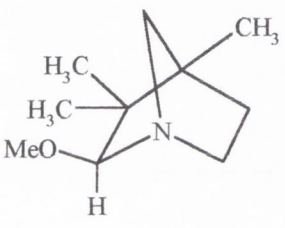


(60)



(61)



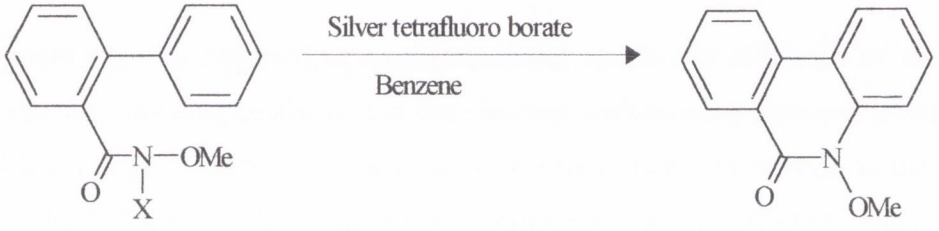
(63)

On the other hand the skeletally rearranged products, (**60**), (**61**) and (**63**), obtained from silver ion catalysed solvolysis of the chloramine (**58**), could only be explained on the basis of Wagner-Meerwein type rearrangements of an initial nitrenium ion (**74**). Thus, Gassmann summarised by concluding that "while the imine (**72**) was completely absent in the methanolysis of *N*-chloroamine (**58**), it was a major product of all the reactions, which proceed *via* the nitrogen radical (**70**). This suggests that both silver ion promoted and non catalysed methanolysis of (**58**) proceed via heterolytic cleavage of the *N*-Cl bond as was previously suggested".

1.3.4. *N*-alkoxy-*N*-acylnitrenium ions as intermediates.

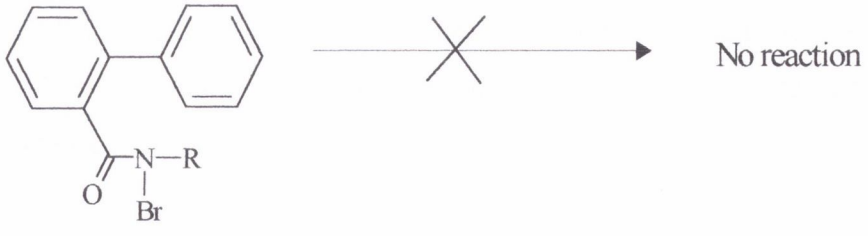
Prior to 1981 most literature references to nitrenium ions referred to the use of *N*-chloroamines as starting materials. In 1981, Ford[52] provided further evidence for the existence of nitrenium ions, by means of a molecular orbital treatment of these ions. According to his calculations, it was predicted that nitrenium ions would be stabilised

by adjacent electron releasing aryl groups in that both singlet and triplet states are lowered in energy. Therefore, *N*-alkoxy-*N*-acyl groups should facilitate the formation of nitrenium ions. In 1984, this fact was appreciated by Glover,[26] who succeeded in completing intramolecular electrophilic aromatic substitution reactions using *N*-halageno-*N*-methoxybiphenyl-2-carboxamides (**75**) as starting materials. *N*-methoxyphenantriodones (**76**) were obtained as products. In addition to this, 2,1-benzoxazines (**77**) were also prepared in good yield. Glover noticed, however, that substrates of the type (**78**) failed to produce any cyclised products, thus again emphasising the importance of a methoxy group attached to nitrogen in the substrate.



(75) X= Cl, Br, I **(76)** 50%

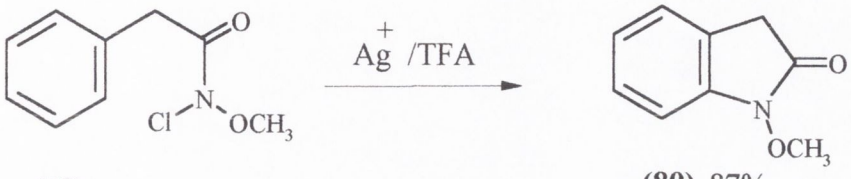
(77)



(78) R = Me, Ac

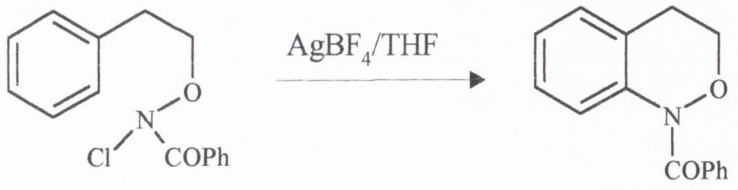
At about the same time as Glover's group, Kikugawa and Kawase[53] were also exploring the possibilities of using nitrenium ions in the synthesis of nitrogen

heterocyclics. They investigated electrophilic aromatic substitution with a nitrenium ion, generated from an *N*-chloro-*N*-methoxyamide. In this case, the systems under study were *N*-chloro-*N*-methoxy phenylacetamides (**79**), which upon successful cyclization gave 1-methoxy-2-oxindoles (**80**) using silver salts and trifluoroacetic acid.

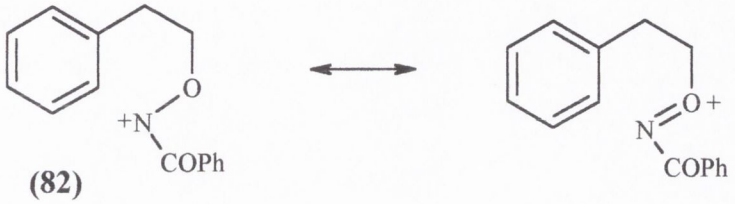


(79) **(80)** 87%

A nitrenium ion was proposed as an intermediate, which was stabilised by the effect of the electron donating methoxy and the electron withdrawing carbonyl groups. In 1987, Glover *et* al [54] published a paper in which they stated, in relation to the results obtained by Kikugawa, that "the same cyclisation can be effected under milder conditions, which in addition we have optimised". They obtained near quantitative yields of 2,1-benzoxazines (**81**) using $AgBF_4$ in THF, as the example shown below illustrates. They appeared to have obtained a lower yield of the indole of the type synthesised by Kikugawa (**80**) above. This is attributed to Kikugawa's use of trifluoroacetic acid as solvent which Glover says is much more effective at solvating a nitrenium ion. This suggests that a solvent such as TFA does not stabilise nitrenium ions of the type (**82**), but does stabilise ions such as (**83**). Glover found that competitive intermolecular reactions occurred when benzene was used as solvent. Glover also claims, as a result of MNDO calculations, that the acyl substituent plays little or no role in the stability of alkoxy nitrenium ions, and that Kikugawa's assertion, that *N*-alkoxy-*N*-acyl nitrenium ions are stabilised by the combined donating effect of the alkoxy substituent and the withdrawing effects of the carbonyl group, cannot be tenable.



(81) 98 %



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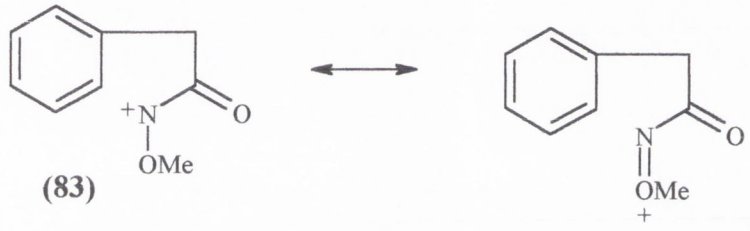
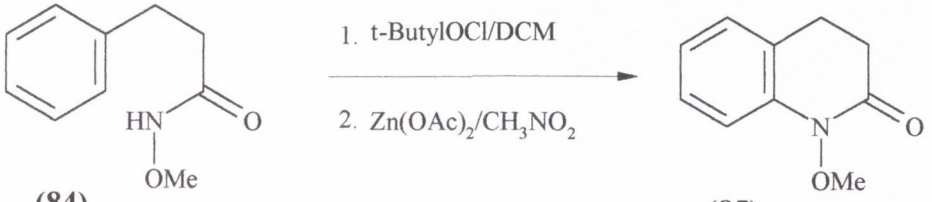
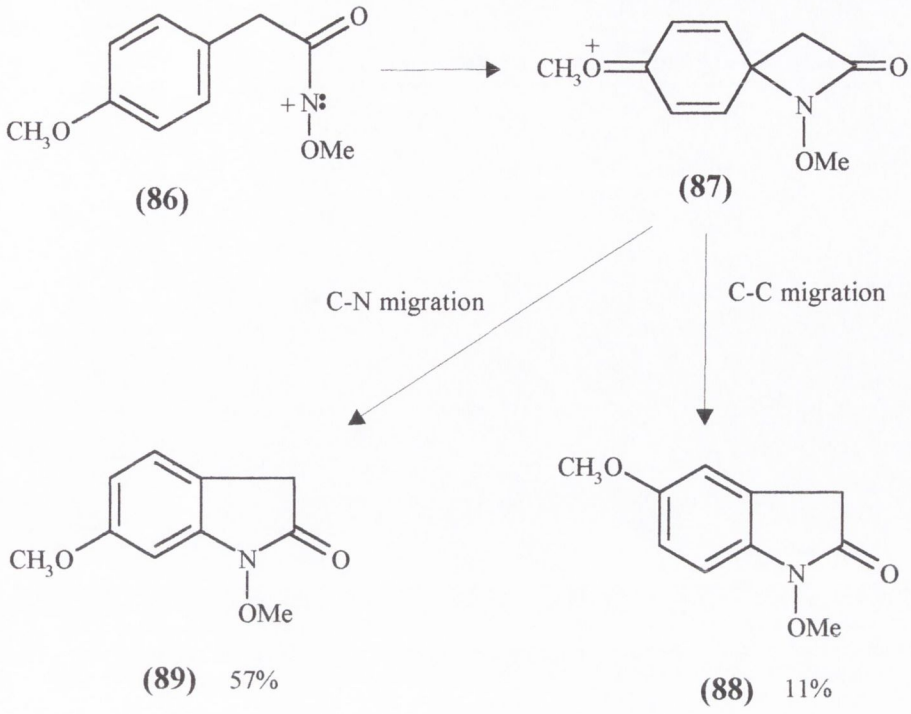


(83)

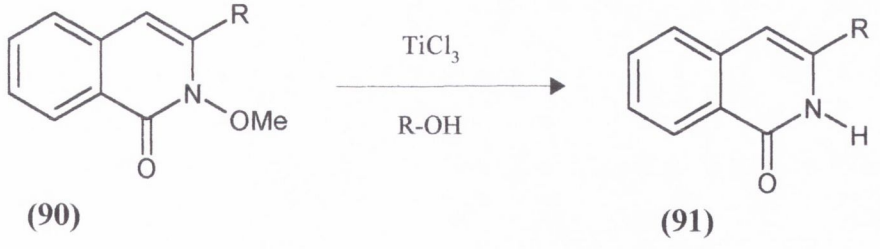
Shortly after this publication and also in 1987, Kikugawa[28] and his group produced another paper describing intramolecular aromatic substitution by an *N*-chloro-*N*-methoxy amide group into an aromatic nucleus. In this paper Kikugawa improved the cyclisation reaction by switching from the highly expensive silver salts and the highly acidic TFA to anhydrous zinc acetate in refluxing nitromethane, which gave an excellent yield of (**85**). Kikugawa also noticed that when *N*-chloro-*N*-methoxy(*p*-methoxyphenyl)acetamide was used, in addition to the expected formation of (**89**), a rearranged product (**88**) was also formed *via* a nitrenium ion (**86**) and then a spiro intermediate (**87**). Kawase has since incorporated the preparation of (**85**) using this method, into the ten step total synthesis of eupolauramine.[55]



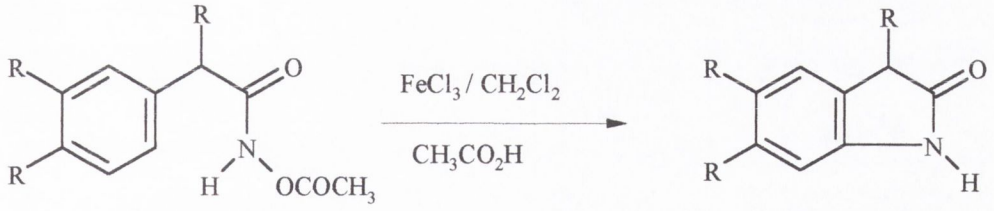
(84) **(85)** 94%



The products obtained from these cyclisations contain an *N*-methoxyamide functional group, which is not very common in naturally occurring molecules. Hydrolysis of the methoxy group to give unsubstituted amides is needed. For example, in 1993 Fisher *et al* [56] developed a method for the conversion of *N*-methoxy amides into amides by treatment with Ti(III) chloride (aqueous or anhydrous) in ethanol. Thus, the following conversion of (**90**) into (**91**) was realised in good yield.



In 1989, Cherest[27] reported that the action of iron(III) chloride on *N*-acetyloxy-amides (**92**) leads to an electron deficient nitrogen species, which can react intra or intermolecularly with an aromatic group to give oxindoles (**93**) or analogues.

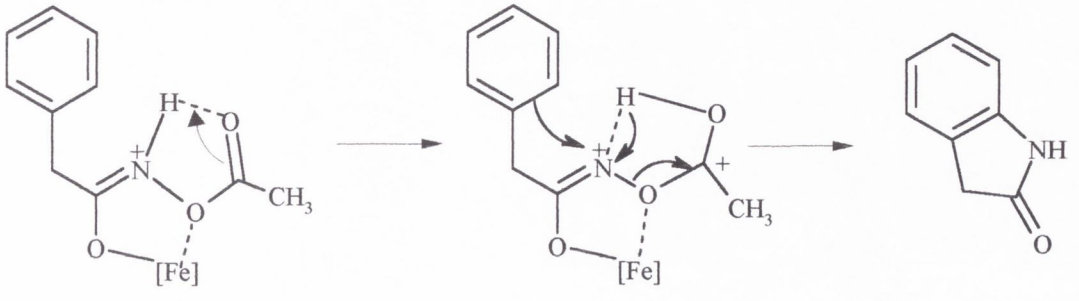


An oxindole

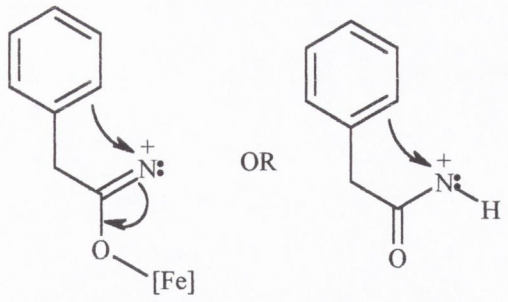
(92) **(93)**

This procedure offered two improvements over the previous reactions, namely that it avoided a chlorination step and the product was the unsubstituted amide, and hence the $TiCl_3$ catalysed hydrolysis step was eliminated.

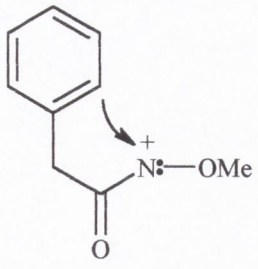
This reaction is an example of a Friedel-Crafts alkylation, in which the aromatic ring attacks a nitrogen electrophile as opposed to the normal carbon based systems. The mechanism of the reaction is proposed to involve a transition state such as (**94**), which then leads to the oxindole (**96**). The complexation of iron with hydroxamic acids is well known, but Cherest suggests that such complexation is also possible with their *O*-acetyl esters. This latter suggestion is evidenced by the fact that the UV spectrum of the ester in the presence of iron is altered somewhat from that without iron.[27] This complexation through the enol form (**94**) makes the amidic proton more acidic, thus promoting intramolecular protonation of the acetoxy group and making it a good leaving group, as in (**95**). The resulting nitrenium ion (**97**) is analogous to those proposed by Glover and Kikugawa[26, 28] (**98**). The discrete nitrenium ion, which is proposed here (**97**), does however differ from the previous examples, in that (**97**) does not contain the electron donating methoxy group of (**98**), which was earlier assumed to be of vital importance to the stability of this ion.



(94) **(95)** **(96)**

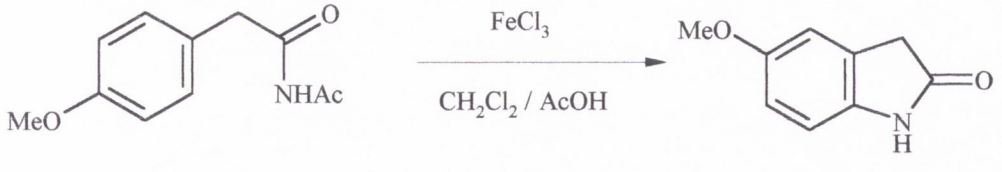


(97)



(98)

As was the case for Kikugawa[28] in 1987, Cherest also found that when an activating group was placed para to the amide then spiro intermediates were obtained, which can give rise to two products depending on whether C-N bond migration or C-C bond migration occurs. In Cherest's case, the latter rearrangement occurred exclusively as in the following preparation of (**99**). This is in direct contrast to the C-N migration product (**89**) which Kikugawa obtained as the major product. This fact was not explained by Cherest but it implies that the methoxy group in spiro intermediate (**87**) anchimerically assists C-N migration. For the spiro intermediate (**99A**) in Cherest's synthesis which contains an unsubstituted amide, reaction via C-C migration is evidently more favourable.



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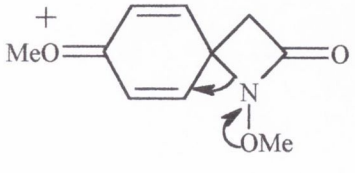
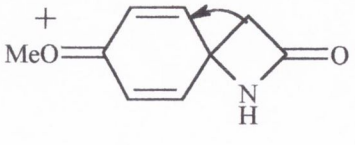
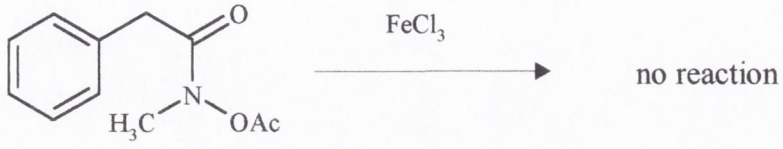


(87)



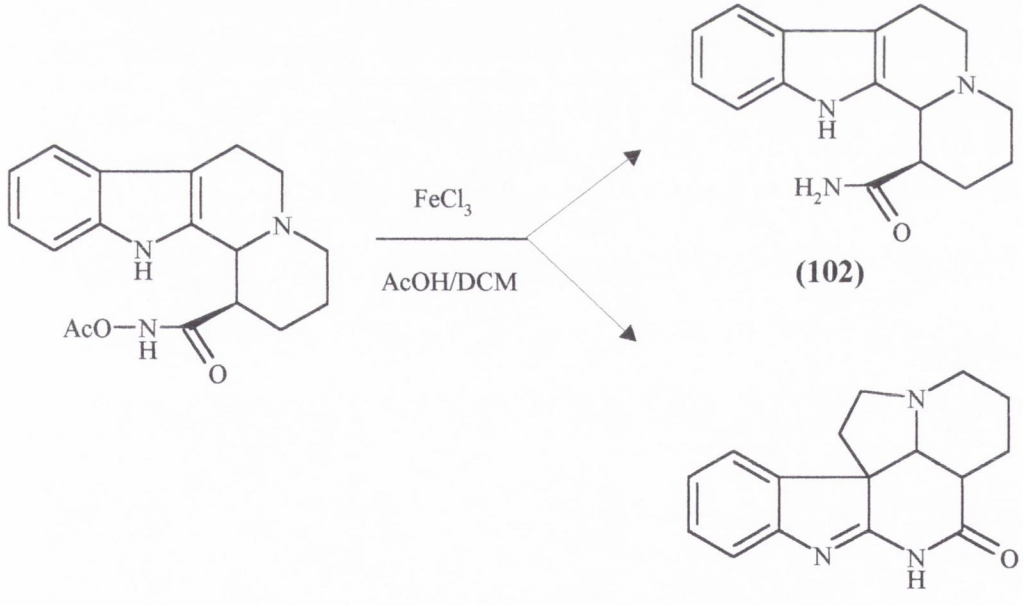
(99A)

Cherest also proves in this paper that the presence of a hydrogen atom on the amide nitrogen is essential, by observing that the *N*-methyl derivative (**100**) was recovered unchanged after being subjected to these conditions.



(100)

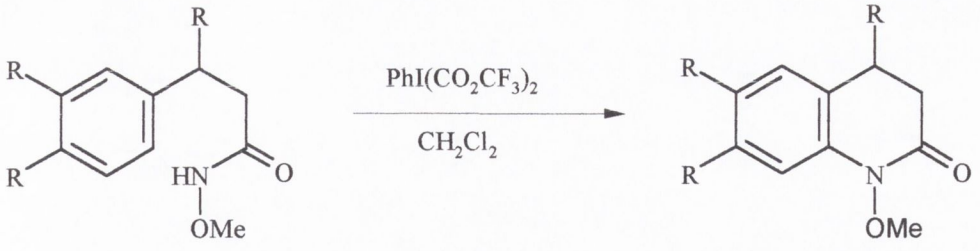
Shortly after Cherest's original publication, his group reported [57] another example of the use of an *O*-acetyl hydroxamate, as the substrate for a $FeCl_3$ catalysed cyclisation, involving a nitrenium ion intermediate. The yields obtained were low and in addition to the cyclised product (**101**), appreciable amounts of a primary amide (**102**) were also isolated.



(102)

(101)

In 1990, Kikugawa[58] published a paper in which it was claimed that previous cyclisation methods had been improved by the use of a hypervalent iodine reagent such as $PhI(CO_2CF_3)_2$, instead of the silver salts/TFA or zinc salts/nitromethane systems previously used. The starting materials were once again the *N*-methoxy amides (**103**) and products such as (**104**) were produced in good yield.



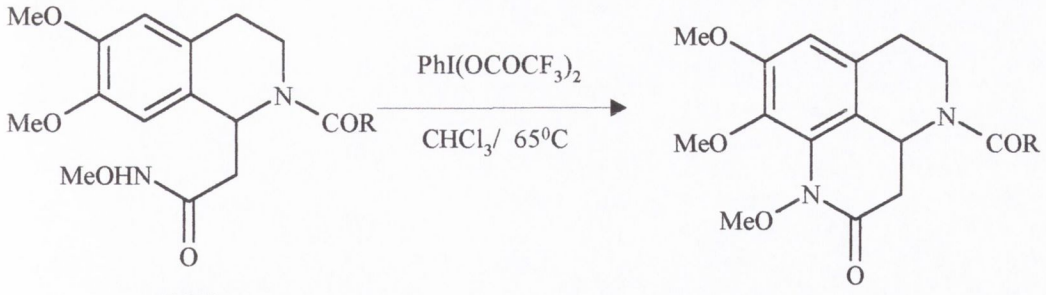
(103) R = H

(104) 83%

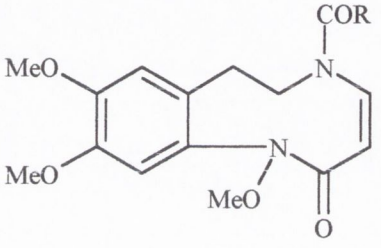
This procedure avoids pre-chlorination of the methoxyamide and is therefore a significant improvement. The reaction was unsuccessful with *N*-methylamides or *N*-acyloxyamides under similar conditions, indicating that the methoxy group is crucial for formation of the intermediate (**105**) and the stabilisation of the nitrenium ion (**106**) formed by the loss of iodobenzene from (**105**).

(105) **(106)**

The hypervalent iodine reagents have long been the focus for synthetic applications, especially oxidations.[59, 60] Their use as cyclisation reagents is relatively new. A recent comprehensive review of hypervalent iodine reagents has appeared.[61] Unfortunately, attempted cyclisations with $PhI(CF_3CO_2)_2$ do not always give the desired products, as in some cases spirocyclisation gives rise to alternatives. Thus, in the attempted conversion of (**107**) to (**108**), Kikugawa [62] produced (**109**) in 65 % yield.

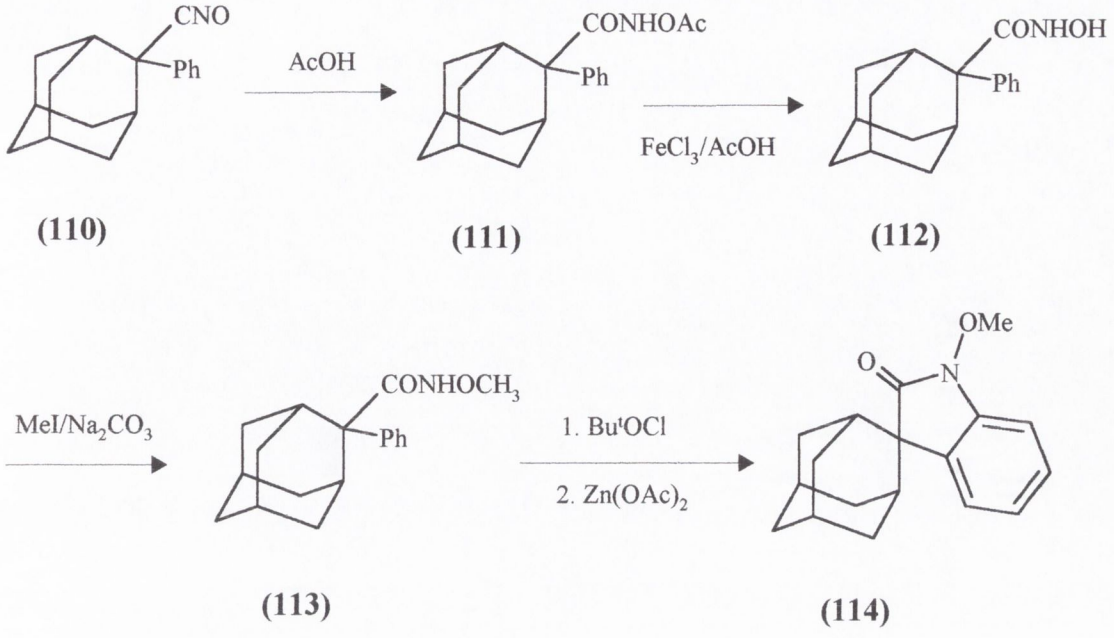


(107) **(108)**



(109)

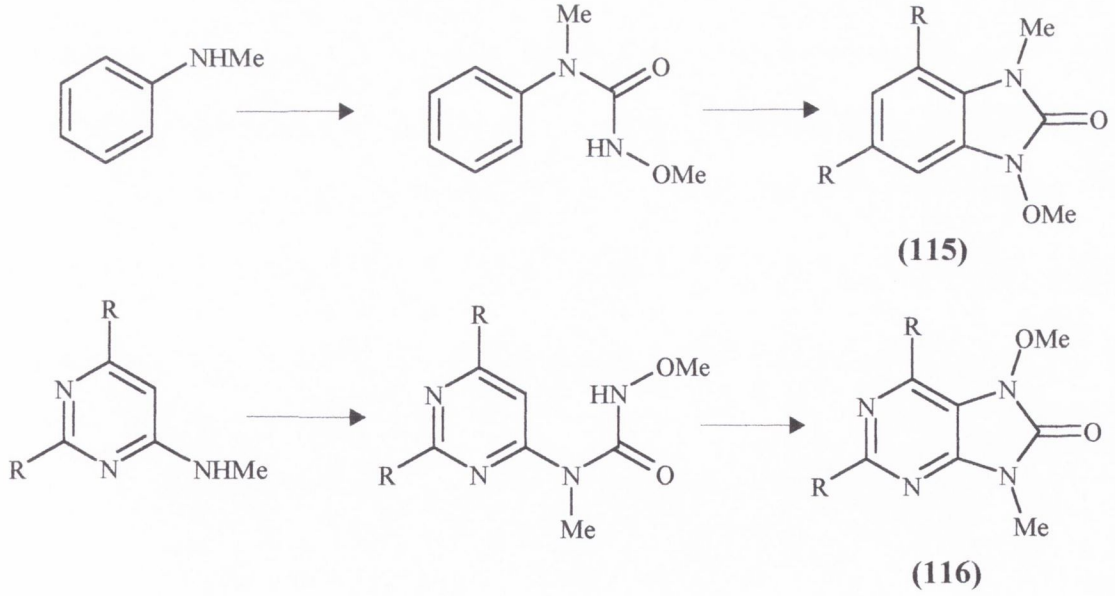
Fleming and co-workers[63] have also synthesised an *O*-acetylhyroxamate (**111**) by the addition of acetic acid to the nitrile oxide (**110**). However, these workers failed in their attempts to adapt Cherest's iron catalysed reaction in their synthesis of the oxindole (**114**). In fact, the product obtained upon treatment of (**111**) with $FeCl_3$ was the corresponding hydroxamic acid (**112**) in 85 % yield, which is formed by acetic acid catalysed hydrolysis of the iron complexed substrate. The required cyclisation to (**114**) was achieved using Kikugawa's method involving zinc acetate catalysed cyclisation of the *N*-chloro *O*-methyl hydroxamate (**113**).[28, 34, 64] The failure of the $FeCl_3$ catalysed reaction demonstrates that this reaction is not applicable to every system, and that cleavage of the substrate to the corresponding hydroxamic acid will be a significant side reaction, even in systems which favour cyclisation.



(110) **(111)** **(112)**

(113) **(114)**

A more recent use of a hypervalent iodine reagent was that reported by Romero,[65] who used $PhI(CO_2CF_3)_2$ for the oxidative cyclisation of acyclic ureas to give *N*-substituted 2-benzimidazolines (**115**), as shown in the two step process below.

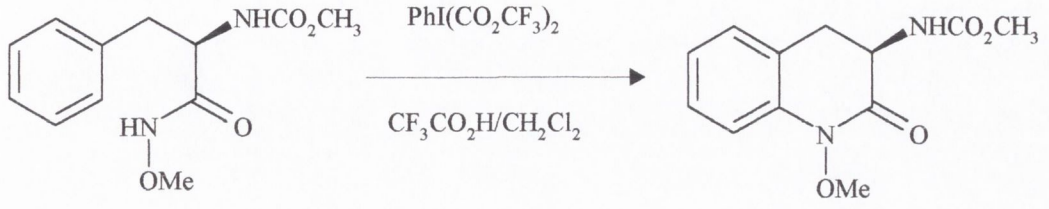


(115)

(116)

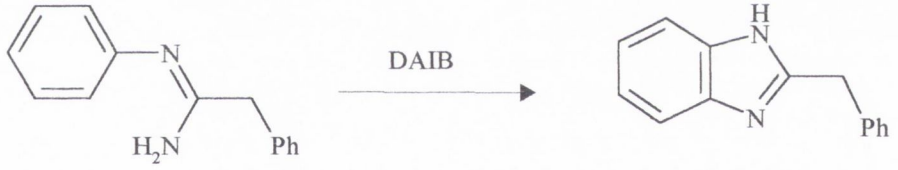
Efforts to use these reactions, in an attempt to prepare products of the type (**116**), will be discussed later. More recently, Romero reported the synthesis and oxidative cyclisation of *N*-methoxyamides.[66] Various reagents were employed for the cyclisation, including PhI $(CO_2CF_3)_2$. An improvement in the cyclisation procedure

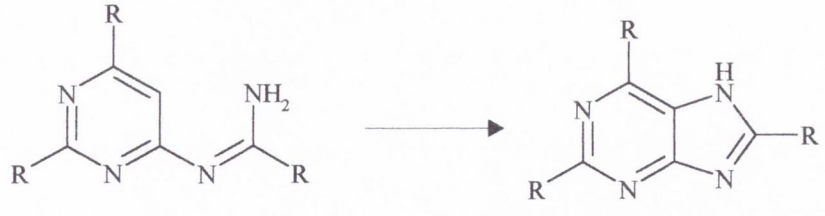
was achieved by the addition of three equivalents of trifluoroacetic acid. Thus, the following transformation of (**117**) into (**118**) occurred in 85 % in the presence of TFA, and in moderate yield in its absence. The TFA is proposed to facilitate reactions involving nitrenium ions by effectively solvating the ion once formed.



(117) **(118)** 85 %

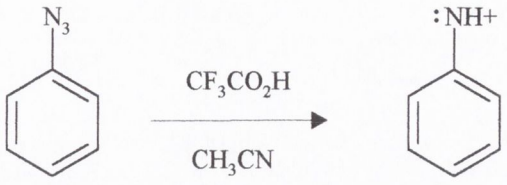
The hypervalent iodine reagent (diacetoxyiodo)benzene or (DAIB) has been used recently [67] to cyclise amidines, as in the following transformation. It may be possible to adapt this synthesis to the pyrimidine series, as in the following example.



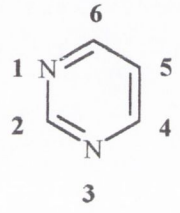


The uses of hydroxamic acids and their derivatives in organic synthesis has been reviewed by Kikugawa,[42] whose own laboratory has been at the forefront of most of the developments in this field. Recently, Abramovitch[68] has suggested that a nitrenium ion, which underwent an intra molecular cyclisation reaction, can be generated from an aryl azide, by treatment with TFA in acetonitrile. This is unusual as azides normally decompose to give nitrenes. However, in this case, the nitrene is

protonated in the highly acidic media to give a nitrenium ion, which is stabilised by the TFA.



1.4. Electrophilic substitution of pyrimidines

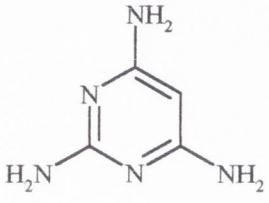


(120)

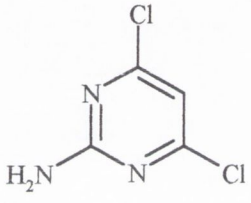
The dominant feature of the pyrimidine nucleus (**120**) is the electron deficiency of the ring compared to benzene. This is due to the strong inductive effect of the ring nitrogens, and which makes the positions *ortho* to these nitrogens, namely the 2-, 4- and 6-position, especially electron deficient. The result of this electronic effect is that substituents at these positions easily undergo nucleophilic substitutions. A chloro group in any of these positions for example, can easily be converted into a hydroxy, mercapto, alkoxy or amino group using the appropriate reagents. The chloro group itself facilitates these reactions since it also has a strong inductive effect on the ring carbon making it especially susceptible to attack by nucleophiles. If a pyrimidine carries a strong electron-donating group such as amino, then further substitution at the remaining 2-, 4- or 6-position is difficult.

The 5-position in the unsubstituted pyrimidine nucleus is more electron rich than those positions *ortho* to the nitrogens. However, it is not as electron rich as a corresponding position in benzene and electrophilic substitution is difficult. It is only when the pyrimidine is substituted at the 2-, 4- or 6-position with electron releasing groups, such as amino, hydroxy and methoxy groups, that electrophilic substitutions

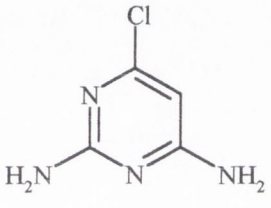
at the 5-position become much easier. In some cases, the 5-position may become markedly more electron dense than benzene as in, for example, 2,4,6-triaminopyrimidine (**121**). The introduction of electron donating groups at the 2-, 4- or 6-position significantly affects the possibility of carrying out nucleophilic substitutions at these positions. For example, a compound such as 2-amino-4,6-dichloropyrimidine (**122**) is relatively easily converted into 4-chloro-2,6-diamino pyrimidine (**123**) by virtue of the fact that the combined inductive effects of the chloro substituents outweighs the donating effect of the amino group, thereby leaving either of the equivalent chlorines open to attack by ammonia.



(121)



(122)

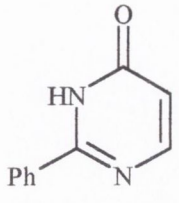


(123)

However, the product so obtained (**123**) is highly unreactive towards nucleophiles due to the combined releasing effects of the amino groups, which makes replacement of the remaining chlorine extremely difficult. The manipulation of substituents on a pyrimidine ring is therefore a kind of electronic cat and mouse game. This became evident in many of the pyrimidine experiments carried out in the course of the present work, the aim of which was to discover if intramolecular cyclisation by electrophilic nitrogen could be achieved onto a pyrimidine ring.

In the work to be described, attention was focused on three distinct series of pyrimidines, which differed in the substitution at the 2-position. These were 2-phenyl-, 2-amino-, and 2-oxopyrimidines (**124-126**). Most of the work was carried out on 2-phenylpyrimidines since the phenyl group conferred greatly improved solubility on the pyrimidine system. Some work was also done on the 2-amino and 2-pyrimidinones, especially in view of the widespread occurrence of these systems in biological molecules. The 4(3*H*)-pyrimidinone structure shown above in all three pyrimidines is a structural element, which occurs, widely in naturally occurring

pyrimidines and fused pyrimidines. The initial aim in all three series was therefore to try and include this moiety in the target molecules.



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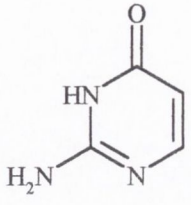

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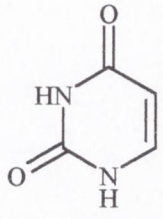


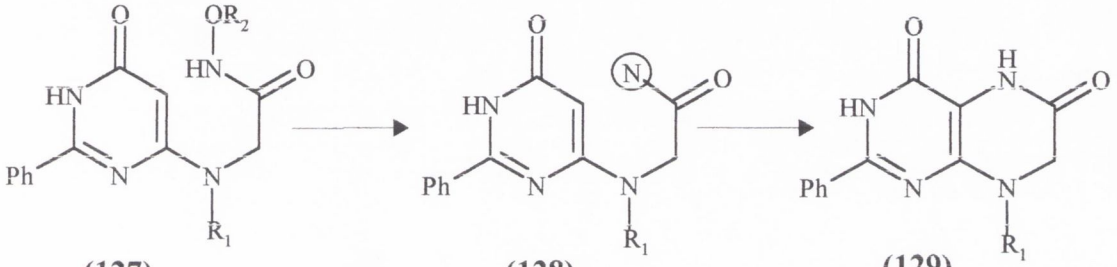
(126)

Chapter two

2-phenylpyrimidines

Introduction

Preliminary experiments were designed to furnish compounds of the general type (**127**). These are hydroxamic acid derivatives, which should be capable of acting as useful precursors for the generation of electrophilic nitrogen species such as (**128**). The latter should then cyclise to the desired pteridine molecule (**129**).



(127) **(128)** **(129)**

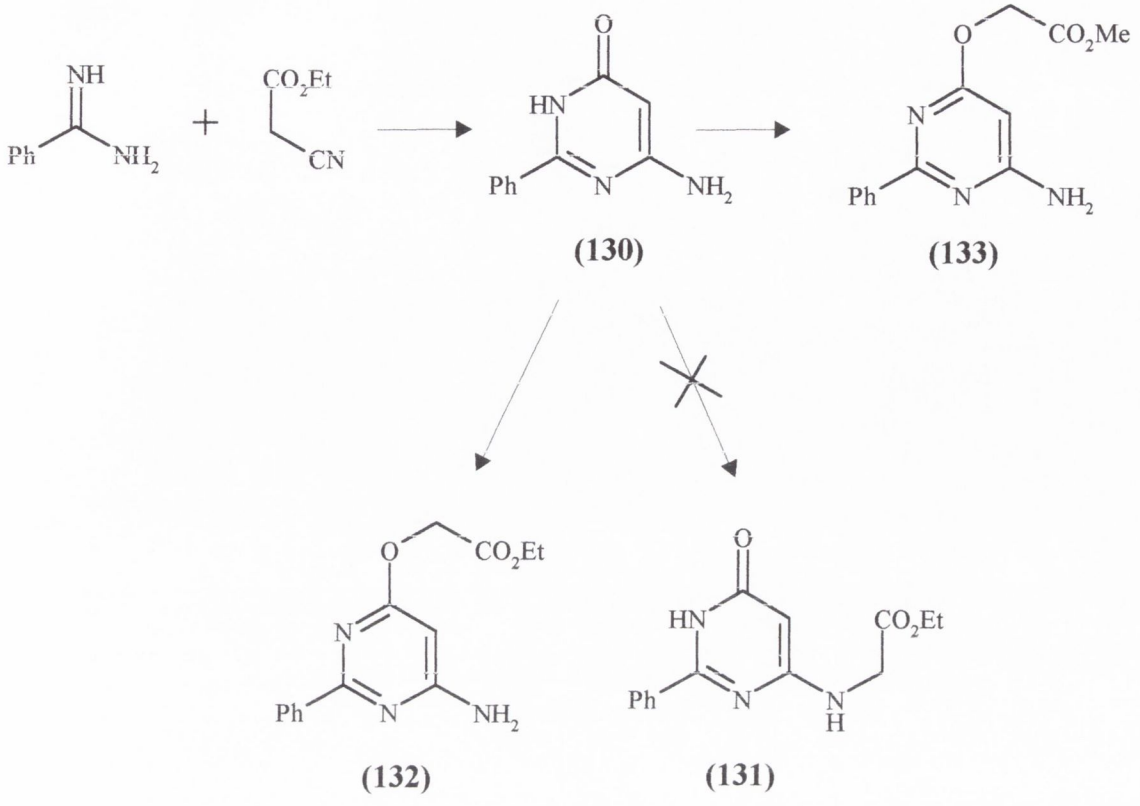
R_1 =H, Alkyl

R_2 = Alkyl, Acyl

Ⓝ= electrophilic nitrogen

2.1. Reactions starting from 6-amino-2-phenyl-4(3*H*)-pyrimidinone (130) and 6-hydroxy-2-phenyl-3(4*H*)-pyrimidinone (143)

6-Amino-2-phenyl-4(3*H*)-pyrimidinone (**130**) was prepared readily by the base catalysed condensation of benzamidine hydrochloride with ethyl cyanoacetate.[69] It was found necessary to dehydrate the benzamidine HCl by heating the salt under vacuum above its melting point. Direct use of the hydrated salt as sold commercially resulted in poor yields of the pyrimidine product. In an effort to prepare 6-ethoxycarbonylmethylamino-2-phenyl-4(3*H*)-pyrimidinone (**131**), the 2-phenylpyrimidine (**130**) was treated with ethyl bromoacetate and sodium carbonate, when a white crystalline product was obtained.



(130) **(133)**

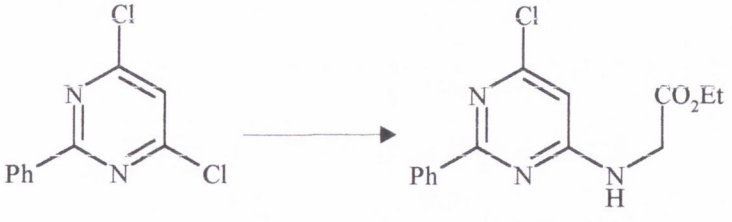
(132) **(131)**

The spectroscopic properties of the product, however, showed that it did not have the required structure (**131**), but rather the structure (**132**). This showed that alkylation had occurred at the 4-oxygen atom rather than at the 6-amino position.

For example, the UV spectrum of the new product (**132**) in 0.1 M NaOH showed an absorption band at 234 nm, which is at a significantly lower wavelength than the absorption band at 272 nm obtained for the starting material in the same solvent. In 95 % EtOH the UV spectrum of (**132**) showed two absorption bands at 236 and 260 nm, in contrast to the starting material (**130**) which shows only a single band at 231 nm. In 0.1 M HCl the product shows two bands at 248 and 296 nm, while the starting material gives one absorbance at 272 nm. This is evidence for the presence of a significantly different chromophore in the new product. If the alkylation had occurred at the desired 6-amino position in (**130**) then the original chromophore should not have changed so radically. These UV data therefore suggest that alkylation has not occurred at the 6-amino group of (**130**), and are consistent with the proposed structure (**132**). The IR spectrum of (**130**) showed three bands at 3489, 3321, and 3178 cm^{-1} and the spectrum of (**132**) showed

almost identical bands at 3428, 3334, and 3233 cm^{-1}. This indicates the presence of an amino group in both (**130**) and (**132**).

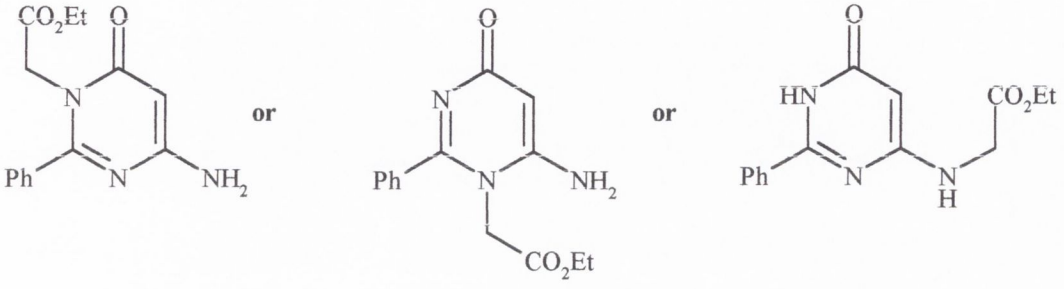
Further evidence was provided by the proton NMR spectrum of product (**132**), which showed a two proton singlet at 6.85 ppm, which disappeared on addition of D_2O. This provides evidence for the presence of an amino group in the product (**132**). The amino group in the starting material (**130**) has a similar chemical shift value of 6.63 ppm. In addition to this, the signal at 11.9 ppm in the starting material (**130**) due to the lactam NH has disappeared in the spectrum of the product (**132**). These data provide evidence for the existence of an amino group and the absence of a lactam NH in the product (**132**). Yet more evidence for these conclusions comes from a consideration of the NMR data of some other related pyrimidines. Also in the 2-phenyl series, 4-chloro-6-ethoxy-carbonylmethylamino-2-phenylpyrimidine (**135**) was prepared by reacting 4,6-dichloro-2-phenylpyrimidine (**134**) with glycine ethyl ester. The side chain in this product (**135**) is unambiguously located at the 6-position. In addition, the methylene protons in the side chain are unambiguously located adjacent to nitrogen. These protons appear in (**135**) at 4.22ppm, which is at a significantly higher field than the methylene protons in (**132**), which appear at 4.93 ppm. This confirms that the methylene protons in (**132**) are attached to an oxygen atom rather than a nitrogen atom.



(134) **(135)**

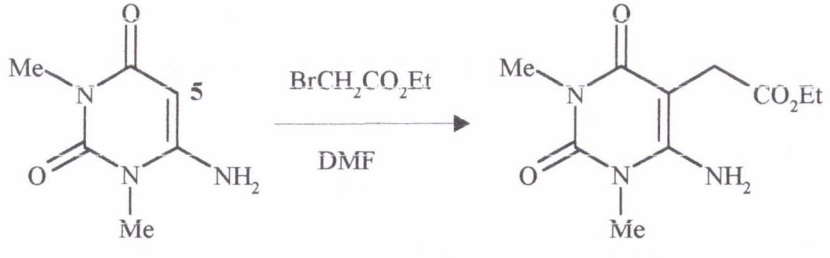
Treatment of compound (**130**) with methyl bromoacetate gave the methyl ester product 4-amino-6-methoxycarbonylmethoxy-2-phenylpyrimidine (**133**). This product had similar spectroscopic properties to (**132**). Structures in which alkylation has

occurred at a ring nitrogen atom (**136**) and (**137**) or exocyclic nitrogen (**131**) are ruled out by the evidence outlined here.



(136) **(137)** **(131)**

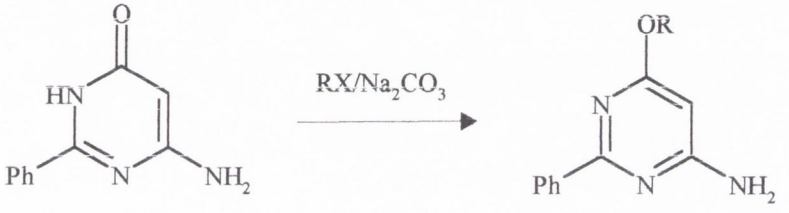
The only remaining position at which substitution could possibly have taken place was the 5-position. Electrophilic alkylation has been shown to take place in the 5-position of certain pyrimidines, most notably the 1,3-dioxopyrimidines, commonly known as uracils. For example, Ogura and co workers showed that 6-amino-1,3-dimethyluracil (**138**) reacted with ethyl bromoacetate at room temperature for 2 weeks to give 4-amino-5-ethoxycarbonylmethyl-1,3-dimethyluracil (**139**) in 25 % yield.[70] Spectroscopic evidence for this structure included the strong bands at 3380 cm^{-1} and 3450 cm^{-1} in the IR spectrum of (**139**) due to an amino group. In addition to this, the proton NMR spectrum of (**139**) did not show the C-5 proton.



(138) **(139)**

The proton NMR spectrum of (**132**) shows a one proton singlet at 5.82 ppm due to the proton at the 5-position. The ^{13}C NMR spectrum shows a C-H peak at 83.5 (DEPT), due to the 5-carbon atom, again supporting the proposed structure (**132**).

6-Amino-2-phenyl-4(3*H*)-pyrimidinone (**130**) was also alkylated with methyl iodide, benzyl chloride, and 1-bromo-3-chloropropane under conditions identical to those used for the production of (**9**). The products were the *O*-alkylated derivatives (**140-142**) respectively. Thus for example, alkylation of 6-amino-2-phenyl-4(3*H*)-pyrimidinone (**130**) with methyl iodide gave a pure crystalline product. The proton NMR spectrum of this product showed the presence of an amino group and a methoxy group, as well as the absence of a lactam NH proton, corresponding to 4-amino-6-methoxy-2-phenylpyrimidine (**140**).



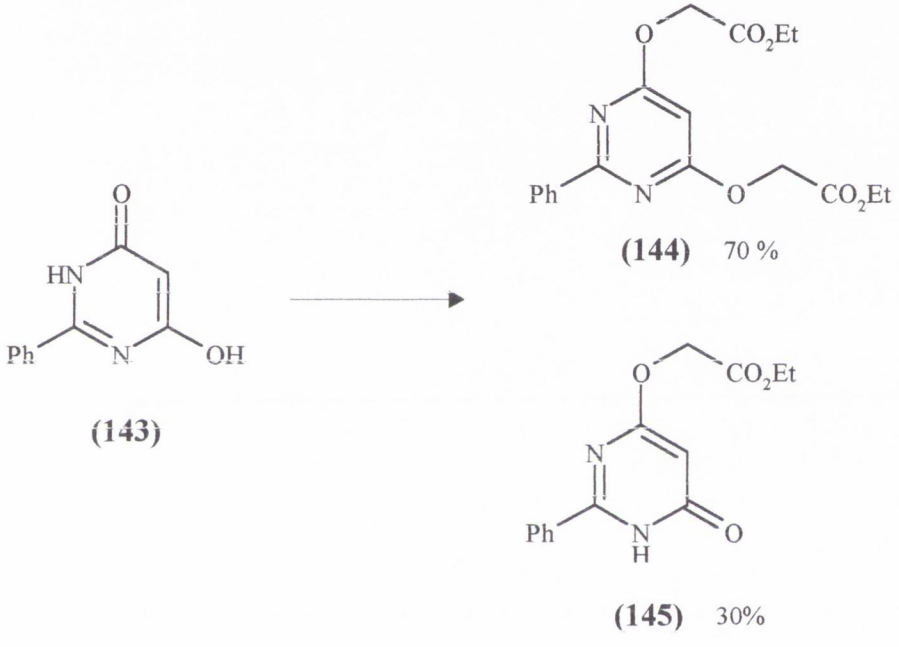
(130)

(140) R = Me
(141) R = CH_2Ph
(142) R = $(CH_2)_3Cl$

Further alkylation reactions were carried out on 2-phenyl-4(3*H*),6(1*H*)-pyrimidindione (**143**)[71] when it was found that alkylation once again occurred on oxygen. Thus, treatment of (**143**) with ethyl bromoacetate and Na_2CO_3 gave a 70/30 mixture of two products, which were separated by flash chromatography. These were shown to be 4,6-di(ethoxycarbonylmethoxy)-2-phenylpyrimidine (**144**) and 6-ethoxycarbonyl-methoxy-2-phenyl-4(3*H*)-pyrimidinone (**145**). The main product (**144**) was presumably formed by reaction of the initially formed monosubstituted compound (**145**). This was shown to be the case by reacting pure (**145**) with ethyl bromoacetate under conditions of the original experiment to give the disubstituted product (**144**). Future experiments should be conducted to ascertain the conditions necessary for the exclusive production of the mono alkylated product (**144**). The assignment of structures (**144**) and (**145**) to these products was made on the basis of the following spectroscopic and analytical data.

Elemental analysis showed a molecular formula of $C_{18}H_{20}N_2O_6$ for (**144**). This eliminated the possibility of a charged species such as (**146**) having formed. Elemental

analysis of (**145**) showed a molecular formula of $C_{14}H_{14}N_2O_4$. The NMR spectra of both products (**144**) and (**145**) were almost identical, in that the chemical shifts for the side chains appeared at exactly equivalent positions in both products, with the major product (**144**) showing exactly double the integration values of the minor product (**145**). This suggests that both side chains in (**144**) are existing in the same chemical environment, which is consistent with the proposed structure.



(143)

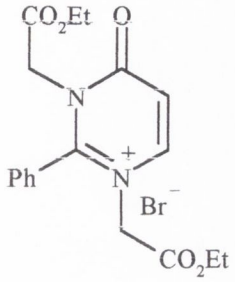
(144) 70 %

(145) 30%

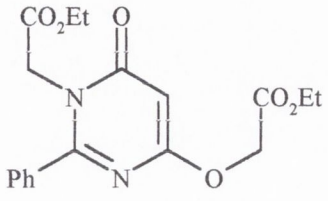
For example, the methylene groups of both side chains in (**144**) appear together as a four proton singlet at 5.07 ppm. If the compound had contained a mixture of *N*- and *O*-alkylated chains then one would expect that the two methylene groups would resonate at different positions. In addition, the chemical shift of the methylene protons of (**144**) at 5.07 is very close to that of the methylene group in (**132**) at 4.93 ppm, again supporting (**144**) as a wholly *O*-alkylated product. Substitution at the 5-position is ruled out in both (**144**) and (**145**) due to the presence of a proton at the 5-position, as shown by signals at 6.45 ppm and 5.8 ppm respectively.

The starting material (**143**) shows an IR stretching frequency at 1623cm^{-1} due to the lactam carbonyl carbon. The disubstituted product (**144**) shows only the high stretching

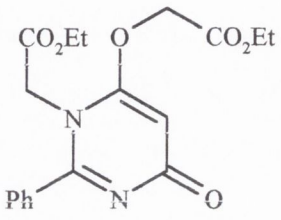
frequency due to the ester groups at 1741cm^{-1}. Thus, the lactam absorption that would be expected in a structure such as (**147-148**) is absent.



(146)

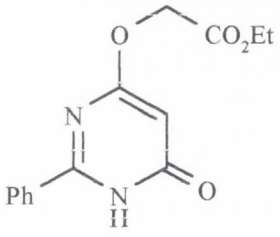


(147)

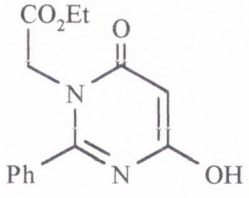


(148)

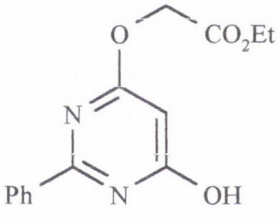
The evidence shows that the monoalkylated product (**145**) is also an *O*-alkylated product and not one of the other possible isomers (**149-150**)



(145)



(149)

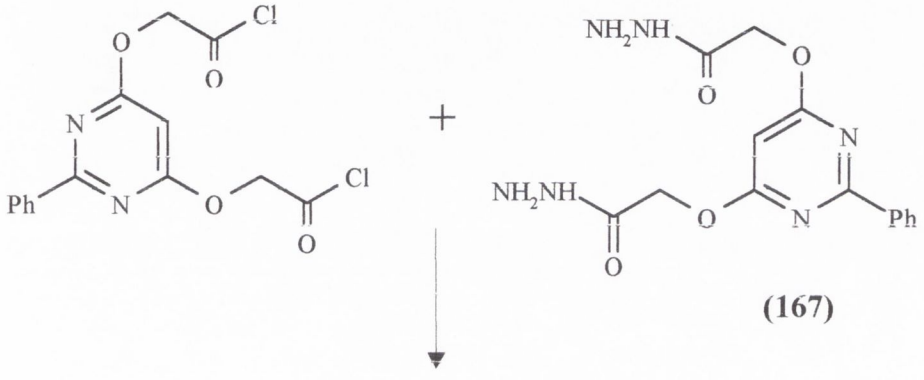


(150)

This is shown by the proton NMR of (**145**), which showed a single side chain containing methylene and ethyl group protons at the same chemical shift as those for the disubstituted product (**144**). The side chain must therefore be located on the oxygen atom, ruling out the *N*-substituted derivative (**149**). The IR spectrum of (**145**) shows a peak due to a lactam carbonyl at 1654 cm^{-1}, ruling out the isomeric structure (**150**).

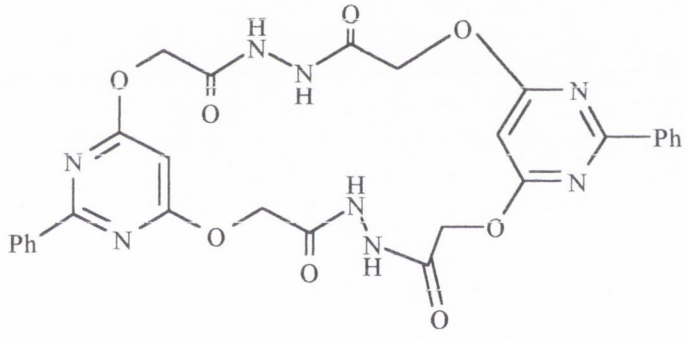
Thus, it was demonstrated that alkylation of oxopyrimidines with alkyl halides may proceed readily on oxygen to give the corresponding alkoxypyrimidines. This route to alkoxypyrimidines is convenient and complementary to other common routes, such as nucleophilic replacement of chlorine by alkoxide ion in 2-, 4-, or 6-chloropyrimidines.

As described later, the diester product (**144**) can be converted into a diacid and various diamides including its dihydrazide (**167**), which offers itself as a potentially useful starting material for the synthesis of a macrocycle such as (**151**). These latter compounds are important in host guest chemistry.[72]

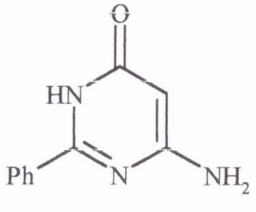


(167)

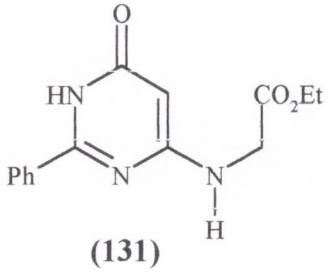
(151)



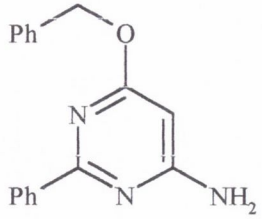
The preceding section had shown clearly that it was not possible to alkylate 6-amino-2-phenyl-4(3*H*)-pyrimidinone (**130**) on the exocyclic nitrogen to give 6-ethoxycarbonylmethylamino-2-phenyl-4(3*H*)pyrimidinone (**131**).



(130)



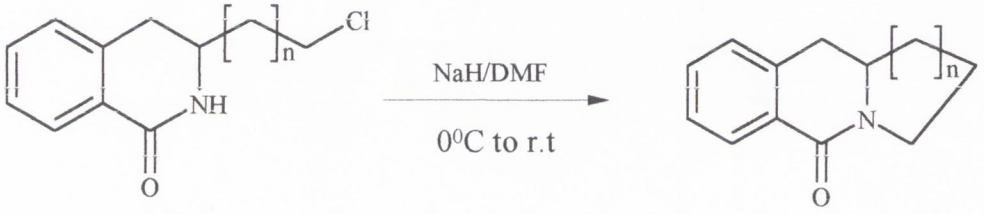
(131)



(141)

Attention was therefore turned to the possibility of alkylating the 4-amino-6-

alkoxypyrimidines (**140-142**) with an α-bromo ester. For example, the amino group in (**141**) should now be free to exert its nucleophilic power on the α-bromo ester. However, it is known that aminopyrimidines are not especially nucleophilic due to the increased electron deficiency of the pyrimidine ring compared to benzene. The question then posed was whether the nucleophilicity of this amino group could be increased. In a recent paper by Fisher,[56] it was shown that an intramolecular cyclisation could take place when an alkyl halide is reacted with the anion created from deprotonation of an amide. Thus the following transformation was achieved.

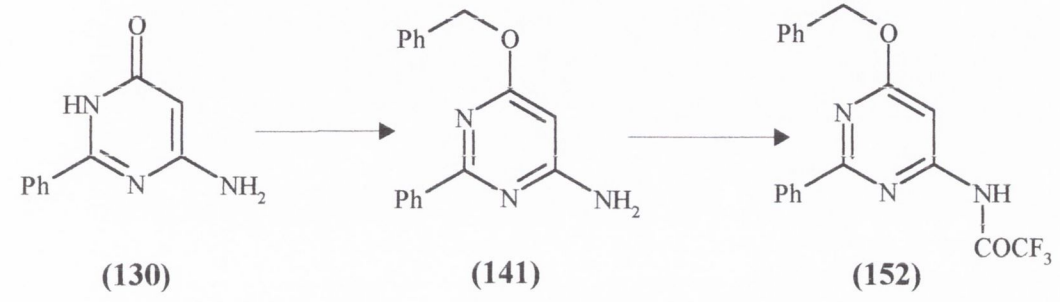


n = 1 or 2

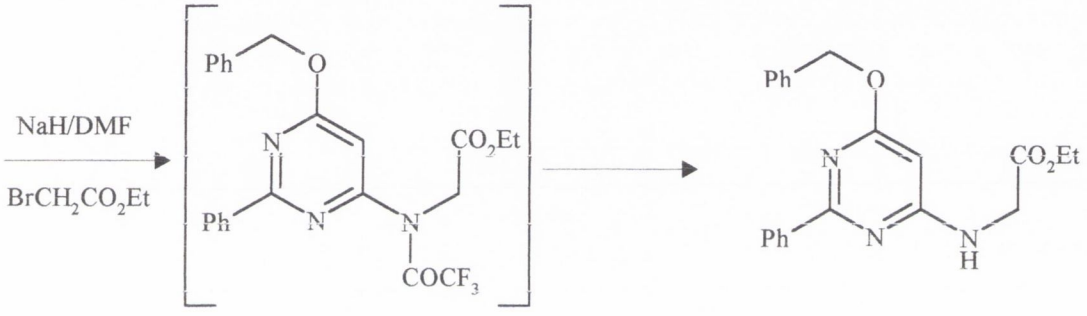
It was decided to adapt this methology to an intermolecular reaction in the pyrimidine series. Having provided the oxygen atom with the necessary protection, the next step was to convert (**141**) into an amide. The trifluoracetamido product was synthesised by refluxing (**141**) in trifluoroacetic anhydride to give 4-benzyloxy-6-trifluoroacetamido-2-phenylpyrimidine (**152**). It was hoped that the strongly electron attracting trifluoroacetyl group would increase the acidity of the amido proton in (**152**), and hence, aid its removal by base to give an anion. This anion, when generated could possibly be made to react intermolecularly with ethyl bromoacetate to give 4-benzyloxy-6-ethoxycarbonylmethyl-*N*-trifluoroacetylamino-2-phenylpyrimidine (**153**). The trifluoroacetyl group could then be removed to give the desired product, 4-benzyloxy-6-ethoxycarbonylmethylamino-2-phenylpyrimidine (**154**).

Thus refluxing (**152**) in DMF with a large excess of NaH containing ethylbromoacetate for 1 day lead to the complete disappearance of the starting material (TLC). The product, which was isolated in low yield, was shown to be that in which both substitution and deprotection had occurred simultaneously to give (**154**). This result was obtained late in the research and was therefore not exploited fully. It

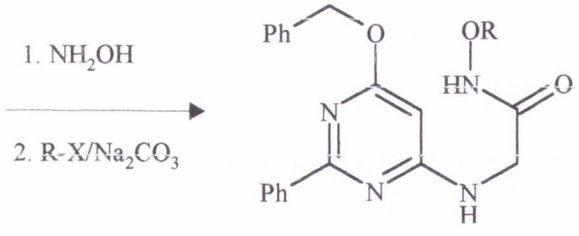
demonstrates however, that the required molecular structure can be constructed directly from simple starting materials and reactions. It should be possible in future studies to use (**154**) to synthesise a possible nitrenium ion precursor such as (**155**).



(130) **(141)** **(152)**

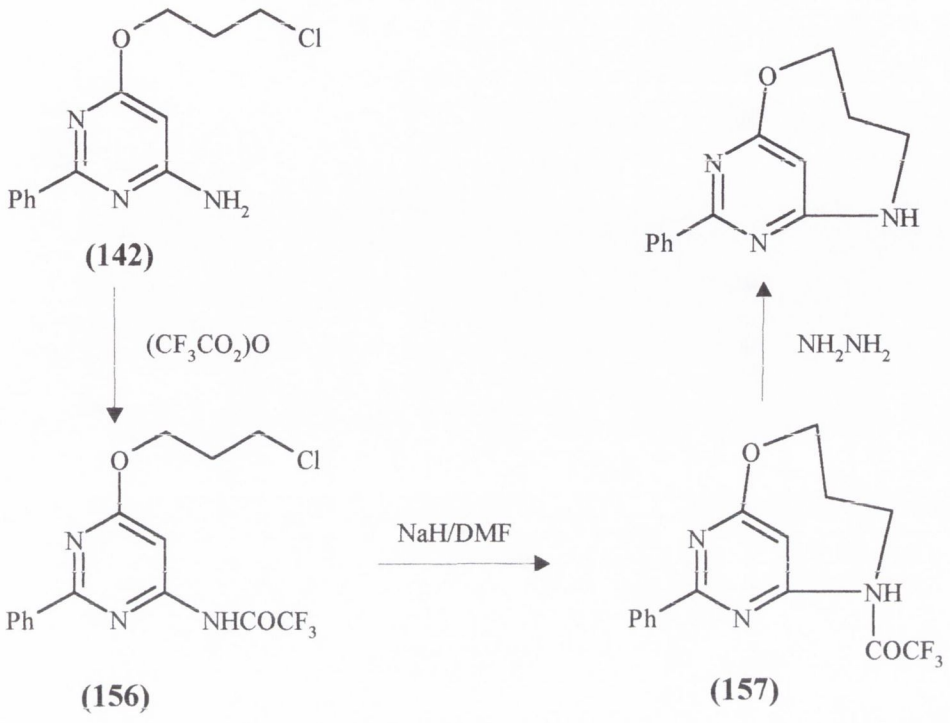


(153) **(154)**



(155)

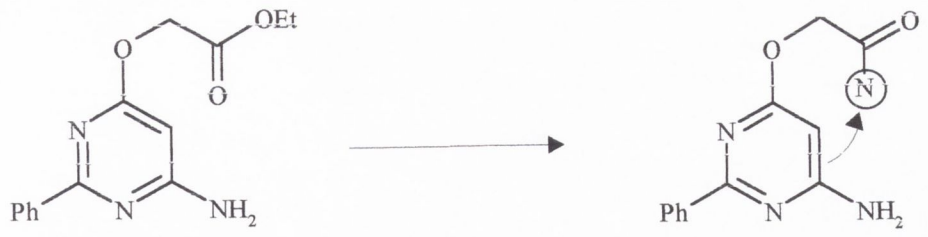
In addition to this type of reaction, it might also be possible to carry out intramolecular reactions of the type conducted by Fischer *et al.*[56] For example, the previously synthesised product 4-amino-6-(3-chloropropoxy)-2-phenylpyrimidine (**142**) was easily converted into the acylamino derivative 4-(3-chloropropoxy)-6-trifluoroacetamido-2-phenylpyrimidine (**156**). This could then be deprotonated and cyclised to give the product (**157**). The cyclisation reaction was however not tried.



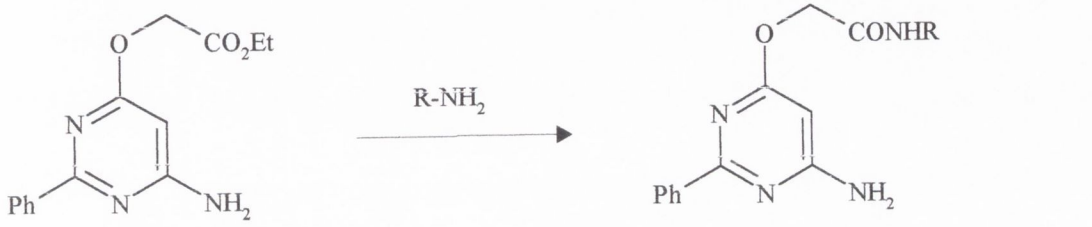
2.2 Reactions starting from 4-amino-6-ethoxycarbonylmethoxy-2-phenylpyrimidine (132) and 4,6-di(ethoxycarbonylmethoxy)-2-phenylpyrimidine (144)

The products from the alkylation of (**130**) and (**143**) were earlier shown to be (**132**) and (**144**)/(**145**) respectively. (**132**) and (**144**) were investigated further to see if they might lead to, as in the case of (**132**), an electrophilic nitrogen species such as (**158**). In the case of product (**145**), no further manipulations were carried out, because of the difficulty of preparing sufficient quantities of (**145**).

Thus, the ester groups in (**132**) and (**144**) were readily converted into the corresponding amides. This transformation was achieved by stirring a solution of the ester in ethanol with the appropriate amine at room temperature overnight. The solid products, which precipitated from the reaction mixture, were filtered and dried to give the amides (**159-168**) in good yield and purity.

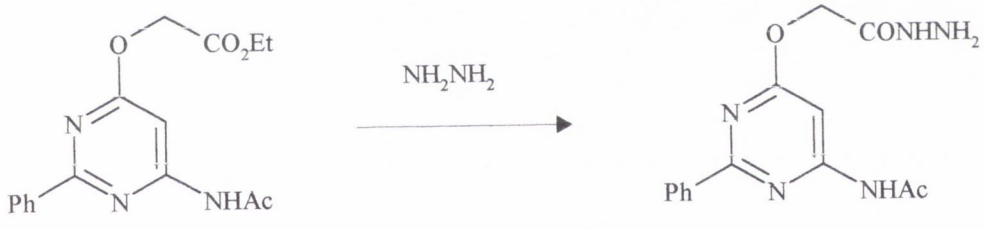


(132) **(158)**

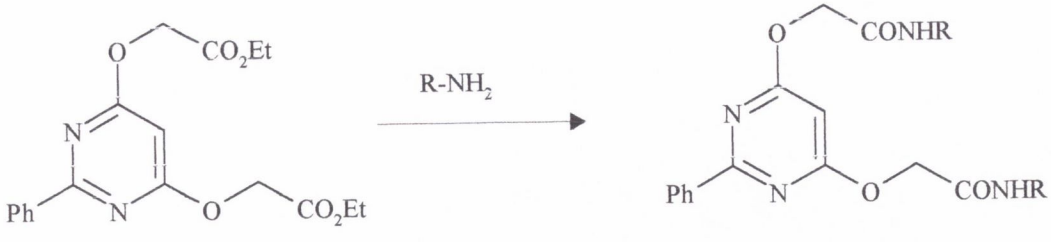


(132)

(159) R = H, **(162)** R =i-Pr
(160) R = NH_2 **(165)** R = CH_2CH_2OH
(161) R – Pr



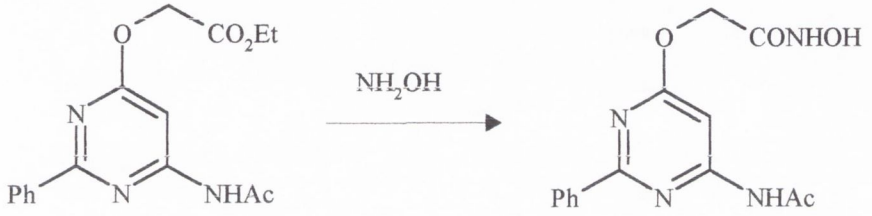
(171) **(163)**



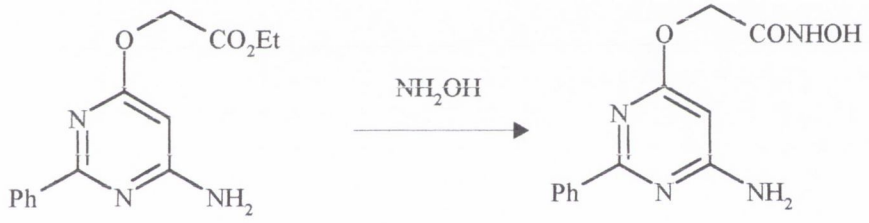
(144)

(167) R = NH_2
(168) R = CH_2CH_2OH

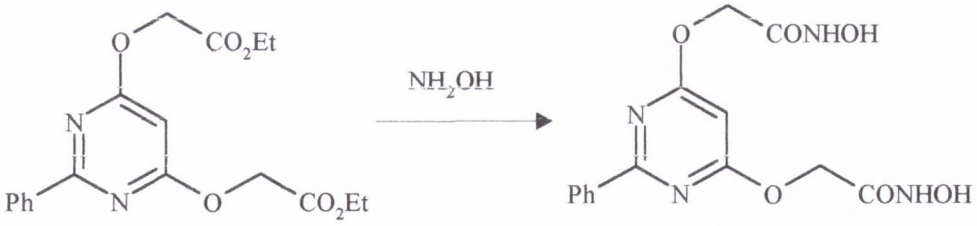
(**132**) was also converted into the hydroxamic acids 4-amino-6-*N*-hydroxycarbamoyl methoxy-2-phenylpyrimidine (**169**) and 4-acetamido-6-*N*-hydroxycarbamoylmethoxy-2-pyrimidine (**172**). (**172**) was made by acetylation of (**132**) to give (**171**), followed by conversion to (**172**) using the method to be described shortly. (**144**) was converted into the dihydroxamic acid 4,6-di(*N*-hydroxycarbamoylmethoxy)-2-phenylpyrimidine (**170**)



(171) **(172)**



(132) **(169)**



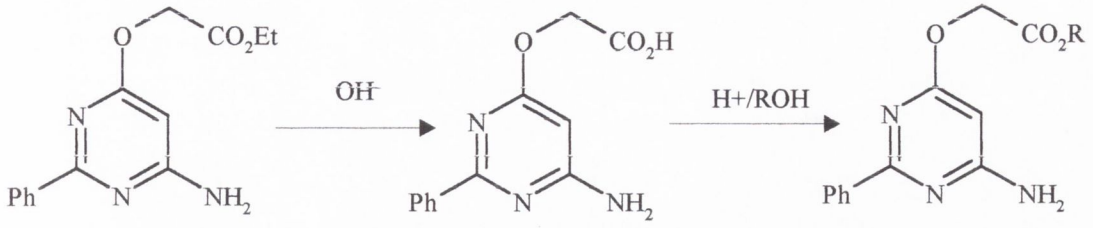
(144) **(170)**

Molecules containing the hydroxamic acid moiety have been shown to have important biological activities.[73-76]. A series of dicarbohydroxamic acids have been investigated for their anti-malarial activity.[77] In addition, hydroxamic acids constitute the initial starting material for the Lossen rearrangement, which uses an *O*-acyl

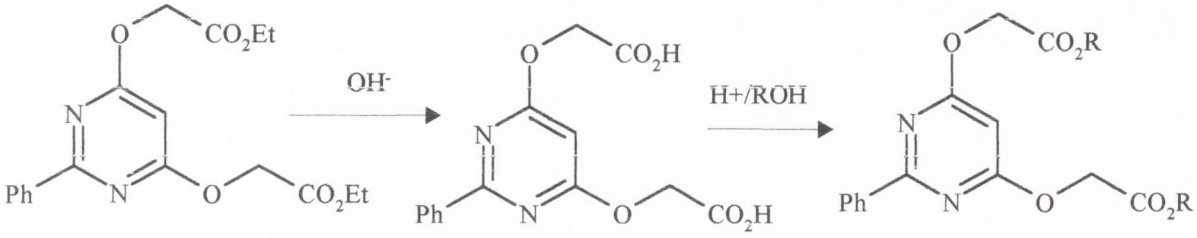
hydroxamic acid ester[78, 79] or alternatively, in the so called 'amide modification', the free hydroxamic acid together with formamide.[80, 81] In the Lossen rearrangement the product is an isocyanate, which can undergo further reaction.

Esters are normally converted into the corresponding hydroxamic acids by treatment with hydroxylamine hydrochloride in the presence of sodium hydroxide. This method did not prove to be of use in the present pyrimidine series. When (**132**) was allowed to react under these conditions, several products were formed. One of these might well have been the acid, formed by hydrolysis. The reaction also appeared to be temperature dependent with temperatures greater than 0^0C, leading to the formation of the unwanted side products. After several experiments, the best procedure was found to involve treating a solution of the ester (**132**) in EtOH at 0^0C with a solution of excess free hydroxylamine in ethanol. The reaction was then initiated by adding sodium ethoxide in EtOH. The progress of the reaction was followed carefully (TLC) to show the exact time at which all of the ester had been consumed. The overall reaction time was found to be important and was also dependent on the substrate used. Extended reaction times led to the formation of an unwanted by-product, which did not give a positive $FeCl_3$ test as strong as for the hydroxamic acid. The preparation and reactions of derivatives of the hydroxamic acids prepared will be discussed later.

The α-alkoxy esters (**132**) and (**144**) also underwent additional reactions on the side chain. For example, treatment of 4-amino-6-ethoxycarbonylmethoxy-2-phenylpyrimidine (**132**) with NaOH solution for 2 hours gave the corresponding acid, 4-amino-6-carboxymethoxy-2-phenylpyrimidine (**173**). Likewise (**144**), under similar conditions, gave the diacid product (**174**). The work up of these hydrolysis reactions involved precipitation of the product by acidification with HCl. When (**132**) was the substrate, it was necessary to ensure that the pH did not drop below 4-5, as this resulted in the formation of the hydrochloride salt of the 4-amino group in (**173**). The resulting acids were easily reconverted back to the ethyl (or any other) esters by acid catalysed esterification. Specifically the propyl esters (**175**) and (**176**) were prepared.

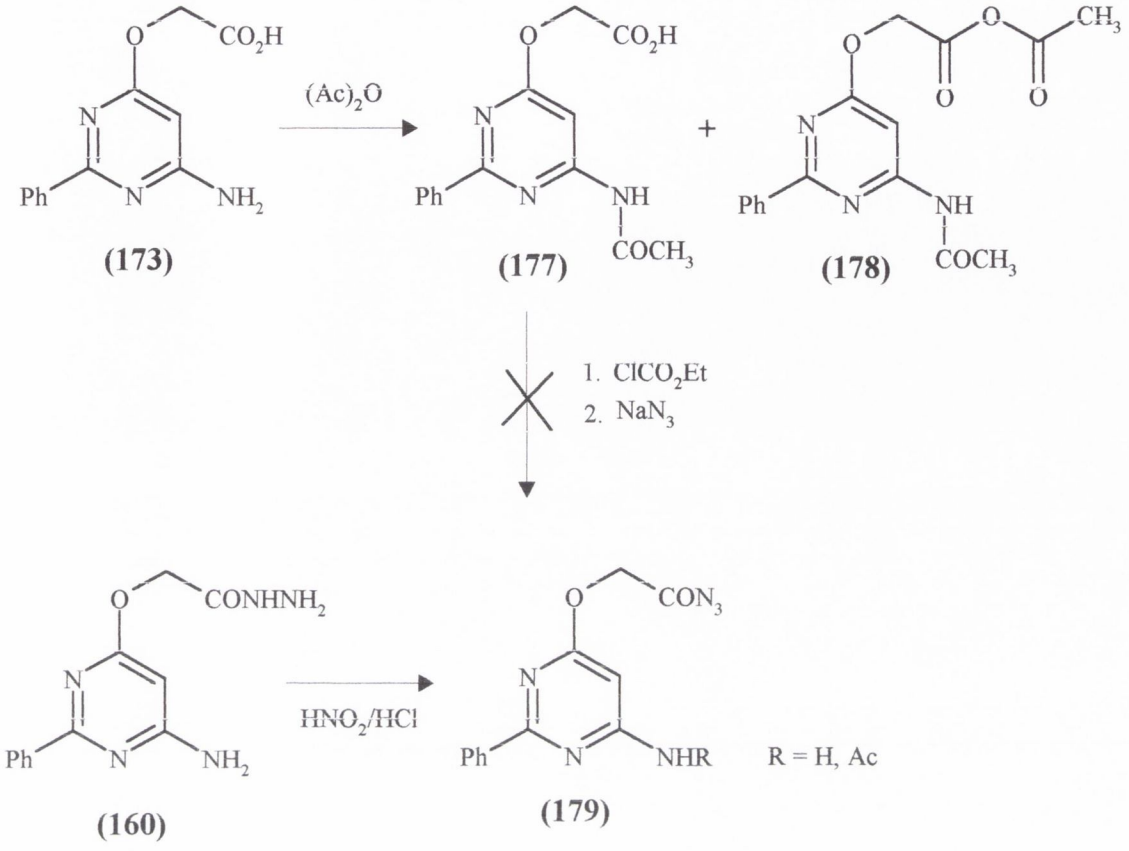


(132) **(173)** **(175)** R = $CH_2CH_2CH_3$



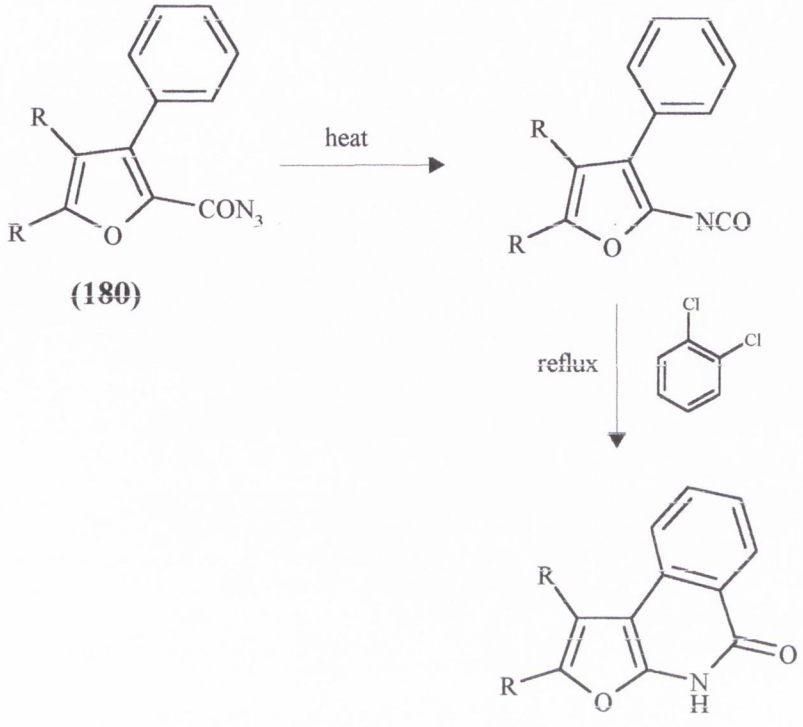
(144) **(174)** **(176)** R = $CH_2CH_2CH_3$

Carboxylic acids are versatile functional groups, which can be converted to potential sources of electrophilic nitrogen species, *e.g.* azides. A method has been found[82], which converts acids into azides in a one-pot procedure. This method involved the initial conversion of an acid into a mixed anhydride by reaction with ethyl chloroformate, followed by, *in situ*, reaction of the anhydride with sodium azide. It was hoped that the pyrimidine azide (**179**) could be produced following this procedure. The starting acid (**173**) was, however, insoluble in common solvents, including DMSO (the literature procedure used aqueous acetone). In addition to this the 4-amino group of (**173**) can react with ethyl chloroformate to give the corresponding urethane derivative. Accordingly, the 4-amino group in compound (**173**) was acetylated with acetic anhydride, when a mixture of two products was formed which were separated by flash chromatography. Spectroscopic analysis of these products showed them to be the required 4-acetamido-6-carboxymethoxy-2-phenylpyrimidine (**177**) (30%) and the mixed anhydride 4-acetamido-6-(2,4-dioxopentoxy)-2-phenylpyrimidine (**178**) (70%). The acid (**177**), when reacted with Ac_2O under the same conditions gave the anhydride (**178**).



Unfortunately, however, attempts to convert (**177**) into the corresponding azide (**179**), using the chloroformate method, [82]gave no useful products.

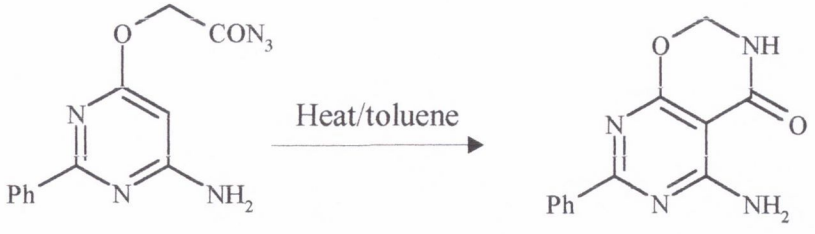
The crude azide (**179**) was prepared successfully by treatment of the hydrazide (**160**) with nitrous acid. This method has been reviewed[83] and has also been shown to work in the pyrimidine series,[84] including uracils[85]. A problem here is that treatment of (**160**) with nitrous acid may lead to nitrosation at the 5-position. In order to minimise this, a low temperature (0^0C) was used in the nitrous acid treatment of (**160**) to give the crude azide (**179**). The IR spectrum of the product showed a band at 2140 cm^{-1} due to the $-N_3$ group. Intramolecular cyclisation of acyl azides unto a benzene ring has been demonstrated in the literature. The reaction, which proceeds *via* an intermediate isocyanate, is essentially a Curtius reaction, and an example is shown in the conversion of (**180**) into (**181**).[86, 87]



(180)

(181)

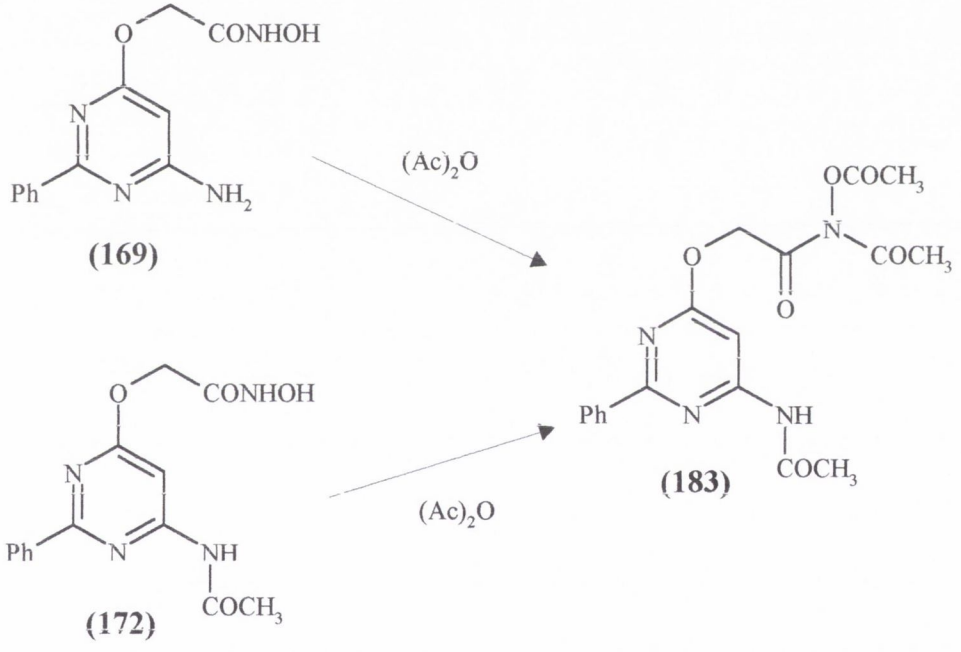
When the crude azide (**179**) was refluxed in toluene, a yellow precipitate formed. This product was not pure (TLC) and at present very little is known about it, except to mention that the IR spectrum of this compound does not contain an azide peak or an isocyanate peak. It could therefore be the cyclised amide (**182**). No photochemical reactions have been conducted on the crude azide.



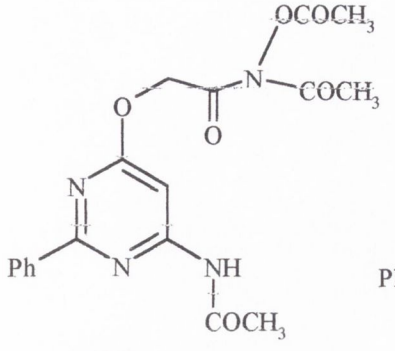
(179) **(182)**

2.3. Preparation of derivatives of pyrimidine hydroxamic acids

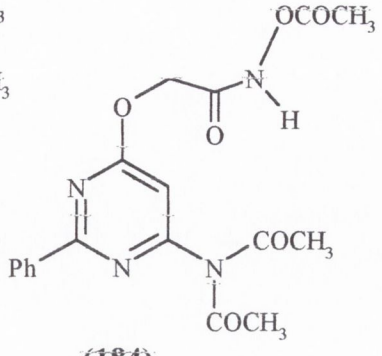
Acetylation experiments were carried out on the hydroxamic acids (**169**), (**170**) and (**172**) in an attempt to synthesise the required *O*-acetyl hydroxamates, similar to those used by Cherest and co-workers.[27] Thus, refluxing 4-amino-6-*N*-hydroxycarbamoyl-methoxy-2-phenylpyrimidine (**169**) in acetic anhydride gave a single product, which was shown to be 4-acetamido-6-*N*-acetoxy-*N*-acetylcarbamoylmethoxy-2-phenylpyrimidine (**183**). The same compound (**183**) was also obtained by treating 4-acetamido-6-*N*-hydroxycarbamoylmethoxy-2-phenylpyrimidine (**172**) with refluxing Ac_2O.



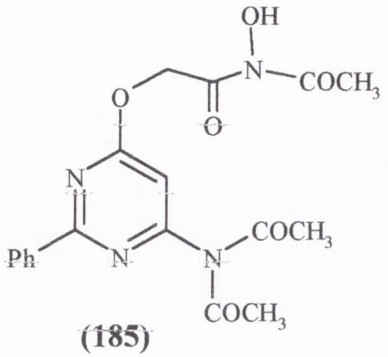
The assignment of structure (**183**) to this product was made with reference to the following facts. The proton NMR spectrum showed the presence of three methyl groups, as expected for a compound such as the 'triacetate' (**183**). In theory there are three possible structures for such a triacetate product. Firstly there is the proposed structure (**183**), and then there are the two isomeric 4-*N*,*N*-diacetamido products, in which either *O*- (**184**) or *N*-acetylation (**185**) has occurred at the hydroxamic acid portion of the molecule.



(183)



(184)



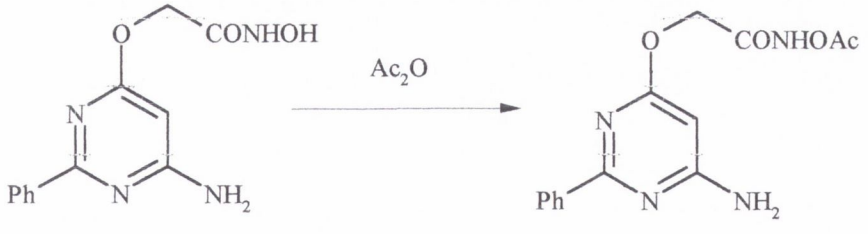
(185)

The product was shown to be (**183**) by looking at the NMR data of this, and other related pyrimidines. For example, proton NMR of the hydroxamic acid 4-acetamido-6-*N*-hydroxycarbonylmethoxy-2-phenylpyrimidine (**172**) shows a single, exchangeable, one proton signal at 7.8 ppm, due to the 4-amido proton. This peak at 7.8 ppm also appears in the proton NMR spectrum of the triacetate (**183**). This is evidence for the presence of a 4-acetamido group in both (**172**) and (**183**). Thus, the alternative isomeric structures (**184**) and (**184**) are ruled out. This triacetate product (**183**) was an unusually electrostatic compound. The proton NMR spectrum of (**183**) also showed that the side chain methylene protons are split into a doublet, which is unlike any of the related pyrimidines so far encountered, all of which show a singlet for these protons. A possible explanation for this might be geminal coupling between the methylene protons, which consequently do not come into resonance at the same frequency. The observation of a classic AB coupling signal in the spectrum of (**183**) is evidence for this theory.

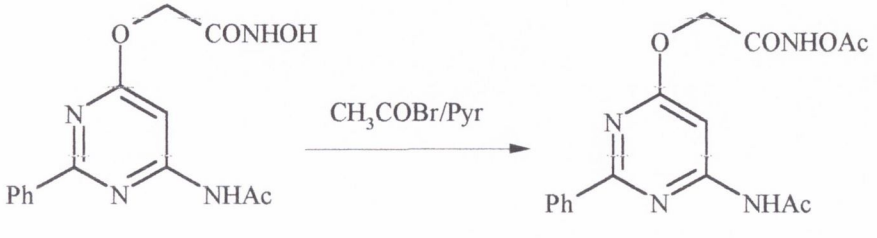
The actual class of compound, which was required, namely an *O*-acetylated hydroxamic acid, could not be obtained easily. Acetylation with acetic anhydride proceeded readily beyond this stage, directly to the triacetate product (**183**). It was noticed however, (tlc) that the production of the triacetate (**183**) proceeded *via* one or more intermediate products, possibly mono and diacetates. By quenching the reaction in the early stages and isolating a mixture, it was possible to separate and chromatographically purify a sample of one of the transient products, 4-amino-6-*N*-acetoxycarbomylmethoxy-2-phenylpyrimidine (**186**), or 'monoacetate.' Acetylation must therefore, initially occur at oxygen rather than either of the nitrogen atoms, as (**186**)

is by far the most abundant intermediate detectable. This method, although satisfactory was not an efficient route to the desired product.

An alternative strategy for the synthesis of an *O*-acetylated hydroxamic acid was to start from 4-acetamido-6-*N*-hydroxycarbamoylmethoxy-2-phenylpyrimidine (**172**) and attempt a controlled acetylation using acetyl bromide. In fact the *O*-acetylated hydroxamic acid 4-acetamido-6-*N*-acetoxycarbamoylmethoxy-2-phenylpyrimidine (**187**) or 'diacetate' was eventually isolated in reasonable yield using (**172**) in pyridine and acetyl bromide. This procedure employed 1 mole of starting material and 1 mole of acetyl bromide in excess pyridine as solvent. Although, it was obviously quicker than the anhydride method in that it avoided the chromatographic separation, it was not without problems. Even when a 1/1 molar ratio of reactants was used there was still some contamination of the product with the triacetate product (**183**). On other occasions, despite long reaction times, there was still starting material contamination of the organic extract. On account of the difficulty in obtaining sufficient quantities of the mono acetate (**186**) and the diacetate (**187**), it was decided initially to test the reactivity of the triacetate product (**183**) under the conditions of the iron catalysed cyclisation.

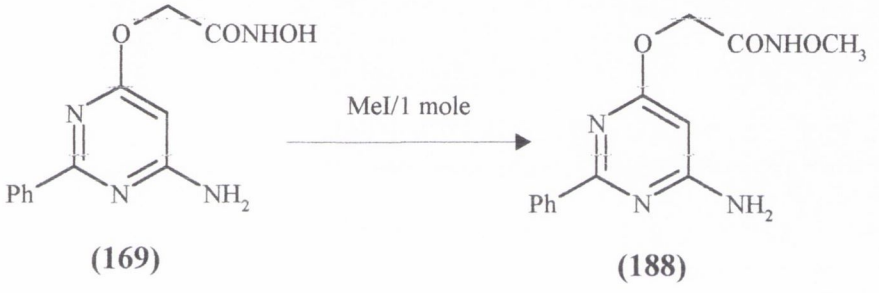


(169) **(186)**

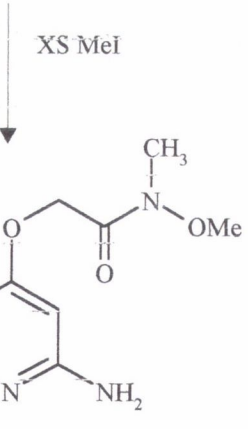


(172) **(187)**

The other desired class of compound was an *O*-methyl ether of a hydroxamic acid. This was obtained, for example, from the methylation of 4-amino-6-*N*-hydroxycarbamoyl-2-phenylpyrimidine (**169**) using either methyl iodide or dimethyl sulphate. Thus, treatment of (**169**) with 1 mole equivalent of methyl iodide gave 4-amino-6-*N*-methoxycarbamoylmethoxy-2-phenylpyrimidine (**188**). When the reaction was repeated using an excess of methyl iodide the result was a mixture of (**188**) and the dimethylated product 4-amino-6-*N*-methyl-*N*-methoxycarbamoylmethoxy-2-phenyl-pyrimidine (**189**). The *O*-methyl ether (**188**) from the previous section was also acetylated to give (**192**). The purpose of this was to ascertain if acetylated amides, other than the hydroxamates could be used to form cyclised products.

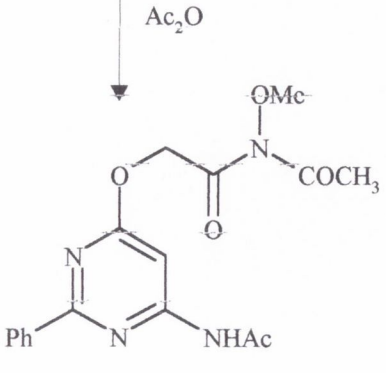


(169) **(188)**



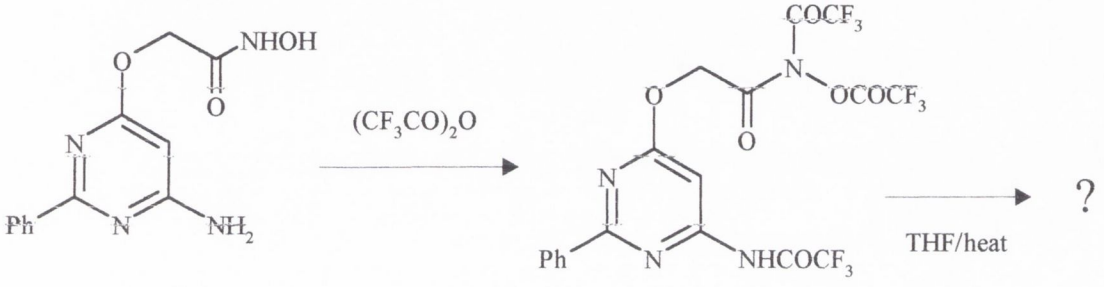
(189)

\+ **(188)**



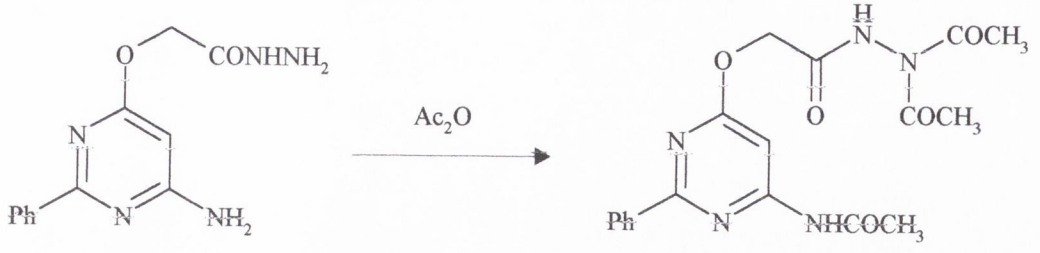
(192)

The hydroxamic acid 4-amino-6-*N*-hydroxycarbamoyl-2-phenylpyrimidine (**169**), when refluxed with trifluoroacetic anhydride gave a bright yellow compound, which reacts when heated in any solvent to give a crude, (TLC) colourless product, which as yet remains unidentified. The initially formed yellow product is presumably the "tris-trifluoroacetate" (**190**), which reacts thermally to give the stable product.

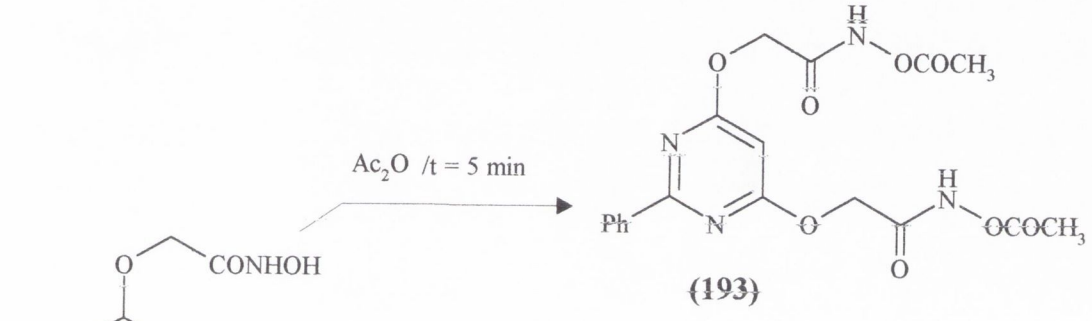


(169) **(190)**

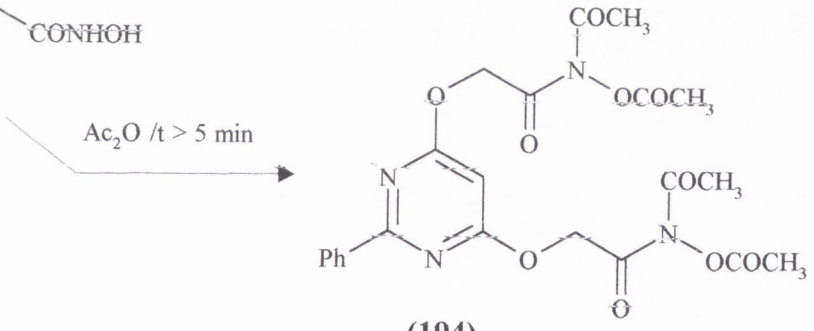
Acetylation of the hydrazide 4-amino-6-*N*-aminocarbamoylmethoxy-2-phenylpyrimidine (**160**) was also carried out. The product from this acetylation was shown to be 4-acetamido-6-N^2,N^2diacetylhydrazinomethoxy-2-phenylpyrimidine (**191**). The dihydroxamic acid (**170**) was also acetylated to give either a di or tetraacetylated product depending on the conditions used. For example, when 4,6-di(*N*-hydroxycarbamoylmethoxy)-2-phenylpyrimidine (**170**) was treated with Ac_2O for 5 min, the diacetate 4,6-di(-*N*-acetoxycarbamoylmethoxy)-2-phenylpyrimidine (**193**) was formed. When the reaction was allowed to proceed beyond 5 min, then the tetraacetate 4,6-di(*N*-acetyl-*N*-acetoxycarbamoylmethoxy-2-phenylpyrimidine (**194**), was formed. This tetraacetate product (**194**) had similar characteristics to the triacetate, (**183**) for example, they are both electrostatic solids and both show the geminal coupling for the side chain methylene groups. In addition to this, the dihydrazide (**167**) was also converted into the diacetate (**195**). It is not known why acetylation of a hydrazide moiety in (**160**) and (**167**) produce different classes of products (**191**) and (**195**) respectively.



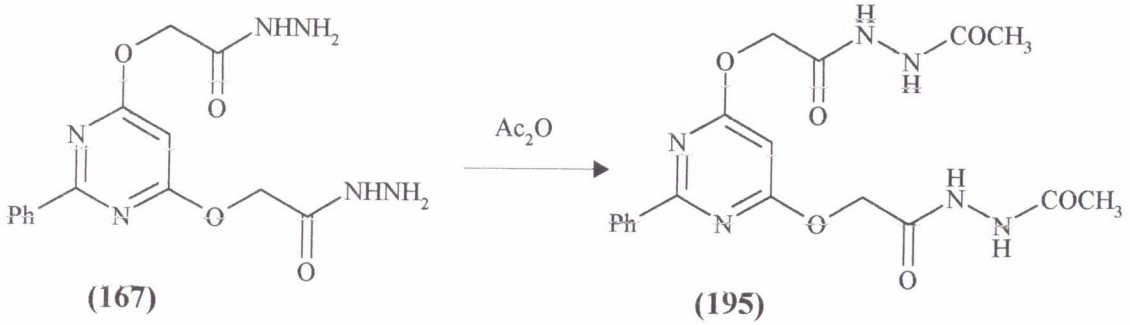
(160) **(191)**



(170) **(193)**



(194)

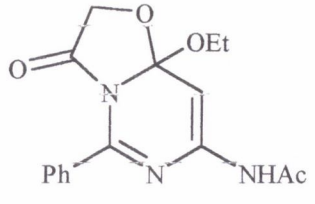


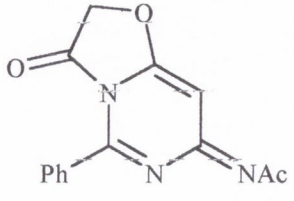
(167) **(195)**

2.4. Iron(III) chloride catalysed reactions of derivatives of pyrimidine hydroxamic acids

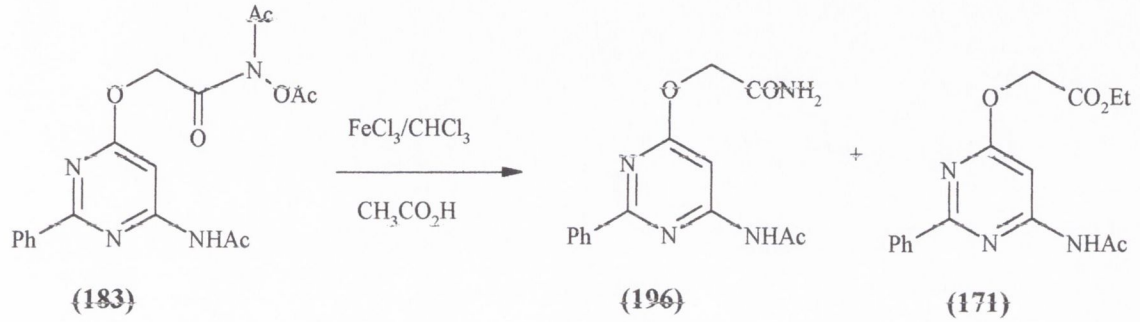
These reactions were conducted according to the conditions employed by Cherest and co-workers.[27] This involved treating 1 mole equivalent of the substrate with 1 mole of acetic acid and 2 moles of $FeCl_3$ in $CHCl_3$ or THF. The closest molecular structures to those used by Cherest were the monoacetate and diacetate, (**186**) and (**187**) respectively. The triacetate (**183**) was more extensively studied, however, due to the easier availability of this compound.

When triacetate (**183**) was reacted with $FeCl_3$ under the above conditions in chloroform, 4-acetamido-6-ethoxycarbonylmethoxy-2-phenylpyrimidine (**171**) was obtained as the major product together with 4-acetamido-6-carbamoylmethoxy-2-phenylpyrimidine (**196**). This was an unexpected result and one without an immediately obvious explanation. The presence of an ethyl group in the main product was difficult to explain. The only possible explanation was that it originated from the $CHCl_3$ used as solvent. Since ethanol is known to be present in $CHCl_3$ as a stabiliser against the accumulation of phosgene, this was plausible. When (**183**) was reacted as before with $FeCl_3$ in THF with added ethanol, the ester (**171**) was again formed. This confirmed that ethanol had been the source of the ethyl group when the reaction had been done in $CHCl_3$. In addition, the corresponding propyl ester was formed when (**183**) was treated with $FeCl_3$/THF with added propanol. Initially it was thought that a cyclisation reaction had occurred, although not at the 5-position as desired (both products clearly contained the same 5-CH in their NMR spectra as had been observed for earlier products). The following structures were initially proposed for the products.

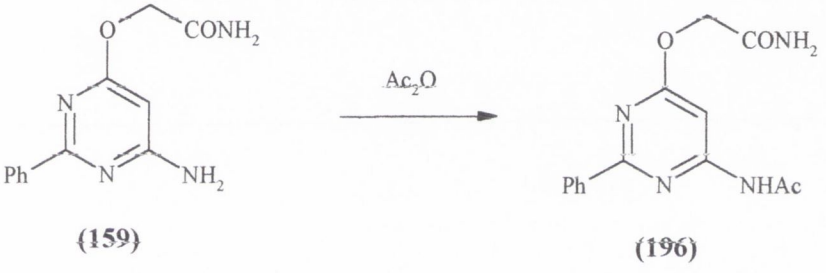




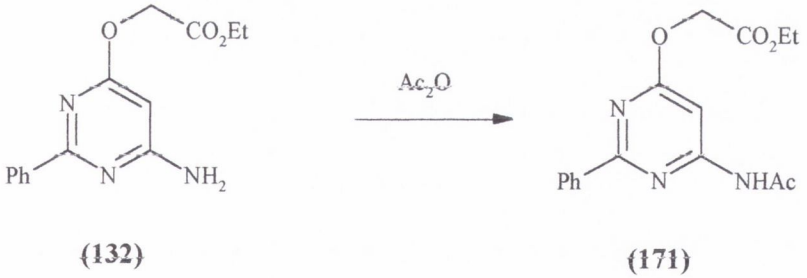
However, upon closer inspection of all of the available data and by comparison of the products with authentic samples of (**171**) and (**196**), it was clear that the products obtained were, in fact, compounds (**171**) and (**196**). The authentic samples of (**171**) and (**196**) were made by acetylation of the 4-amino derivatives (**132**) and (**159**).



(**183**) (**196**) (**171**)



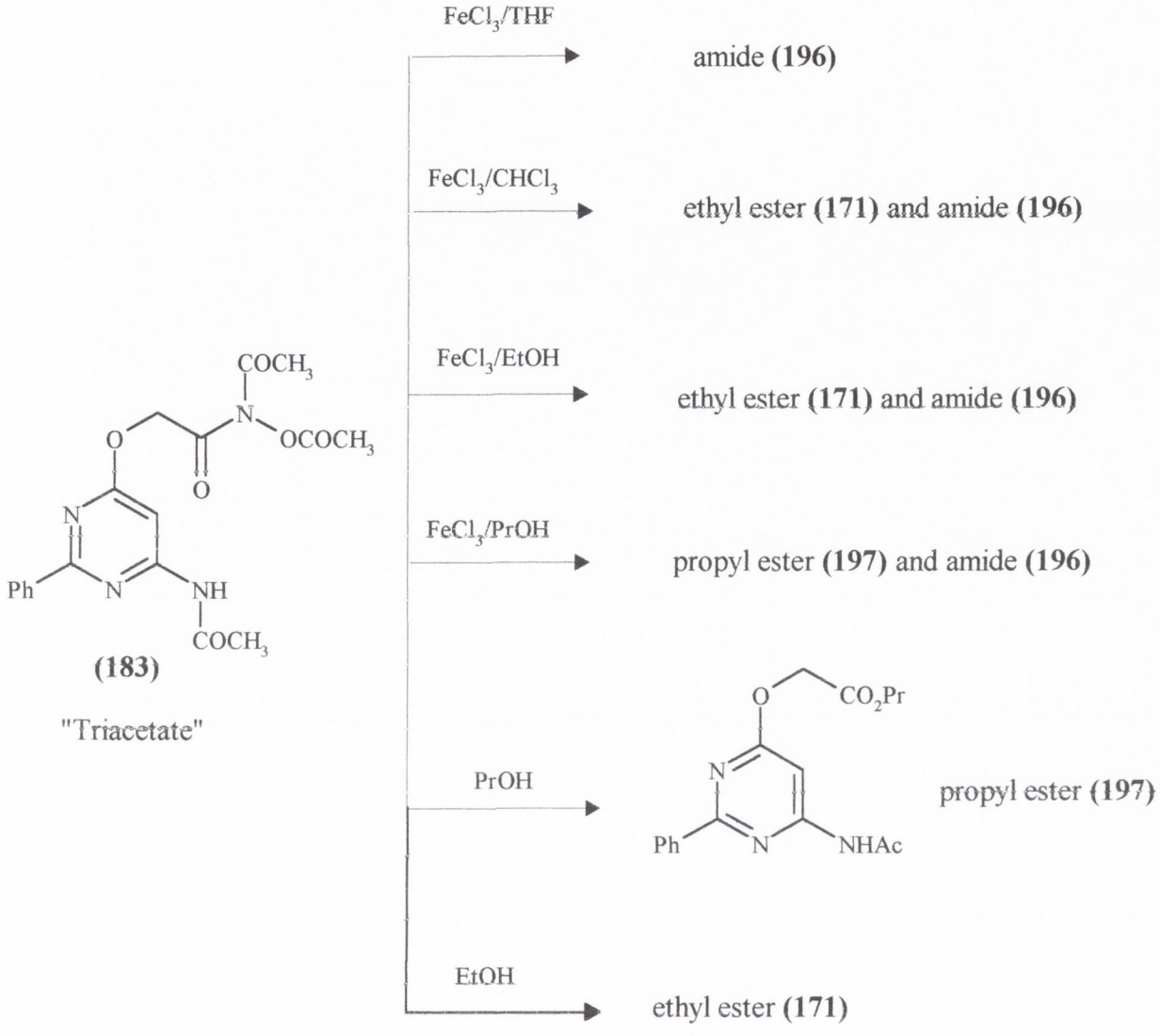
(**159**) (**196**)



(**132**) (**171**)

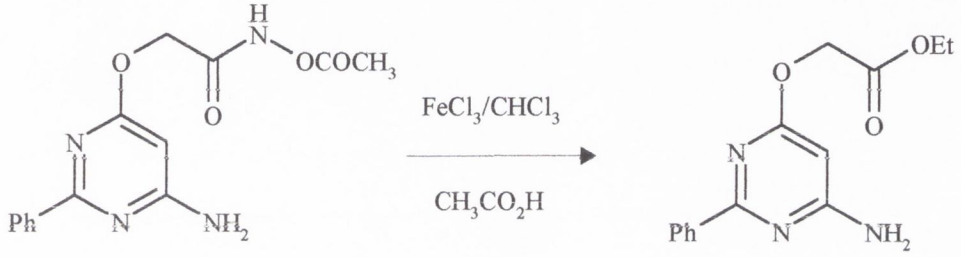
This result showed that the triacetate (**183**) undergoes ethanolysis to form an ethyl ester and also undergoes reduction to form a primary amide. A feature of the reaction is the low yields of both products. It is likely that hydrolysis to the hydroxamic acid and/or the carboxylic acid are significant side reactions with these being removed in the weakly basic aqueous work up. The formation of an amide from an *O*-acetylhydroxamic acid and $FeCl_3$ had previously been observed by Demuynck[57] and Cherest in a follow up paper to Cherest's earlier work.[27] In Demuynck's paper, an *O*-acetylhydroxamate was treated

with $FeCl_3$ to give two products. The primary amide (**102**) was obtained in 16 % yield and a cyclised product (**101**) (illustrated in the introduction p 26) was also obtained in 13 % yield. Both of these products were postulated to have formed after the initial generation of a nitrenium ion. The cyclised product was formed by reaction of this ion with a nearby carbon atom, whereas the primary amide is formed by hydrogen transfer to the nitrenium ion, possibly after spin conversion to a triplet nitrenium ion. The establishment of the pyrimidine amide structure (**196**) was initially complicated by the fact that the NMR was run in d_3-MeOH, which obscured the amide and amido protons. However, when the sample was run in d_6-acetone the picture became clearer. The proton NMR also showed that the amide protons were not equivalent and appeared as two distinct singlets, due to restricted rotation about the C-N bond. When triacetate (**183**) was treated with $FeCl_3$ /CH_3CO_2H in THF, the result was the exclusive formation of the amide (**196**) This experiment confirmed the fact that formation of the ester in the earlier reaction was clearly dependant on the use of $CHCl_3$ as solvent. Thus the amide is formed by the combined action of $FeCl_3$ and CH_3CO_2H. This suggests that in the absence of alcohol, a nitrenium ion intermediate is transiently formed during the reaction, but is transformed into the primary amide by hydrogen transfer before the desired cyclisation unto the 5-position of the pyrimidine ring could take place. The nitrenium ion is clearly too short lived to undergo the desired cyclisation. In view of the results obtained by [43]Gassman, this formation of an amide may have first required that the nitrenium ion convert from an initially formed singlet, to a triplet nitrenium ion. Another possible reason for the lack of a cyclised product may be insufficient electron density at the 5 position. It was also shown that ethyl, (**171**) and propyl (**197**) esters were also produced by simply refluxing the triacetate (**183**) in either of the corresponding alcohols. These reactions occurred considerably slower than the iron catalysed alcoholysis, but nevertheless provide proof that hydroxamic acid derivatives are susceptible to direct alcoholysis.



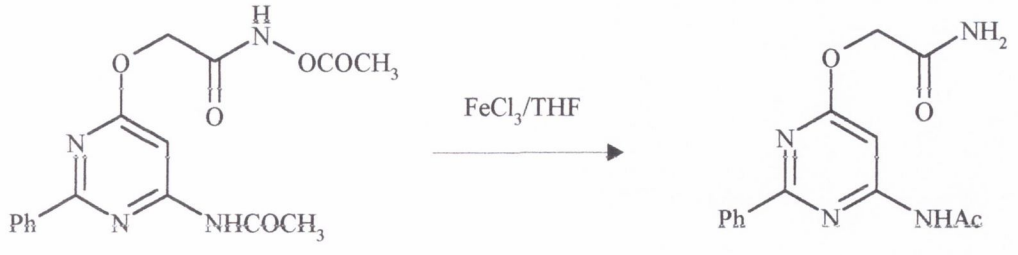
While the triacetate (**183**) gave interesting results, these were not directly comparable to the results obtained by Cherest and Demuynck.[27, 57] This is because these workers had used *O*-acetyl hydroxamic acids as the starting materials, whereas the triacetate (**183**) is both *N*- and *O*-acetylated. Attention was therefore turned to the monoacetate (**186**) and diacetate (**187**), which had also been synthesised, and which are comparable to the substrates used by the aforementioned authors. Thus treatment of 4-amino-6-*N*-acetoxycarbamoylmethoxy-2-phenylpyrimidine (**186**) with $FeCl_3/CH_3CO_2H$ in $CHCl_3$ gave 4-amino-6-ethoxycarbonylmethoxy-2-phenylpyrimidine (**132**). The amide was not isolated from this reaction. There are two possible reasons for this. The first is that the reaction was performed on a smaller scale than with the triacetate, due to the difficulty in

obtaining this substrate. Therefore, it is possible, under these circumstances (small scale), that ethanolysis is the dominant reaction. The second reason could be that the *O*-acetyl hydroxymate (**186**) is more susceptible to ethanolysis than the *O*-acetyl-*N*-acetyl derivative (**183**). The ethanolysis is therefore dependent only on the presence of an *O*-acetyl group. Unfortunately, there were insufficient quantities of this substrate to conduct further reactions in THF.



(186) **(132)**

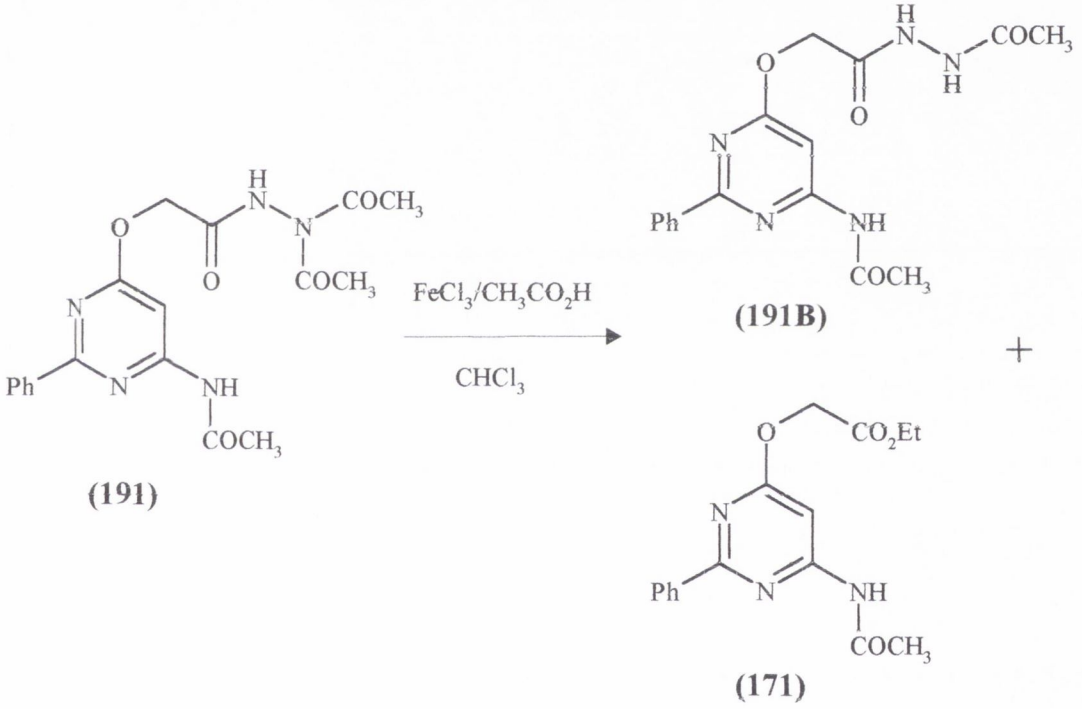
The diacetate 4-acetamido-6-*N*-acetoxycarbamoylmethoxy-2-phenylpyrimidine (**187**), was more easily available. Treatment of (**187**) with $FeCl_3/CH_3CO_2H$ in THF produced only the corresponding primary amide (**196**). This again suggests that mono and diacetylated hydroxamic acids behave similarly under the conditions employed in this reaction. It is therefore reasonable to suggest that the mechanism of the reaction of the triacetate (**183**) with $FeCl_3/CH_3CO_2H$ in THF involves initial cleavage to give the *O*-acetylated diacetate product (**187**), which then reacts *via* a nitrenium ion intermediate to give the observed amide (**196**)



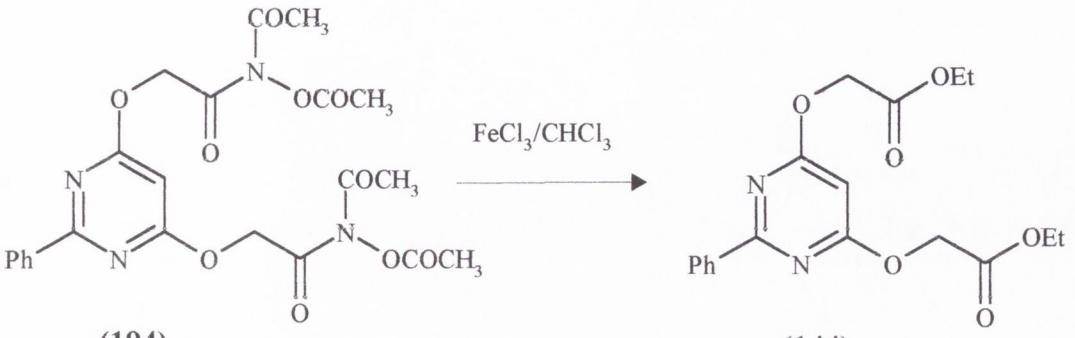
(187) **(196)**

Another substrate, which was tested under the standard conditions, was the triacetylated hydrazide 4-acetamido-6-(N^2-N^2-diacetylhydrazinomethoxy)-2-phenylpyrimidine (**191**), which was prepared by acetylation of the hydrazide (**160**)

Thus, when (**191**) was treated with $FeCl_3/CH_3CO_2H$ in $CHCl_3$, a mixture of 4-acetamido-6-(N^2-acetylhydrazinomethoxy)-2-phenylpyrimidine (**191B**) and (**171**) was produced. This reaction shows that selective removal of an acetyl group from an N^2,-N^2-diacetlyhydrazide with $FeCl_3/CH_3CO_2H$ is possible. Secondly, either (**191**) or (**191B**) are attacked by ethanol to give the corresponding ethyl ester and thus behave in a similar fashion to the acetylated hydroxamic acid derivative (**183**).

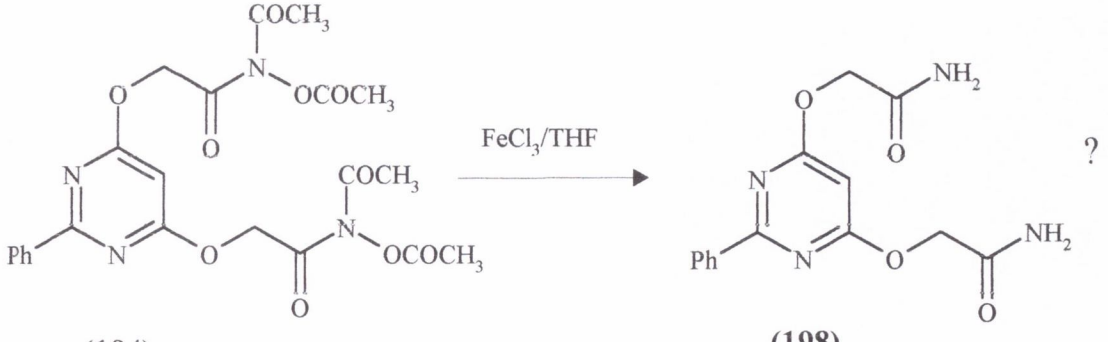


In the series of compounds, which contain two attached side chains, the simplest acetylated derivative to produce was the tetraacetate 4,6-di(*N*-acetoxy-*N*-acetylcarbamoylmethoxy)-2-phenylpyrimidine (**194**). This substrate is both *N*- and *O*-acetylated and thus resembles the earlier triacetate (**183**). When (**194**) was treated with $FeCl_3/CH_3CO_2H$ in $CHCl_3$, the result was conversion into the corresponding diethyl ester (**144**). The amide was not detected to have formed during this reaction. Again as before, the same product (**144**) can be obtained simply by refluxing the tetra acetate (**194**) with ethanol for a prolonged period.

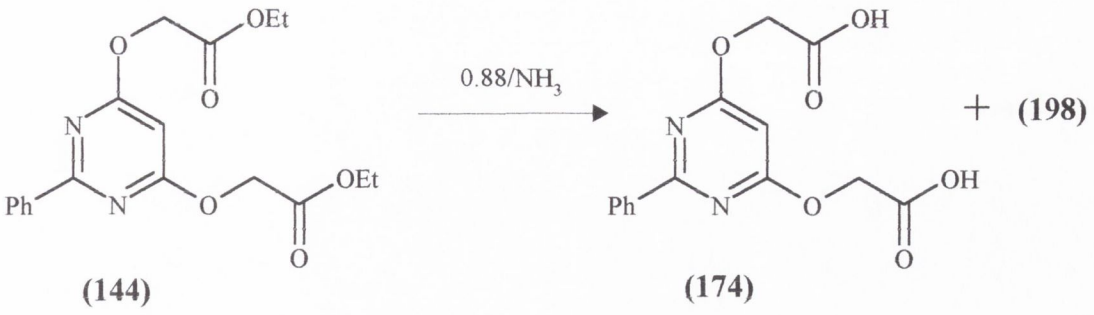


(194) **(144)**

When the tetra acetate (**194**) was treated with $FeCl_3/CH_3CO_2H$ in THF, there appeared to be a reaction taking place as shown by the disappearance of the substrate (tlc). The product being formed was not the diester (**144**), as determined by its R_f value. However, it was not possible to isolate a solid product, as it appeared to be an unstable compound. In an attempt to prepare the diamide (**198**) for (TLC) comparison purposes, the direct ammonolysis of the diester (**144**) was attempted. This reaction was performed by refluxing the diester with 0.88 NH_3 in ethanol. The reaction was surprisingly slow and after 1.5 days there was still some diester (**144**) remaining. In addition, there seemed to be two products (TLC) forming, most likely the desired diamide (**198**) and the diacid (**174**), formed by hydrolysis. It would probably be necessary to conduct the experiment in an ethanolic solution saturated with NH_3 gas in order to obtain the desired diamide (**198**) in good yield.



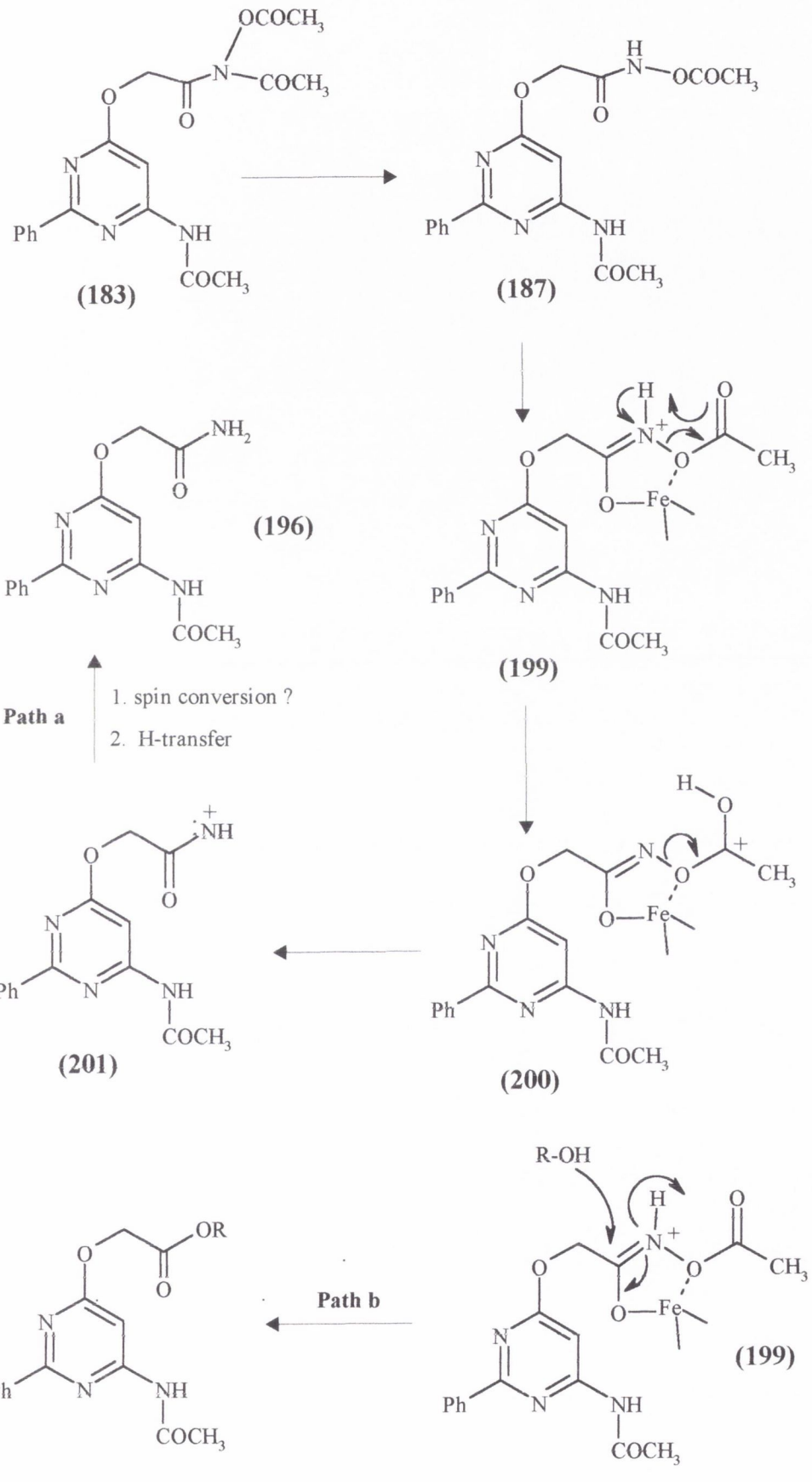
(194) **(198)**



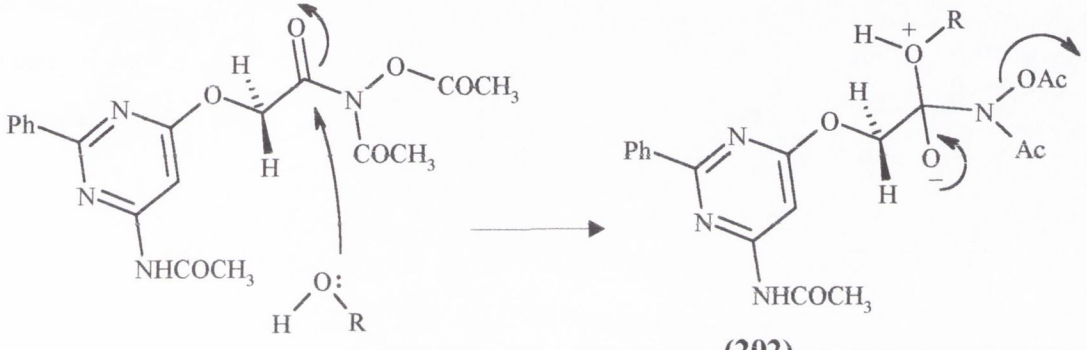
(144) (174)

2.5 The mechanism of reduction of 4-acetamido-6-(*N*-acetyl-*N*-acetoxycarbamoyl-methoxy)-2-phenylpyrimidine (183) with $FeCl_3/CH_3CO_2H$ in THF

The previous discussion of the experimental results clearly shows that the *O*-acetylated (**186**) and (**187**) and *N,O*-acetylated (**183**) hydroxamic acids react in an analogous way to give the amide (**196**) and ester (**171**) in the presence of an alcohol, or exclusively the amide (**196**) in its absence. Thus the first step in any mechanism is conversion of the *N*-acetyl-*O*-acetyloxy group into an *O*-acetyl amide. The key to the mechanism is the complexation of the substrate with the iron atom. It was shown experimentally that the triacetate substrate (**183**) undergoes ethanolysis faster in the presence of $FeCl_3$ than in neat ethanol. This also suggests that the complexation is important, and results in the carbonyl carbon becoming more electron deficient. Once hydrolysis to the diacetate (**187**) has occurred, then the mechanism follows an analogous pathway to that proposed by Cherest[27]. Iron complexation through the enol form (**199**) makes the amidic proton much more acidic. The acetoxy group is then protonated intramolecularly by the amidic proton to provide a good leaving group as in (**200**). Removal of the acetoxy group leaves a nitrenium ion (**201**), which then reacts by hydrogen transfer (**path a**). In the presence of alcohol the iron/enol complex (**199**) is attacked at the carbonyl carbon to give the ester (**171**) (**path b**).


(183)
(187)
(196)
(199)
Path a
1. spin conversion ?
2. H-transfer
(201)
(200)
R-OH
Path b
(199)

The mechanism of direct ethanolysis of the triacetate (**183**) can be explained with reference to the structure of (**183**). The carbonyl carbon atom in (**183**) has increased electrophilicity and is susceptible to attack by a nucleophile such as alcohol to give the intermediate (**202**), in which the acetylated hydroxylamine derivative can act as a leaving group to furnish the product (**171**) directly. Complexation with the iron atom increases the rate of ethanolysis



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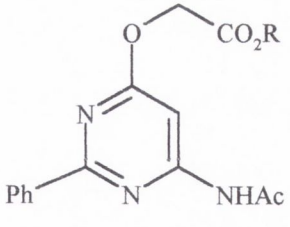
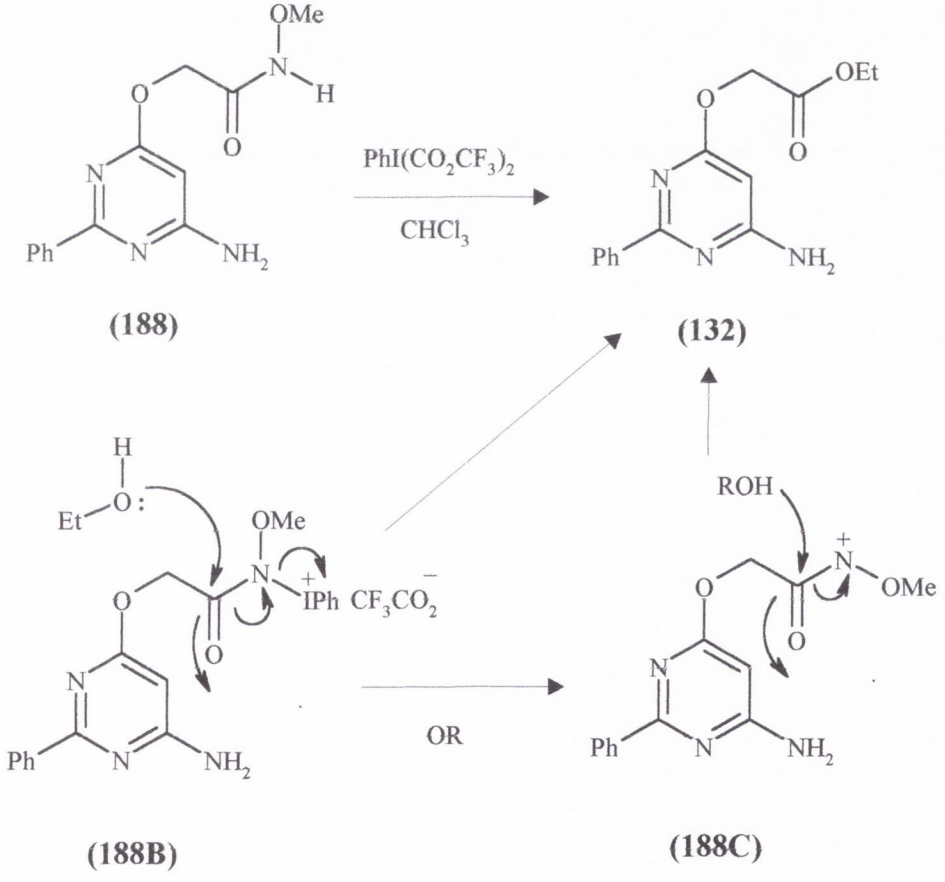


(171)

2.6 Hypervalent iodine catalysed reactions of pyrimidine hydroxamic acid derivatives.

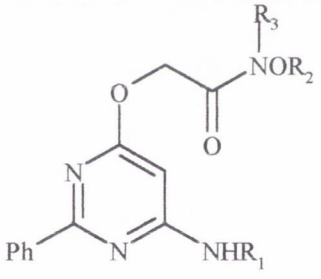
Kikugawa and co-workers had found in their studies of cyclisation reactions using hypervalent iodine reagents, that $PhI(CO_2CF_3)_2$ gave optimum results.[58] This reagent was therefore chosen, and reacted with the *O*-methyl ether of a hydroxamic acid as Kikugawa had done. The reaction of 4-amino-6-*N*-methoxycarbamoylmethoxy-2-phenylpyrimidine (**188**) with $PhI(CO_2CF_3)_2$ in $CHCl_3$ resulted in the formation of the corresponding ester (**132**). This result showed that the *O*-methyl ether and *O*-acetyl esters of hydroxamic acids behave similarly and that ethanolysis was independent of the reagent used. The mechanism may involve either of the paths from (**188B**) or (**188C**).



Treatment of 4-amino-6-*N*-methoxycarbamoylmethoxy-2-phenylpyrimidine (**188**) with $PhI(CO_2CF_3)_2$ in THF containing 3 mole excess of TFA, as used by Romero,[66] only lead to what is possibly the trifluoroacetic acid salt of (**188**). The product shows no sign of an amino group, but neither does it show the amido hydrogen, which would be expected so that the structure of this product remains uncertain.

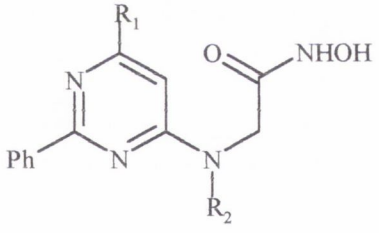
2.7. Reactions of 4,6-dichloro-2-phenylpyrimidine (134)

The previous section has dealt with attempted cyclisation reactions of derivatives of pyrimidine hydroxamic acids of the type (**203**) under the influence of either iron(III) chloride or a hypervalent iodine reagent. Attempts were also made to prepare pyrimidine hydroxamic acids of the type (**204**).



R_1 = H, Ac
R_2 = H, Me, Ac
R_3 = H, Ac

(203)



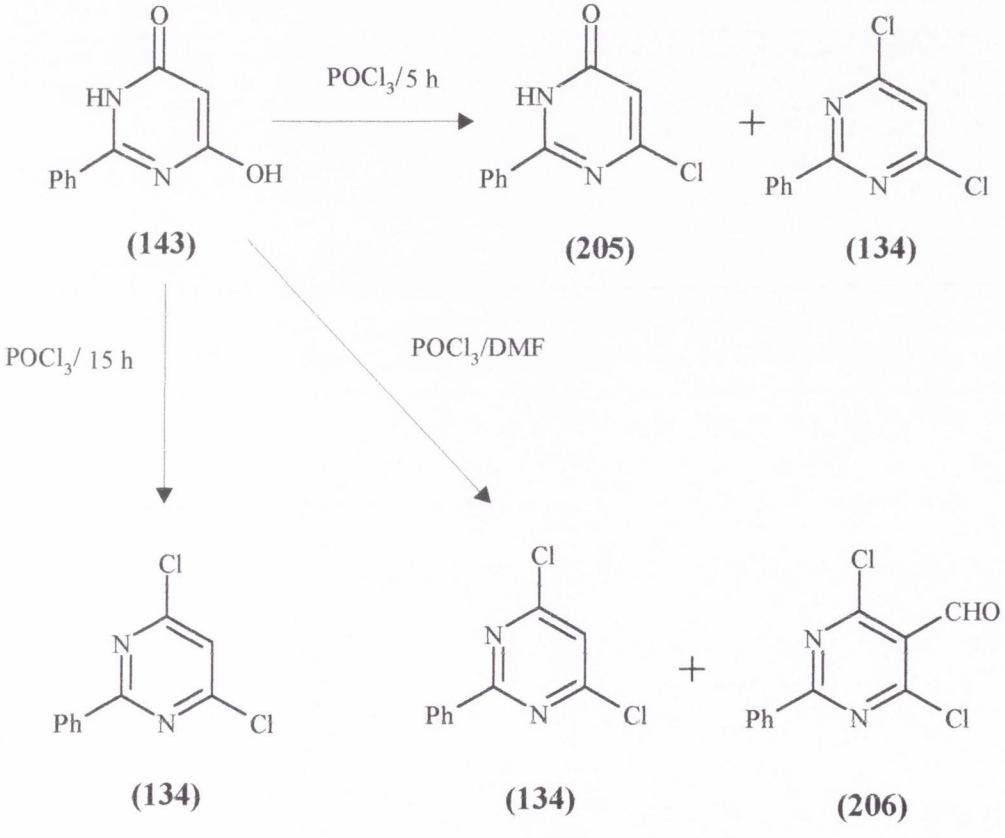
R_1 = Cl, OH, OMe, OEt
R_2 = H, Me, CH_2Ph

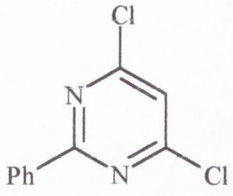
(204)

When 2-phenyl-4(3*H*),6(1*H*)-pyrimidinone (**143**)[71] was refluxed with $POCl_3$ for 15 hours, 4,6-dichloro-2-phenylpyrimidine (**134**) was obtained.[88] It was noticed that reaction times shorter than 15 hours produced mixtures of (**134**) and the monochloro product 6-chloro-2-phenyl-4(3*H*)-pyrimidinone (**205**), which were separated by recrystallisation. In these reactions, it was necessary to ensure that the starting material (**143**) was completely free of DMF, from which it was recrystallised. If traces of DMF are present during the chlorination, this results in the formation of the required dichloro

product (**134**) together with 4,6-dichloro-5-formyl-2-phenylpyrimidine (**206**) *via* a Vilsmeier reaction. [89]

The dichloropyrimidine (**134**) is a reactive molecule due to the combined inductive effect of the chlorine atoms, which makes the pyrimidine ring electron deficient, and facilitates substitution of one of the chlorine atoms by a nucleophile. The dichloro compound was accordingly converted into its substitution derivatives (**135**) and (**207**) - (**209**), by reaction with the appropriate amine in DMF.





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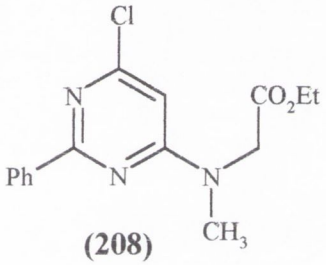

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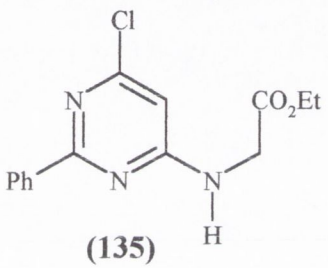
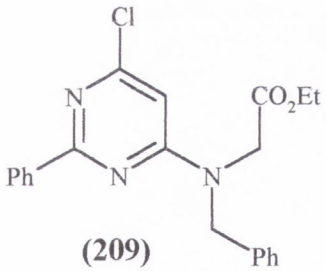


(135)



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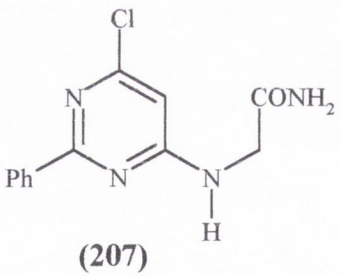
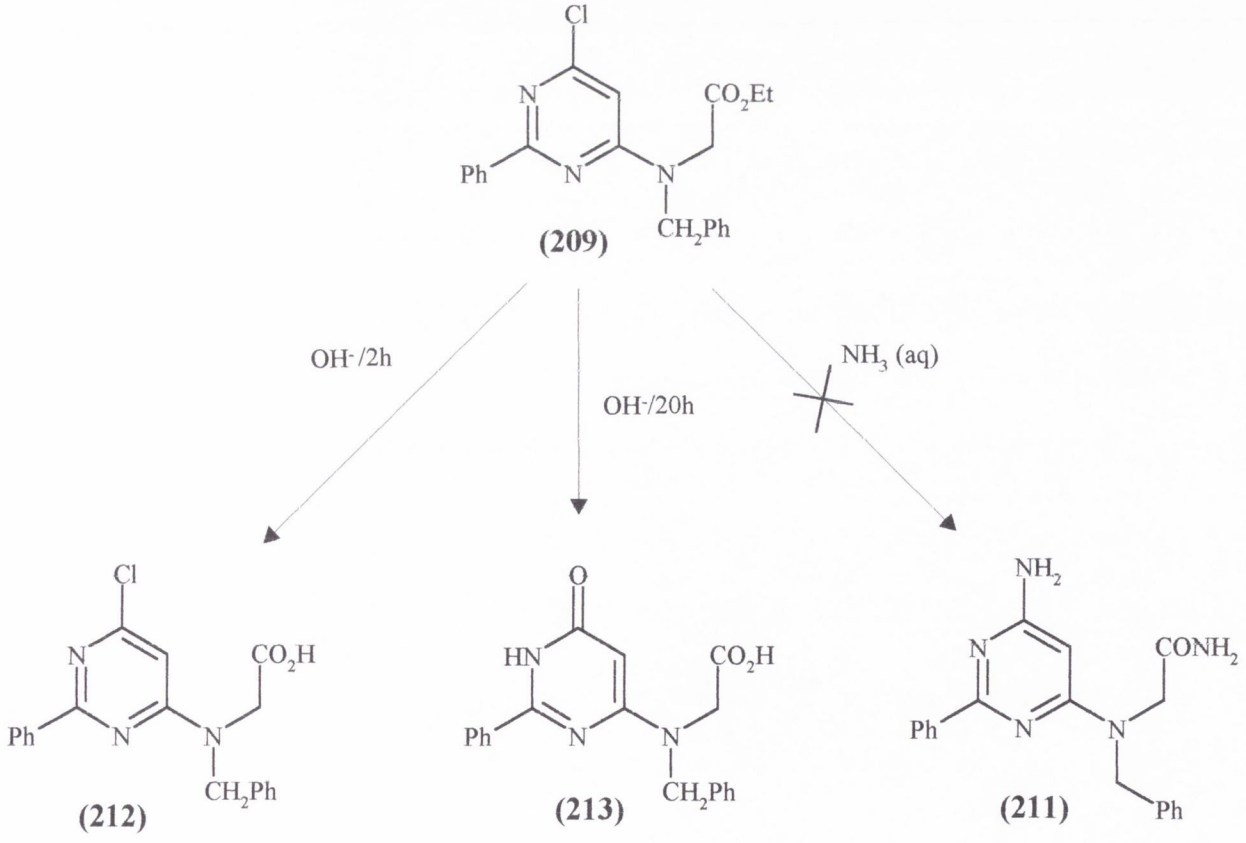


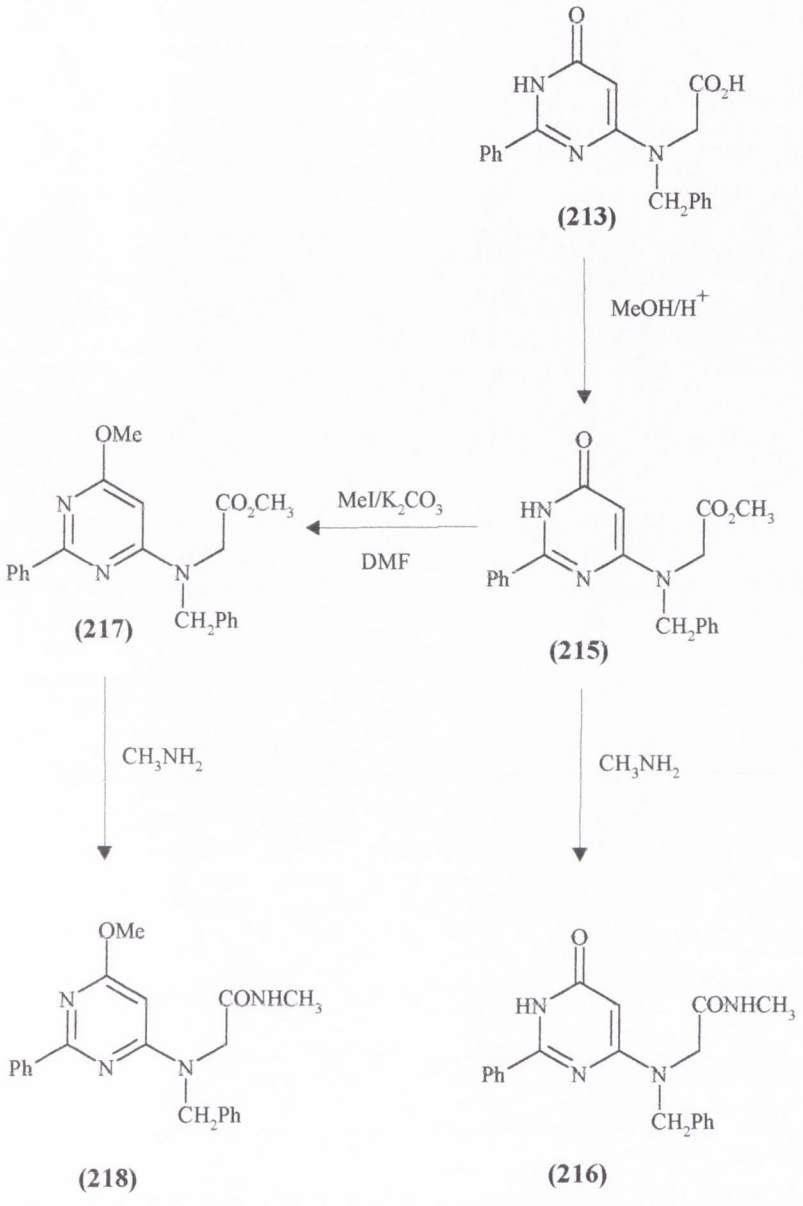
(207)

Since the chlorine atom in these compounds deactivates the pyrimidine 5-position towards electrophilic substitution, efforts were next devoted to replacing the chlorine atom with an electron donating group. This chloro substituent turned out to be relatively inert. For example, refluxing (**209**) in ethanol containing concentrated aqueous ammonia for 24 hours failed to produce the required aminopyrimidine (**211**). Reaction of(**209**) with ethanolic ammonia solution at 120^{0}C in a sealed tube also failed to produce any useful products.

Attempts were also made to hydrolyse the chlorine atom in (**209**) using hydroxide ion. Thus 4-chloro-6-(ethoxycarbonylmethyl-*N*-benzyl)amino-2-phenylpyrimidine (**209**)

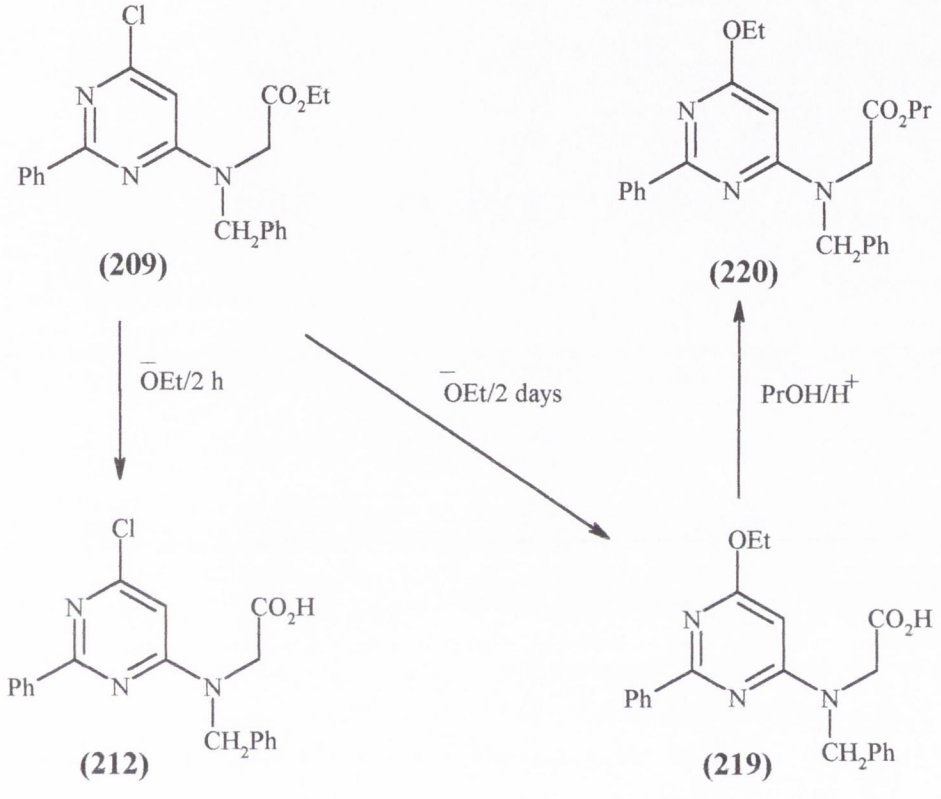
when refluxed with NaOH solution for two hours gave 4-chloro-6-(carboxymethyl-*N*-benzyl)amino-2-phenylpyrimidine (**212**). When chloropyrimidine (**209**) was refluxed with NaOH for 20 hours a different product was obtained, which was shown by its NMR spectra to have the structure (**213**), in which both the 6-chloro substituent and the ester group had been hydrolysed. The fully hydrolysed product (**213**) was successfully converted into its methyl ester (**215**), which in turn was converted into its *N*-methyl amide (**216**). The ester (**215**) could not, however, be converted to the corresponding hydroxamic acid. It was therefore decided to protect the pyrimidinone oxygen as its methyl ether using the methology developed previously. Thus (**215**) was converted into (**217**) in good yield, and the latter was then converted into its *N*-methyl amide (**218**). Again, however, the ester (**217**) could not be converted into a hydroxamic acid. This contrasts with the ease with which esters of the previous series, *e.g.* (**132**), could be converted to their hydroxamic acids.





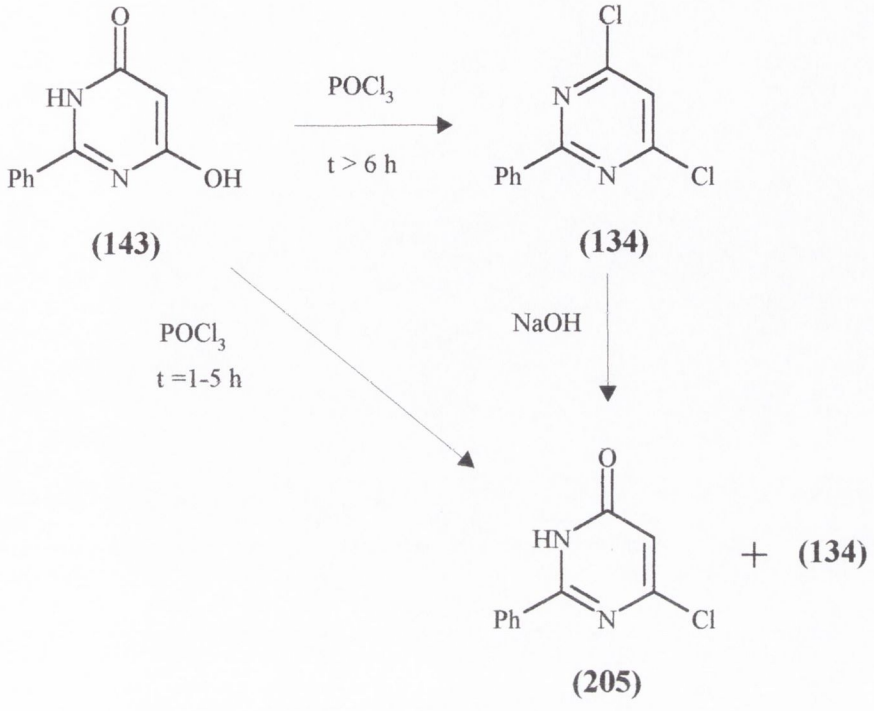
The third and final approach to removing the chlorine atom in (**209**) was by attempting to replace it using alkoxide ion. Thus, when 4-chloro-6-(ethoxycarbonylmethyl-*N*-benzyl)amino-2-phenylpyrimidine (**209**) was treated with ethoxide ion in ethanol for 2 hours, the only product obtained was 4-chloro-6-(carboxymethyl-*N*-benzyl)amino-2-phenylpyrimidine (**212**). When this reaction was repeated with a reaction time of two days, the product was shown to be 4-ethoxy-6-(carboxymethyl-*N*-benzyl)amino-2-phenylpyrimidine (**219**). This result showed that removal of the chloro group was possible using alkoxide ion. However, the product

(**219**) was obtained only in low yield, and was accompanied by substantial amounts of unreacted starting material (**209**). Product (**219**) was further characterised by converting it into its corresponding n-propyl ester (**220**).

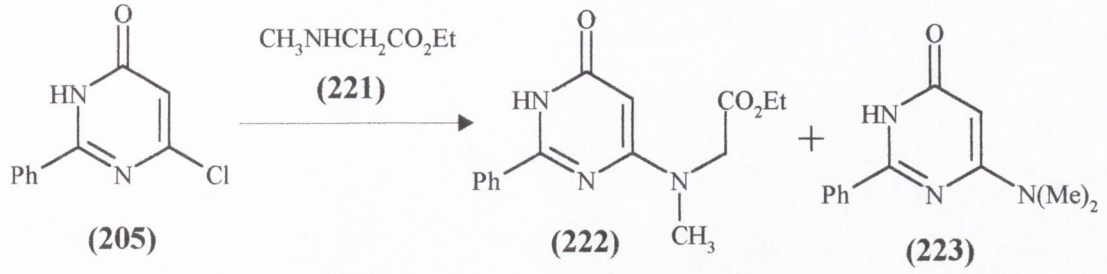


2.8. Reactions of 6-chloro-2-phenyl-4(3*H*)-pyrimidinone (205)

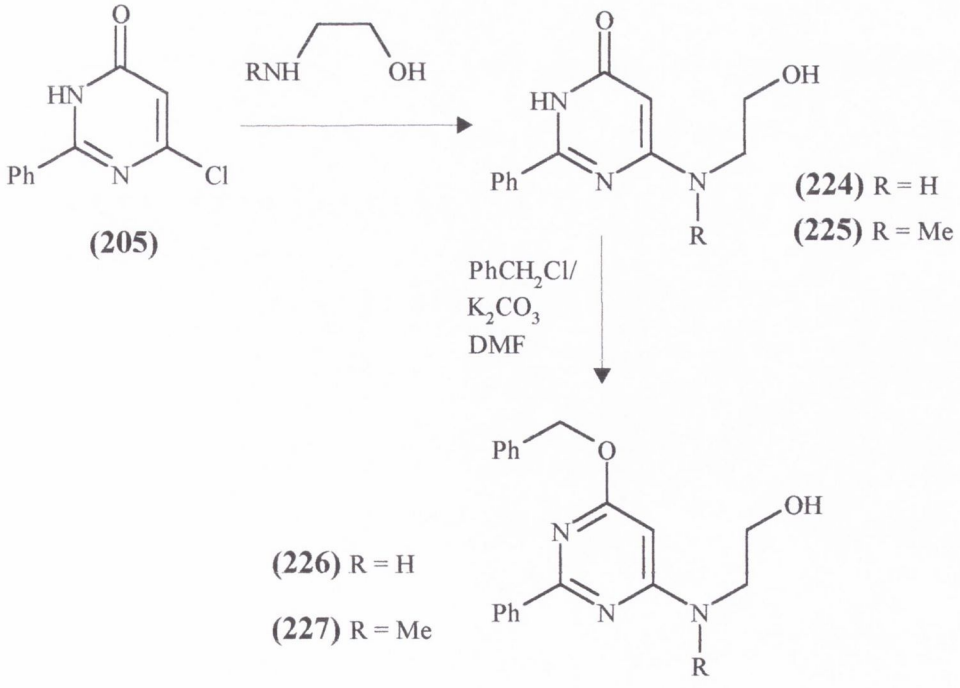
The monochloro compound 6-chloro-2-phenyl-4(3*H*)-pyrimidinone (**205**) was prepared by the partial hydrolysis of the corresponding dichloro compound (**134**) with aqueous sodium hydroxide.[90] As mentioned earlier, (**205**) is also obtained as a significant by-product in the chlorination of (**143**), especially with short reaction times.



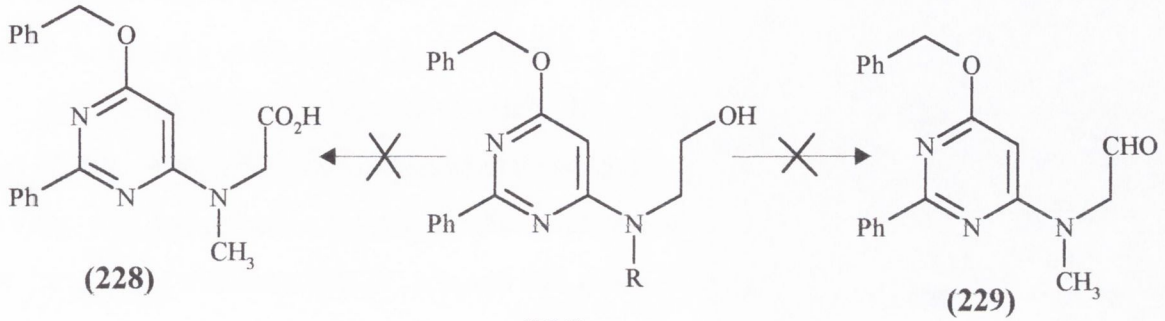
The chlorine atom in this monochloro compound (**205**) is markedly less susceptible to nucleophilic replacement than are the chlorine atoms in the dichloro compound (**134**). For example, reaction of (**205**) with sarcosine ethyl ester (**221**) resulted in a mixture of products, which were not easily separated. Proton NMR analysis indicated a possible mixture of 6-(ethoxycarbonylmethyl-*N*-methyl)amino-2-phenyl-4(3*H*)-pyrimidinone (**222**) and 6-*N,N*-dimethyl-2-phenyl-4(3*H*)-pyrimidinone (**223**). When the same starting material (**205**) was reacted with *N*-benzyl glycine ethyl ester, the only product isolated was shown from its proton NMR spectrum to be 2-phenyl-6-*N,N*-dimethyl-4(3*H*)-pyrimidinone (**223**). This product (**223**) is probably formed by attack on the chloropyrimidine (**205**) by an *N,N*-dimethyl radical, the latter being generated by thermal decomposition of DMF. This type of reaction is not new in the pyrimidine series and many chloropyrimidines have been converted into their *N,N*-dimethyl derivatives by refluxing in DMF for up to several days. [91]



While the monochloro compound (**205**) reacted unsatisfactorily with amino acid esters, it was found to react readily, however, with a variety of other more nucleophilic amino nucleophiles, including ethanolamine and its *N*-methyl derivative. It was hoped to be able to oxidise the side chain primary hydroxyl group in the products obtained from the latter reagents. The substrate (**205**) reacted well with both ethanolamine and *N*-methyl ethanolamine to give the corresponding β-hydroxyethylaminopyrimidines (**224**) and (**225**). Both products (**224**) and (**225**) were extremely insoluble in common organic solvents and this caused problems in efforts to oxidise them. Accordingly, both (**224**) and (**225**) were converted into their 4-*O*-benzyl derivatives (**226**) and (**227**). Both of these products were readily soluble in dichloromethane. However, all efforts to oxidise

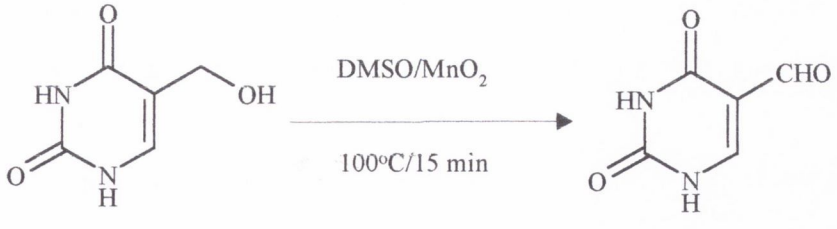


the primary hydroxyl group in (**227**) to either an acid (**228**) or an aldehyde (**229**) were unsuccessful.



(228) **(226)** R = H **(227)** R = Me **(229)**

For example, the attempted oxidation of 4-benzyloxy-6-(2-hydroxyethyl-*N*-methyl)amino-2-phenylpyrimidine (**227**) was carried using various reagents. Thus, when (**227**) was treated with potassium permanganate in alkaline solution, no useful products were isolated. Activated manganese dioxide is a widely used oxidising reagent in organic synthesis due to its ease of handling and work up. When (**227**) and MnO_2 in DMSO were stirred together at room temperature or refluxed, no detectable (TLC) reaction occurred. This was suprising since Brossmer *et al* successfully oxidised the pyrimidine primary alcohol (**230**) to the corresponding aldehyde (**231**) using the same conditions.[92]

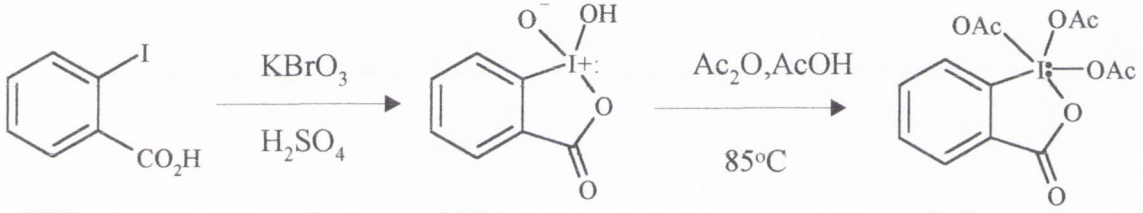


(230) **(231)** 85 %

Barium manganate is a modified permanganate reagent, which is a mild and effective oxidant for alcohols.[93] It has also been reported to act as a dehydrogenating agent.[94] The blue green solid barium manganate is prepared easily by precipitating it with $BaCl_2$ from an alkaline solution of $KMnO_4$ containing KI. Oxidations employing this reagent

involve stirring a large excess of $BaMnO_4$, at room temperature, with the substrate in dichloromethane. While many of the literature examples were completed in hours and in excellent yield, (**227**) was found, after 1 week, to have only partially reacted under these conditions, and no product was isolated.

The Dess-Martin periodinane (DMP), 1,1,1-triacetoxy-1,1-dihydro-1,2-beniodoxol-3(1*H*)-one (**234**) has recently enjoyed increasing use as an oxidant,[95] and is claimed to be a very mild and effective reagent for the oxidation of carbonyl compounds. As DMP is no longer sold commercially, an attempt was made to prepare it from 2-iodobenzoic acid (**232**). Oxidation of (**232**) to the hydroxyiodinane (**233**) was successful. Difficulties were encountered, however, in the conversion of (**233**) to (**234**), and since the intermediate (**233**) is known to be highly explosive, this line of investigation was not continued further.



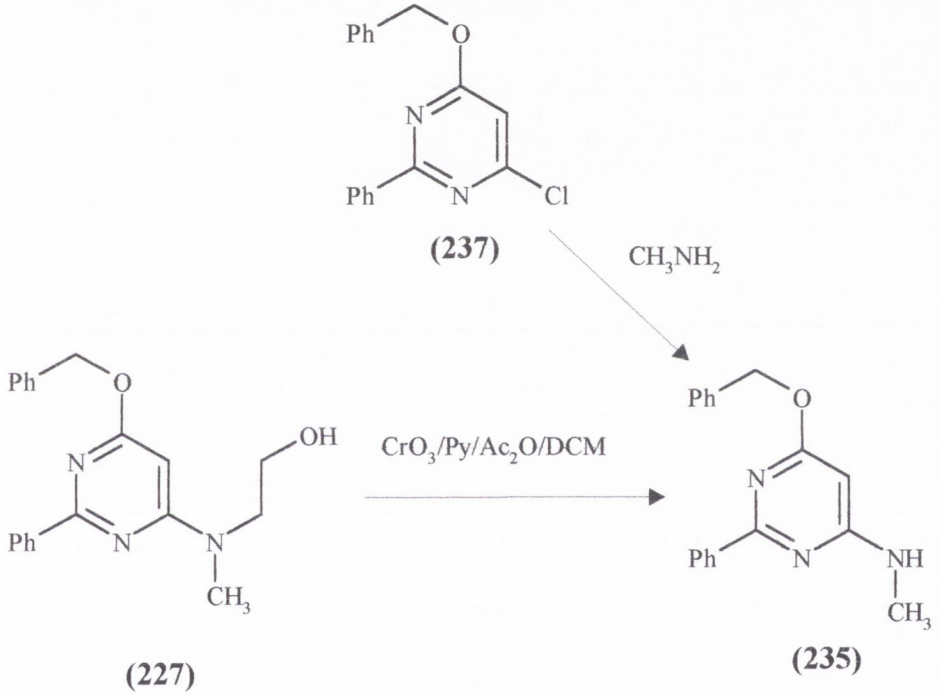
(232) **(233)** **(234)**

Tetrapropylammonium perruthenate, $Pr_4N^+RuO_4^-$, is a modern oxidising agent, the use of which has been reviewed recently.[96] For the oxidation of alcohols, a catalytic amount of the reagent is used, together with 1 equivalent of the alcohol, 1.5 equivalents of *N*-morpholine oxide, (as a co-oxidant) and finely powdered molecular sieves, producing the aldehyde or ketone. When (**227**) was treated under these conditions, two new products were formed (TLC). Appreciable amounts of substrate remained, however, even after extended reaction times, and the resulting product mixture could not be separated.

There are several Cr(VI) reagents commonly used in synthesis, some of which were tested. For example, when (**227**) was treated with potassium dichromate in acidic solution, no useful product could be isolated, even though the orange Cr(VI) was reduced

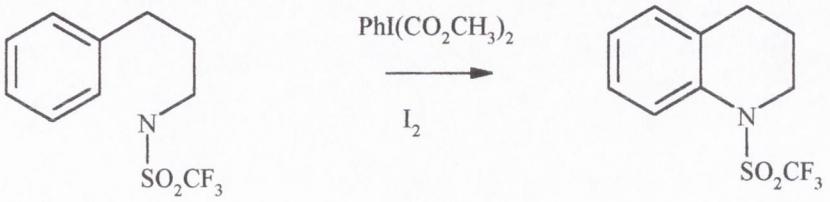
to the green Cr(III) ion. Experiments with pyridine chlorochromate as oxidising agent were similarly unsuccessful.

When (**227**) was oxidised with chromium trioxide in dichloromethane containing pyridine and acetic anhydride,[97] a product was obtained in low yield. This was shown to be the *N*-methyl amino compound (**235**), in which the hydroxyethyl side chain has been cleaved. The same product (**235**) was obtained directly by treatment of 4-benzyloxy-6-chloro-2-phenylpyrimidine (**237**) with methylamine.

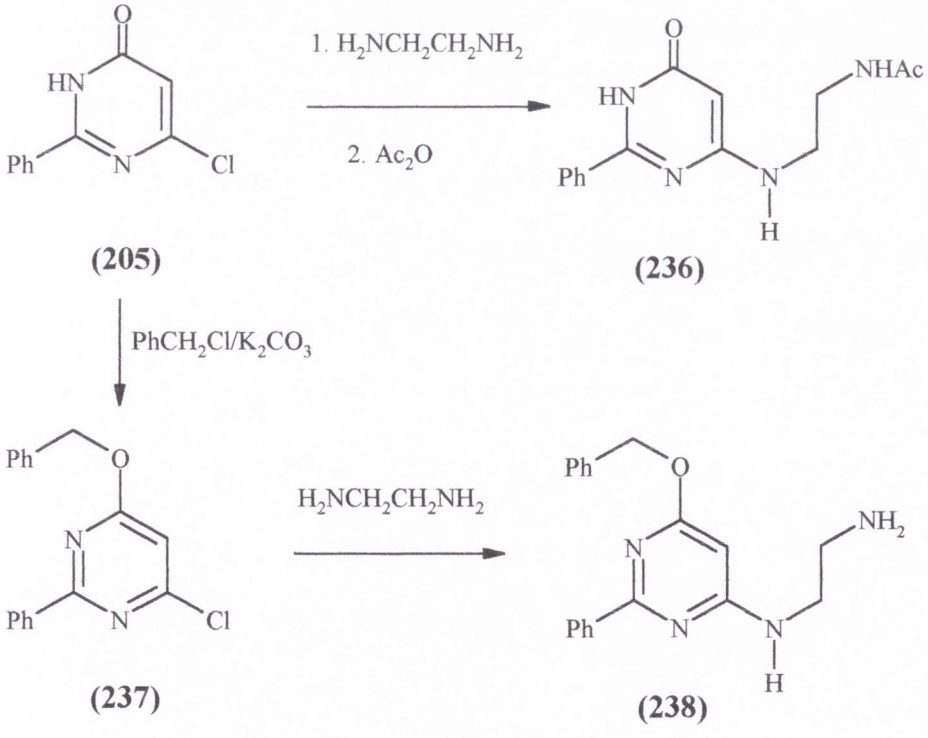


The third and final methology adopted when using the monochloro pyrimidine (**205**) was to react the latter with ethylenediamine. Thus, (**205**) reacted with ethylenediamine to give a new product, which could not be isolated as a solid. The oily product obtained was instead derivatised to an acetyl compound (**236**) by heating with acetic anhydride. 6-Chloro-2-phenyl-4(3*H*)-pyrimidinone (**205**) was easily converted into 4-benzyloxy-6-chloro-2-phenylpyrimidine (**237**), which reacted with ethylenediamine to give 4-ethylenediamino-6-benzyloxy-2-phenylpyrimidine (**238**). The reason for this synthetic sequence is in order to test the applicability of this product (**238**) to a recently reported literature method for the intra molecular cyclisation of amides.[98] In particular the

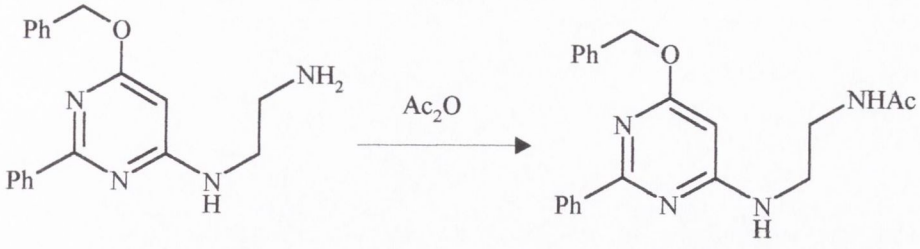
authors found that amines, when acylated with strongly electron withdrawing groups, such as trifluoromethanesulphonyl, can be induced to undergo intramolecular cyclisations in the presence of a hypervalent iodine reagent.



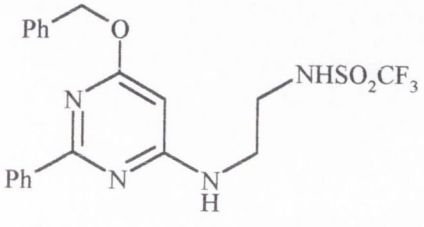
In the event, attempts to convert (**238**) into the corresponding trifluoromethanesulphonamido compound (**238A**) proved unsuccessful. Acetylation to give (**238B**) was more successful but the acetamido derivatives were found to be the least reactive in the literature study.



(205) **(236)** **(237)** **(238)**



(238) **(238B)**



(238A)

Chapter three

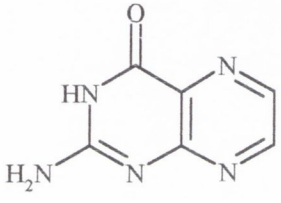
Amino and Oxopyrimidines

3.0 Introduction

The 2-amino pyrimidines are possibly the most important class of pyrimidines. The 2-amino functionality occurs ubiquitously in biological systems and is often associated with the 4(3*H*)-pyrimidinone structure, usually as part of a fused ring system as in pterin (**239**), the nucleotide base guanine (**240**), or in the vitamin co factor folic acid (**241**).

The 2-amino-4(3*H*)-pyrimidinone group is an essential element in a molecule such as guanine and plays a vitally important role in the stability of DNA. It is the hydrogen bonding at this portion of the molecule to an adjacent molecule of cytosine

2-amino-4(3*H*)-pyrimidinone structure



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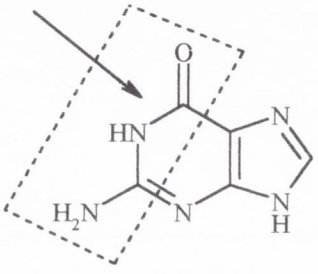

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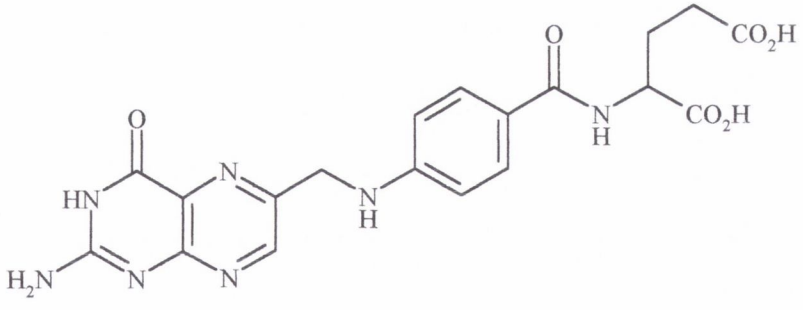

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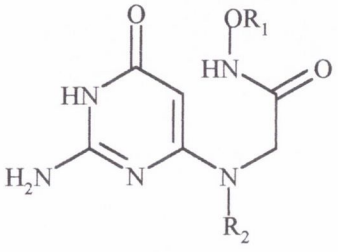


R_1 = alkyl, Ac

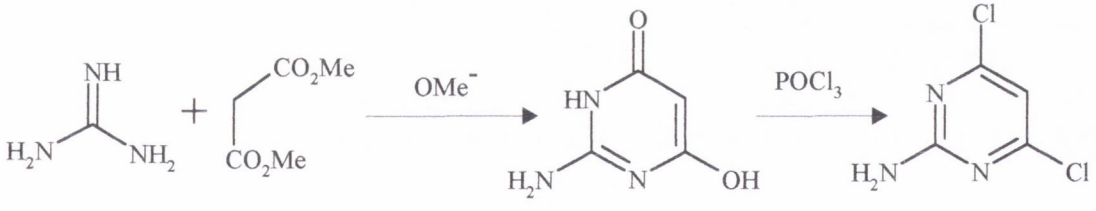
R_2 = H, alkyl

(242)

which enables complementary base pairing to occur and contributes to the stability and robustness of DNA. One could argue that the 2-amino-4(3*H*)-pyrimidinone structure is therefore essential to all life processes, and that attempted syntheses of molecules containing this functionality are of special interest. One consequence of the strong intermolecular hydrogen bonding in this class of molecules is that they are poorly soluble in water or organic solvents. This makes their manipulation into complex molecules more difficult. Despite this, the initial aim was to attempt to synthesise molecules of the general type (**242**).

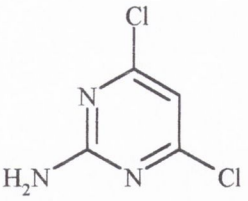
3.1. Reactions of 2-amino-4,6-dichloropyrimidine (244)

2-Amino-4(3*H*),6(1*H*)-pyrimidindione (**243**) is synthesised by the methoxide catalysed condensation of guanidine hydrochloride and dimethylmalonate in methanol,[99] which in turn is converted into 2-amino-4,6-dichloropyrimidine (**244**) by refluxing in $POCl_3$.[100]

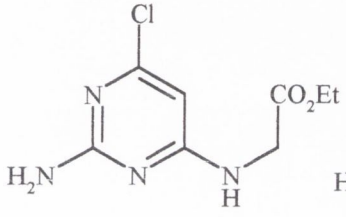


(243) **(244)**

The dichloro product (**244**) is a reactive compound in which either of the chlorine atoms can be replaced using common nucleophiles, including amino acid esters. Thus compounds (**245**) – (**249**) were prepared from (**244**) and the appropriate amino compound. These products are analogous to those prepared in the 2-phenyl series from the 4,6-dichloro-2-phenylpyrimidine (**134**). As with the 2-phenylpyrimidines, the problem of deactivation of the pyrimidine ring by the remaining chlorine atom is the same. 2-Amino-4-chloro-6-ethoxycarbonylmethylaminopyrimidine (**245**), was therefore chosen as a model compound for hydrolysis experiments in an attempt to remove the chlorine atom.



(244)



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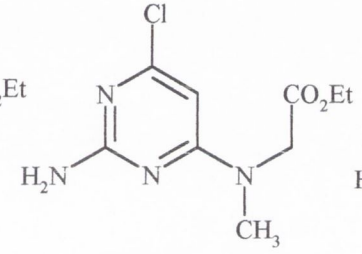

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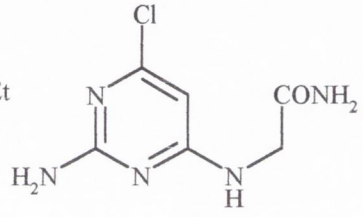

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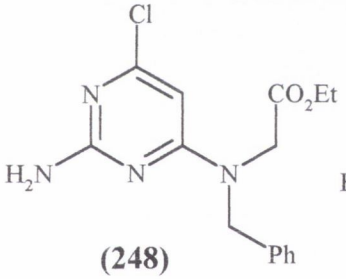

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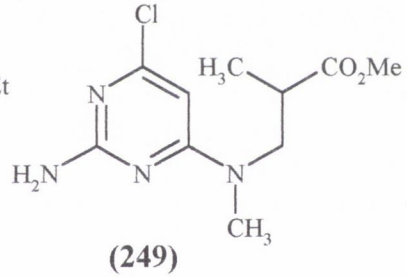
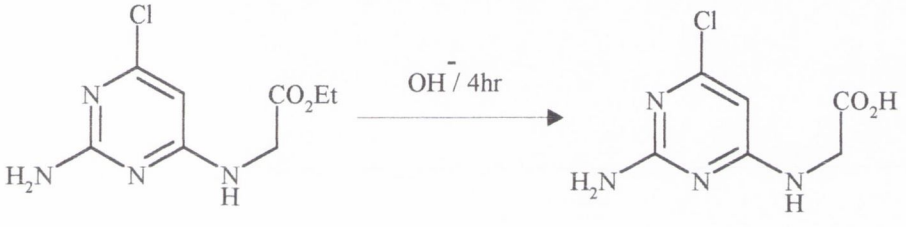


(249)

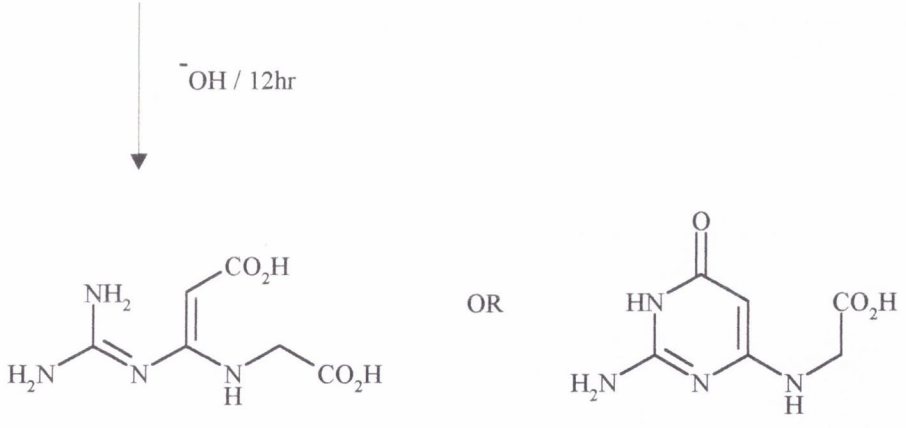
3.2. Hydrolysis reactions of 2-amino-4-chloro-6-ethoxycarbonylmethylamino-pyrimidine (245)

In an effort to prepare 2-amino-6-carboxymethylamino-4(3*H*)-pyrimidinone (**250**), 2-amino-4-chloro-6-ethoxycarbonylmethylaminopyrimidine (**245**) was refluxed with aqueous NaOH for 4 hours. The product from the reaction was not (**250**), however, but rather the chloro acid 2-amino-4-chloro-6-carboxymethyl-aminopyrimidine (**251**). In contrast, refluxing (**245**) with aqueous NaOH for 12 hours afforded a different product, which was extremely insoluble in common solvents, and a satisfactory NMR spectrum could not be obtained. Structure (**252**) is tentatively assigned to this new product, for on refluxing it in either ethanol or methanol containing sulphuric acid, the alkoxy esters (**253**) and (**254**) were obtained.

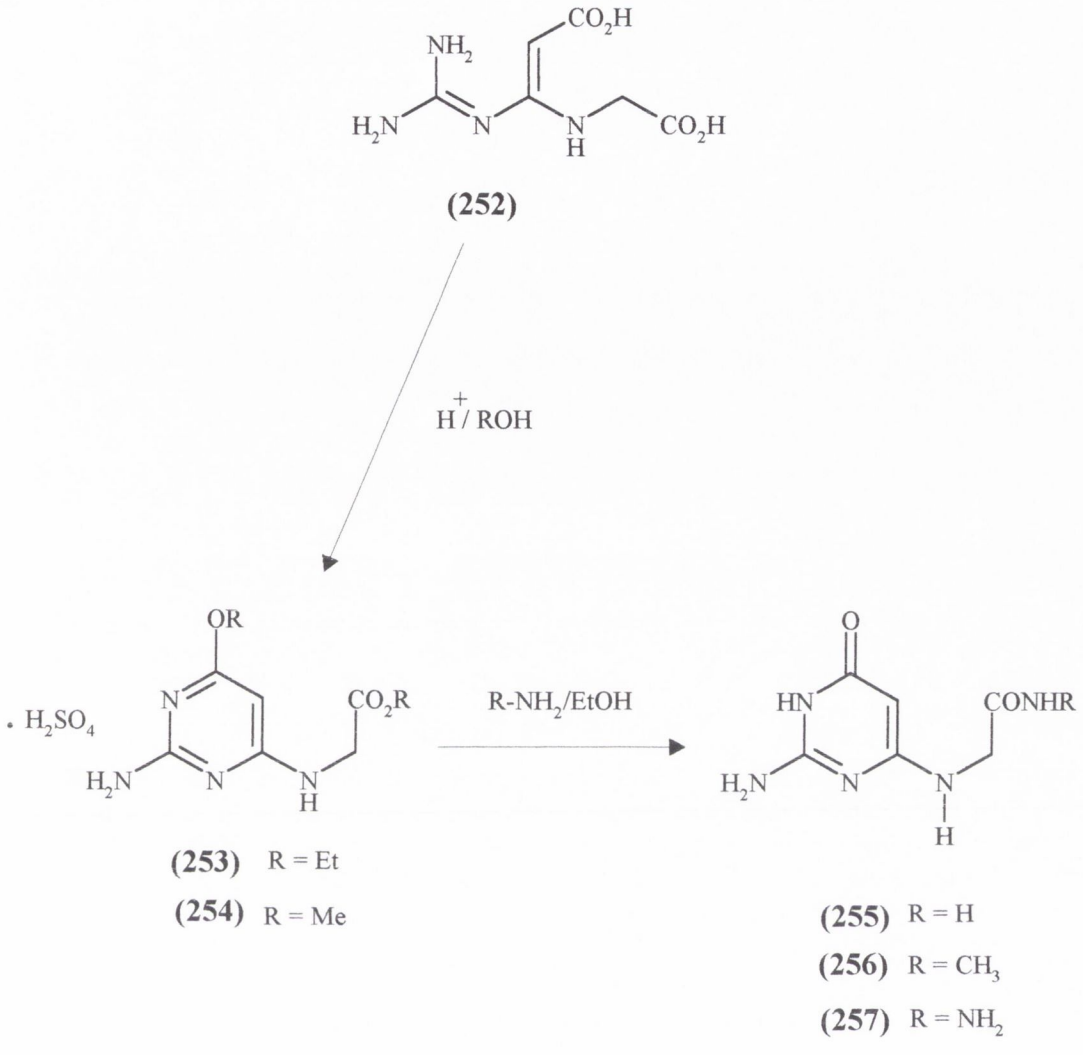
These products were isolated and purified as their sulphate salts and were characterised by their spectra and elemental analysis. The alternative, and desired structure (**250**) for the new hydrolysis product was considered less likely, as it would not be expected to give 4-alkoxypyrimidines such as (**253**) or (**254**) on refluxing in ethanol or methanol containing sulphuric acid. The methyl ester product (**254**) was investigated further. For example, when (**254**) was allowed to react with ammonia, methylamine, or hydrazine, the amides 2-amino-6-carbamoylmethylamino-4(3*H*)-pyrimidinone (**255**), 2-amino-6-*N*-methylcarbamoylmethylamino-4(3*H*)-pyrimidinone (**256**), or the hydrazide 2-amino-6-hydrazinomethylamino-4(3*H*)-pyrimidinone (**257**), were obtained and characterised by their spectroscopic data and elemental analysis. Products (**255**) and (**256**) were isolated and purified as their monohydrates.



(245) **(251)**



(252) **(250)**

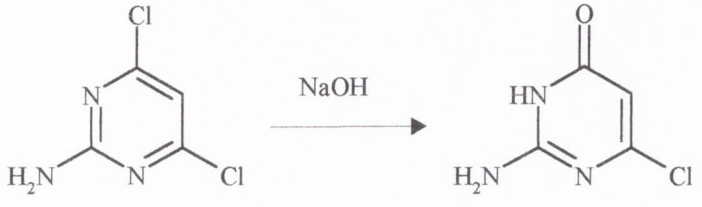


3.3 Reactions starting from 2-amino-6-chloro-4(3*H*)-pyrimidinone (258)

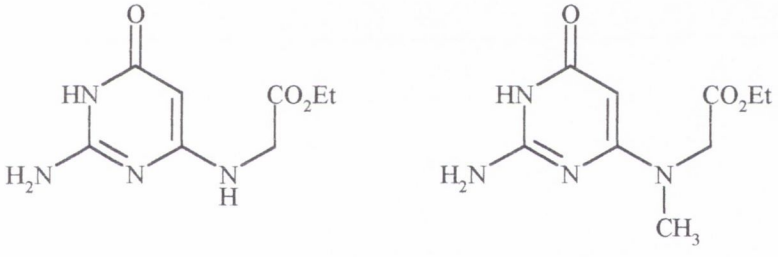
2-Amino-6-chloro-4(3*H*)-pyrimidinone (**258**) was easily prepared by the partial hydrolysis of 2-amino-4,6-dichloropyrimidine (**244**).[101] This product (**258**), unlike the dichloro compound (**244**), did not react well with the range of amino acid esters used with (**244**). The initial target molecule was 2-amino-6-ethoxycarbonylmethylamino-4(3*H*)-pyrimidinone (**250**), which has been reported by Elion.[102] The evidence provided by Elion for the structure of (**250**) was in the form of a UV spectrum only. The product was apparently prepared by fusing together 2-amino-6-chloro-4(3*H*)-pyrimidinone (**258**) and glycine ethyl ester, to give the product (**250**) in very low yield. This procedure has never been repeated or improved upon

since Elion's original work, and therefore it was decided to attempt to design another route to (**250**), or a related derivative, such as (**259**).

Thus, when (**258**) was refluxed with sarcosine ethyl ester/Et_3N/DMF for several days, a mixture of products was obtained from which the starting material could not be separated, nor could the desired product (**259**).

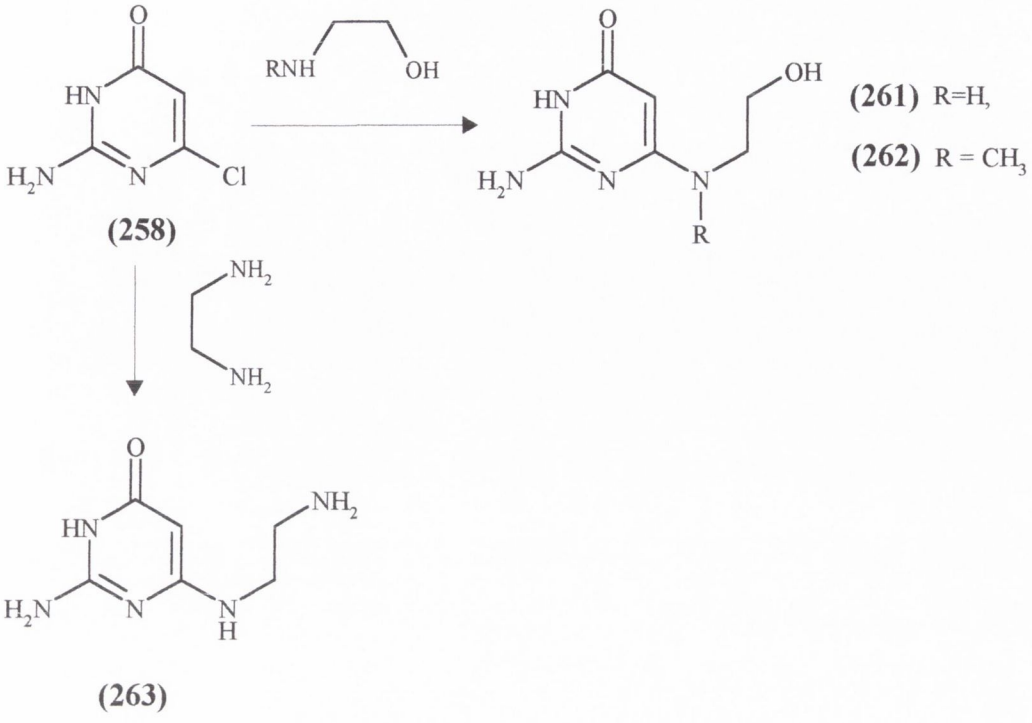


(244) **(258)**



(250) **(259)**

The monochloro compound (**258**) did, however, react quite well with the more nucleophilic ethanolamines and ethylenediamine, and the following transformations were realised.



(258)

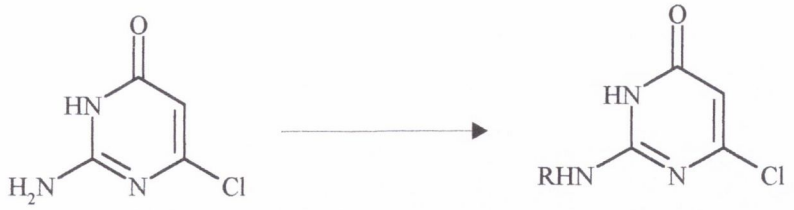
(261) R=H,

(262) R = CH_3

(263)

The products obtained using ethanolamines, for example 2-amino-6-(2-hydroxyethyl-*N*-methyl)amino-4(3*H*)-pyrimidinone (**262**),[103] and 2-amino-6-(2-hydroxyethyl)-amino-4(3*H*)-pyrimidinone (**261**)[103] were generally very polar and insoluble compounds. The ethylenediamine product 2-amino-6-ethylenediamino-4(3*H*)-pyrimidinone (**263**) was also prepared.

The amino group in 2-amino-6-chloro-4(3*H*)-pyrimidinone (**258**) can be easily acylated to give the corresponding acetamido,[104] pivaloylamido or trifluoroacetamido derivatives (**264**)-(**266**) respectively.



(258)

(264) R = $COCH_3$ **(266)** R = $COCF_3$

(265) R = $COC(CH_3)_3$

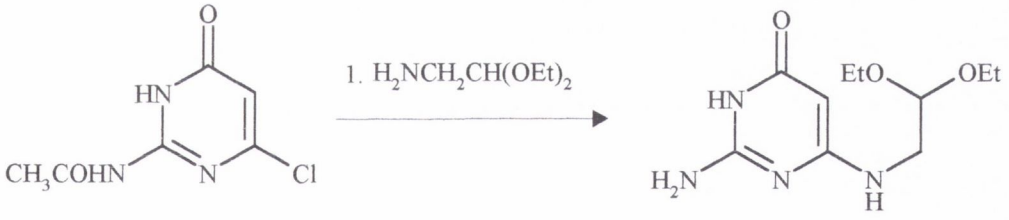
The purpose of introducing the 2-acylamino group in compounds (**264**)-(**265**) was to increase the susceptibility of the chlorine atom to nucleophilic substitution. While this aim was not achieved, the lactam oxygen of these acylamino derivatives was

found to have an increased reactivity towards electrophiles, and 4-alkoxy derivatives of (**264**) were prepared, as described later.

3.4. Reactions of 2-acetamido-6-chloro-4(3*H*)-pyrimidinone (264)

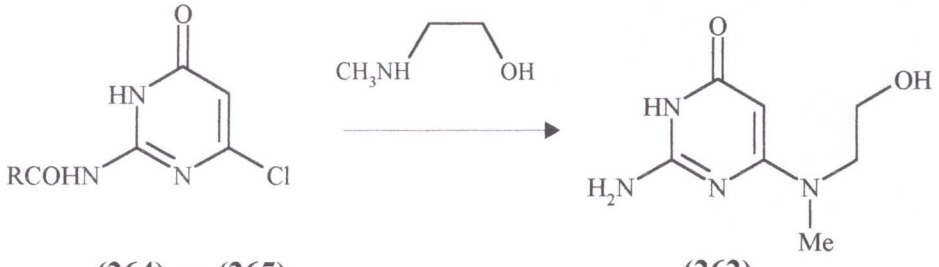
Disappointingly, the 2-acetamido group in (**264**) did not increase the reactivity of the 6-chlorine atom toward nitrogen nucleophiles. In fact, when (**264**) was reacted with sarcosine ethyl ester in DMF containing triethylamine, the only product was the deprotected chloropyrimidine, 2-amino-6-chloro-4(3*H*)-pyrimidinone (**258**). This result was to be the first in a series of reactions, in which, 2-*N*-acylaminopyrimidines on reaction with amino nucleophiles underwent cleavage of the 2-acylamino group, rather than substitution of the chlorine atom.

One possible exception to this was, when (**264**) was treated with aminoacetaldehyde diethylacetal in a sealed tube at 160^{0}C for 16 hours, a small amount of a new product was obtained. This product was not fully characterised, but on the basis of its NMR spectrum it was probably (**267**), in which both substitution and deprotection had occurred.



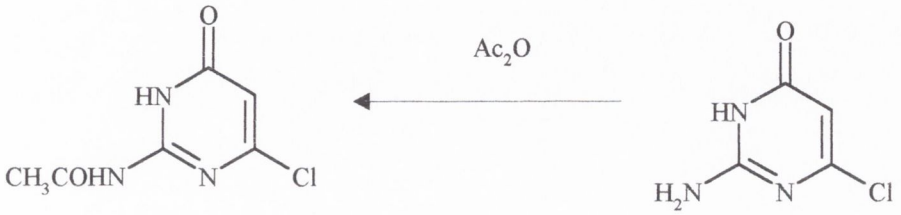
(264) **(267)**

In contrast to the above, when the 2-acetamido and 2-pivaloylamido derivatives (**264**) and (**265**) were treated with *N*-methylethanolamine, both hydrolysis of the 2-acylamino group and substitution of the 6-chloro atom occurred very readily to give 2-amino-6-(2-hydroxyethyl-*N*-methyl)amino-4 (3*H*)-pyrimidinone (**262**).

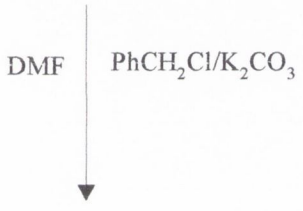


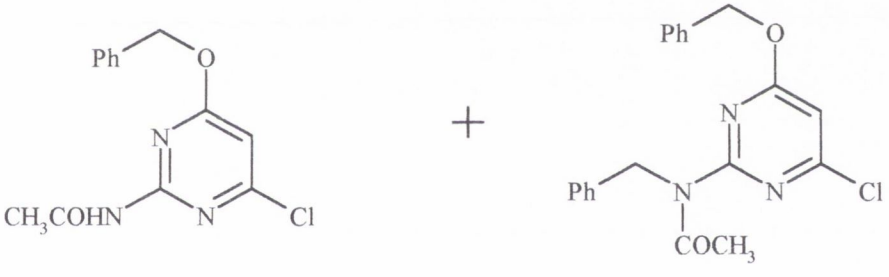
(264) or (265) **(262)**

As mentioned already, the oxygen atom of 2-amino-6-chloro-4(3*H*)-pyrimidinone (**258**) is not sufficiently nucleophilic to react with alkyl halides. On the other hand, the *N*-acetyl derivative (**264**) did react well with benzyl chloride to give a mixture of two products (**269**) and (**270**).

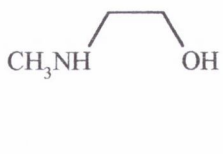


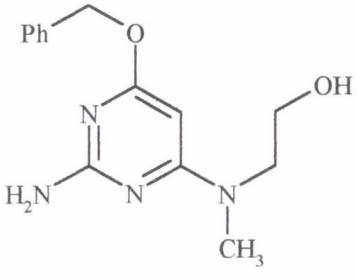
(264) **(258)**





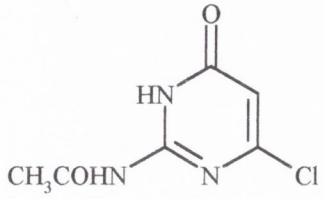
(269) **(270)**





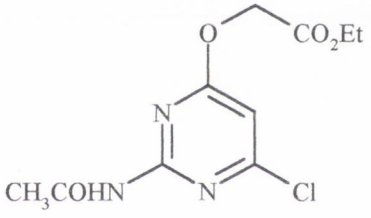
(271)

Alkylation of (**264**) was also carried out using ethyl bromoacetate. As in the previous alkylation, this reaction led to the formation and isolation of a mixture of products, which were shown to be (**272**) and (**273**). In both of the alkylation reactions, starting from (**264**), the mono substituted products (**269**) and (**272**) were the major products in each case.



(264)

DMF | $BrCH_2CO_2Et/K_2CO_3$



(272)

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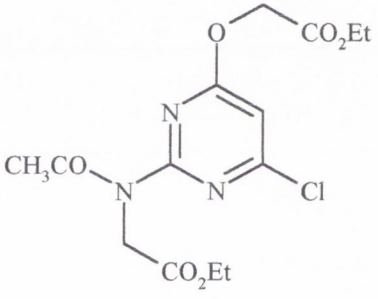
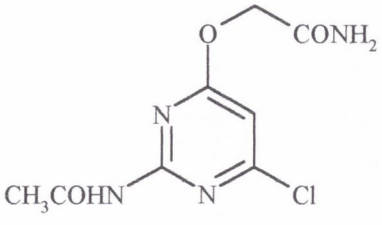


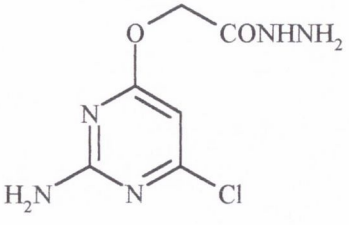
(273)

$NH_3(aq)$

NH_2NH_2



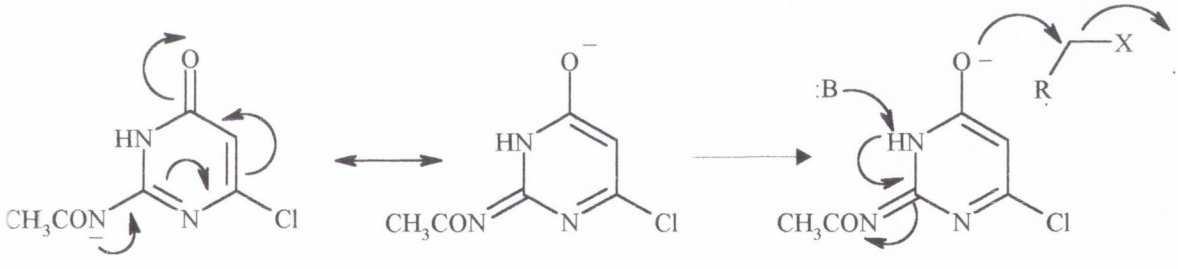
(275)



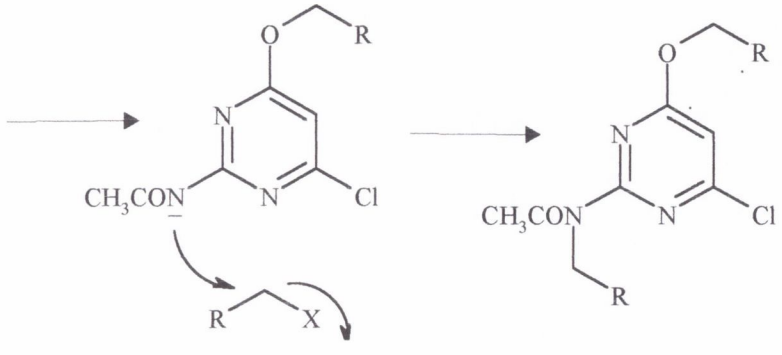
(276)

The side chain ester in product (**272**) was easily converted into the corresponding hydrazide (**274**) with hydrazine hydrate. It was noteworthy that formation of the hydrazide was accompanied by hydrolysis of the amide functional group at position 2. This behaviour has previously been observed in the pyrimidine series.[105] Attempts to prepare the amide (**275**) by refluxing (**272**) in aqueous ammonia only resulted in an intimate mixture of (**275**) and the corresponding deprotected product (NMR analysis). The chorine atom in the major alkylation products (**269**) and (**272**) was relatively inert and could not be replaced using amino acid esters, but was reactive towards *N*-methyl ethanolamine, as in the conversion of (**269**) to (**271**).

In the formation of the minor products (**270**) and (**273**), alkylation of the amide nitrogen under these very mild conditions is unusual. It is possible that alkylation occurs on the resonance stabilised anion (**276**) and (**276a**), formed in the presence of anhydrous potassium carbonate. The extra nucleophilicity imparted to the oxygen atom in resonance form (**276a**) would lead to *O*-alkylation, giving the major products (**269**) and (**271**), followed by further alkylation to give (**270**) and (**273**).



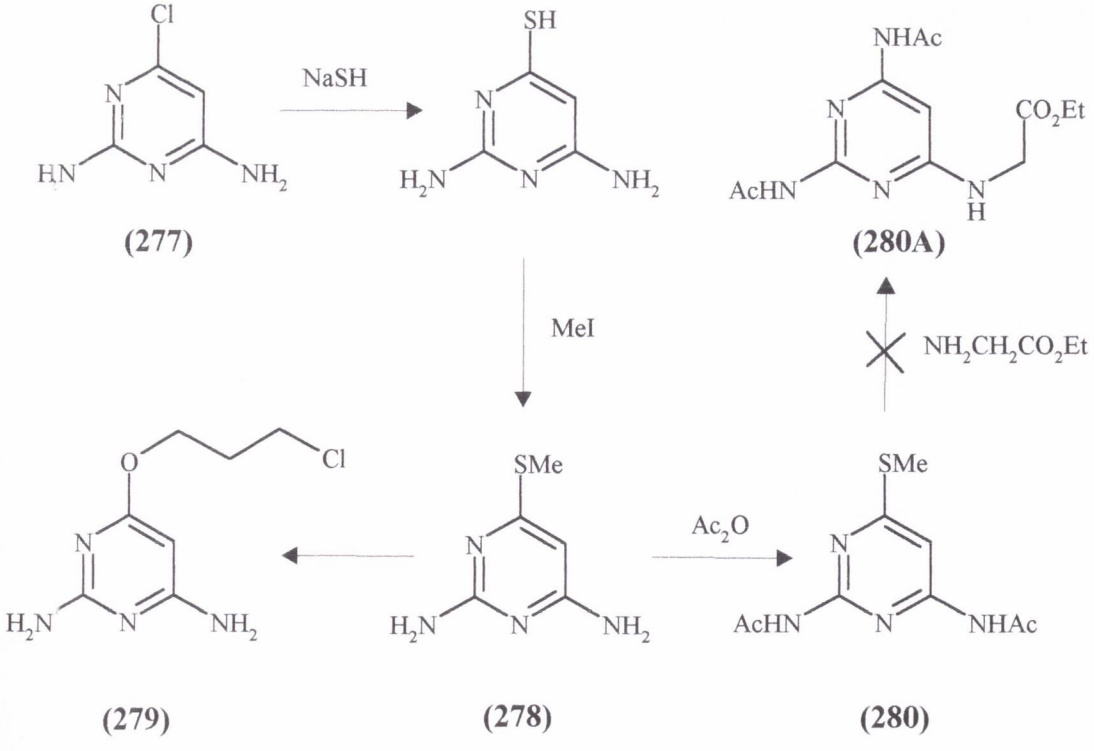
(276) **(276a)**



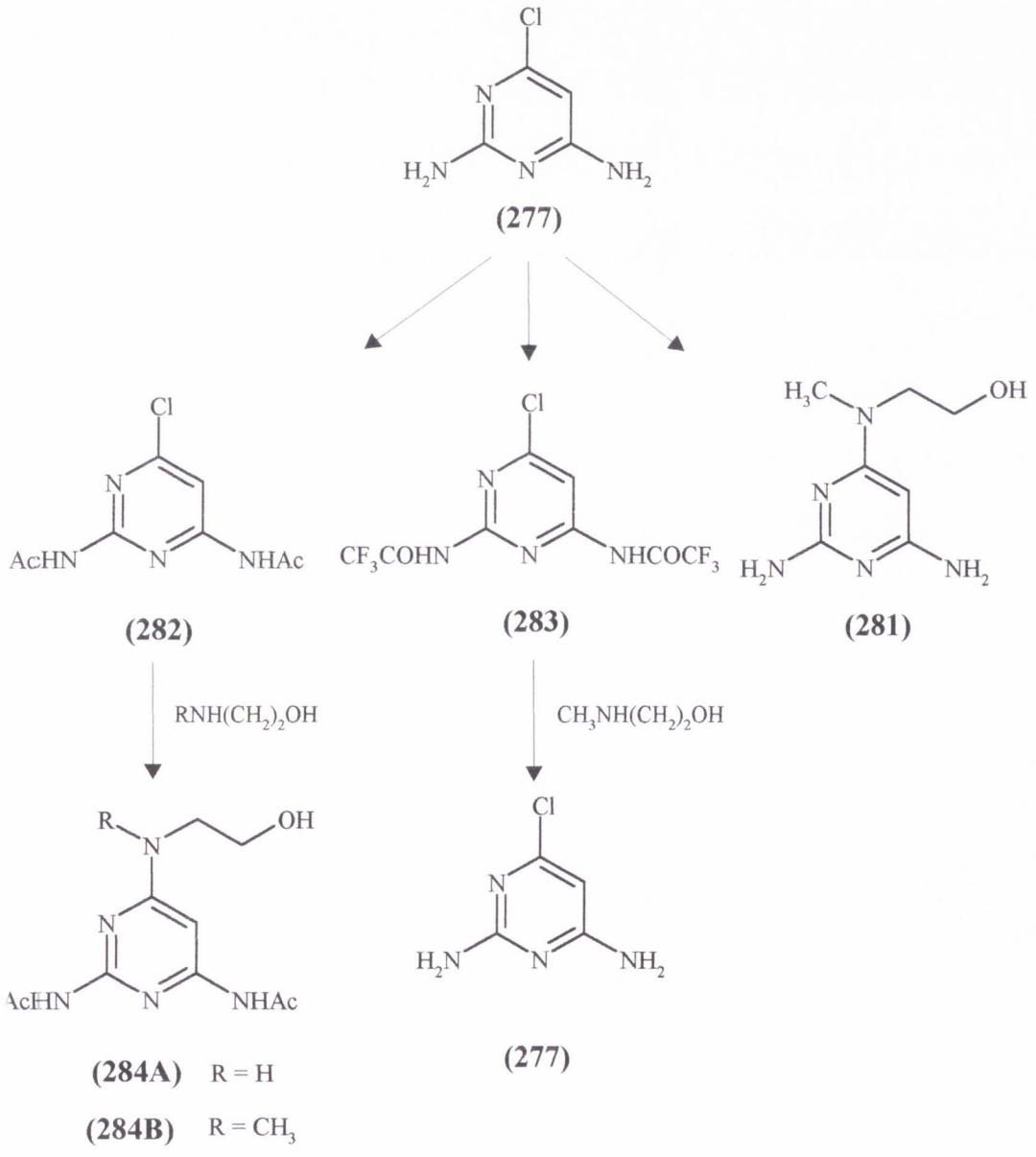
35. Reactions of 4-chloro-2,6-diaminopyrimidine (277)

4-Chloro-2,6-diaminopyrimidine (**277**) is extremely unreactive towards amino acid esters. The combination of two electron-donating amino groups makes replacement of the chlorine very difficult except under extreme conditions, employing the most powerful nucleophiles. Previous workers in these laboratories,[106] have shown, however, that the chlorine atom in (**277**) may be replaced by a mercapto group which was then methylated to give the corresponding methylthio derivative (**278**). The methylthio group in (**278**) acted as a better leaving group than chlorine and could be replaced by 3-chloropropan-1-ol to give 2,4-diamino-6-(3-chloropropoxy)-pyrimidine (**279**). In an attempt to exploit these reactions the methylthio derivative (**278**) was prepared and acetylated to give 2,4-diacetamido-6-methylthiopyrimidine (**280**). However, (**280**) also failed to react with glycine ethyl ester to give the desired product (**280A**).

4-Chloro-2,6-diaminopyrimidine (**277**) was reacted with *N*-methylethanolamine under vigorous conditions and gave 2,4-diamino-6-(2-hydroxyethyl-*N*-methyl)-aminopyrimidine (**281**) in very poor yield. In an effort to improve this reaction the two amino groups of (**277**) were acylated with Ac_2O and $(CF_3CO)_2O$, giving the

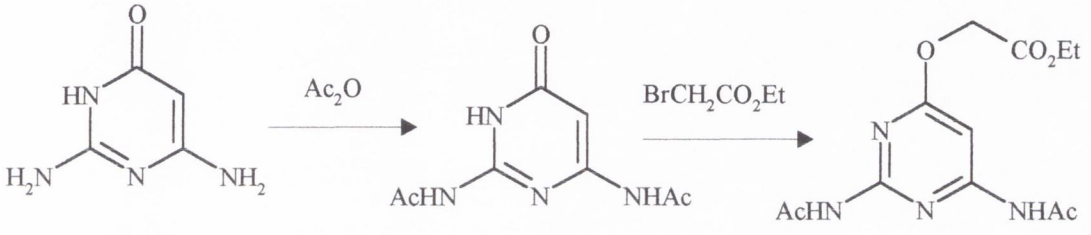


diacylamino products (**282**) and (**283**). These two products (**282**) and (**283**) were also treated with *N*-methylethanolamine. For example 4-chloro-2,6-diacetamido-pyrimidine (**282**) reacted readily to give 2,4-diacetamido-6-(2-hydroxyethyl-*N*-methyl)aminopyrimidine (**284B**) in moderate to good yield. When .4-chloro-2,6-bis(trifluoroacetamido)pyrimidine (**283**) was treated with *N*-methylethanolamine the result was immediate hydrolysis of the trifluoroacetamido groups, regenerating the diamino compound (**277**). This hydrolysis took place almost instantaneously upon mixing the reagents at room temperature. The three products (**281**), (**284A**) and (**284B**) were relatively insoluble and were unsuitable as starting materials for further reactions.



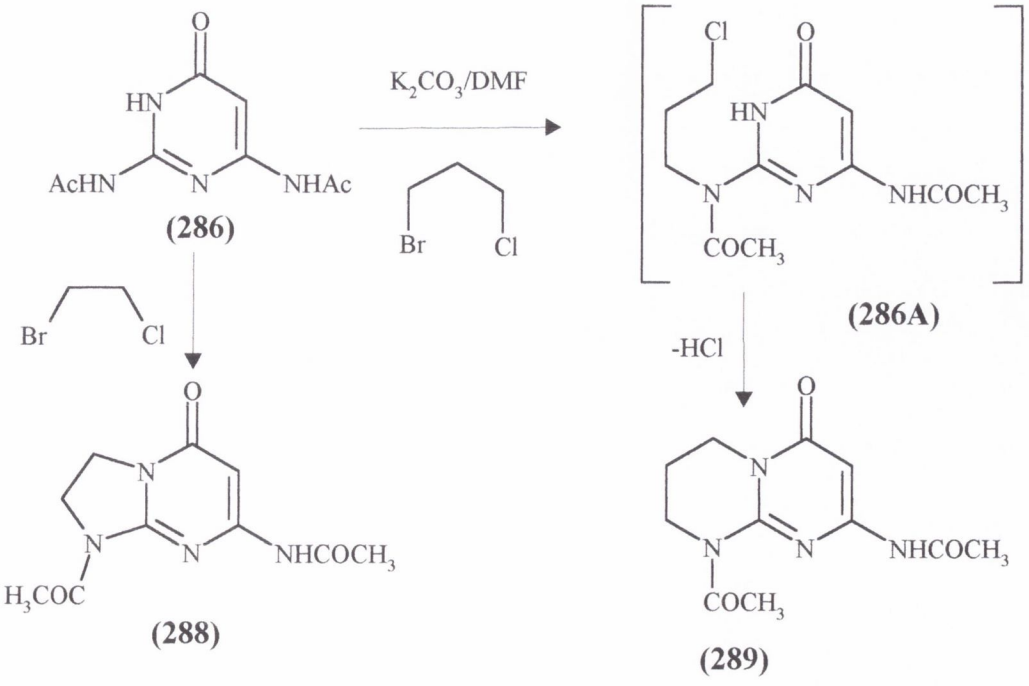
3.6. Reactions of 2,6-diamino-4(3*H*)-pyrimidinone (285)

As discussed previously, acetylation of the 2-amino function in 2-amino-6-chloro-4(3*H*)-pyrimidinone (**258**), enabled the lactam oxygen to be rendered more nucleophilic and reactive towards electrophiles. In a similar manner, acetylation of 2,6-diamino-4(3*H*)-pyrimidinone (**285**) gave (**286**), which reacted with ethylbromo acetate to give the alkoxy product (**287**).



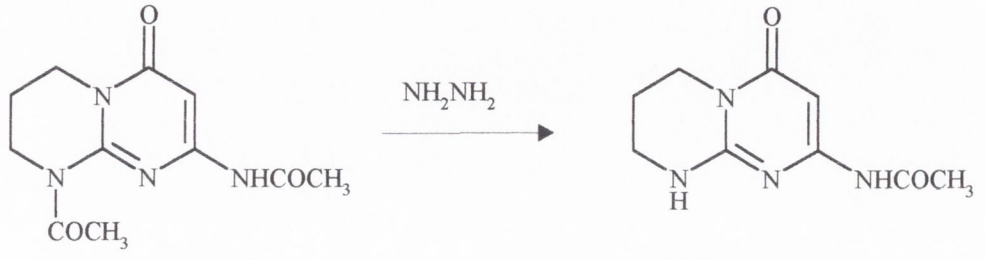
(285) **(286)** **(287)**

In an effort to extend this alkylation reaction to additional alkyl halides, (**286**) was reacted with 1-bromo-2-chloroethane and 1-bromo-3-chloropropane in DMF containing anhydrous K_2CO_3. It was initially expected that the reaction would proceed *via* displacement of bromide ion by the pyrimidine oxy-anion, as in the formation of (**287**), to give β or δ-chloro pyrimidine alkoxides. However analysis of the available data suggested the alternative structures (**288**) and (**289**) for these products.



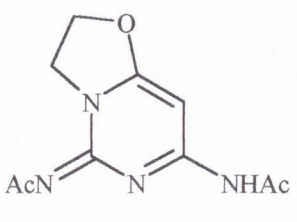
(286) **(286A)** **(288)** **(289)**

These unusual products are thought to have formed (in the case of (**289**) for example) *via* attack by the 2-acetamido nitrogen at the carbon atom alpha to bromine, to give the intermediate (**286A**), which then reacts by intramolecular condensation to give (**289**). In addition, product (**289**), when treated with hydrazine hydrate under mild conditions gave the partially hydrolysed product (**290**)

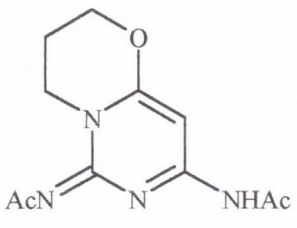


(289) **(290)**

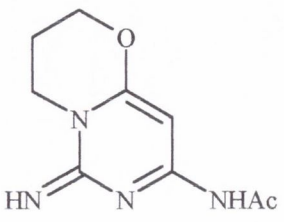
Evidence for structures (**288**), (**289**) and (**290**) came from NMR and elemental analysis. Both (**289**) and (**290**) were analysed, and found to contain no halogen, and both gave acceptable values for the required formulae. The ^{13}C NMR spectrum of product (**287**), which is *O* alkylated shows that the methylene carbon appears at 62 ppm, as this is adjacent to oxygen. The methylene peaks in products (**288**) - (**290**) by contrast, appear at 22, 39 and 42 ppm. These values compare more favourably to the value of 41.7 ppm obtained for product (**245**) (see page 83) in which the methylene carbon is unambigously located next to nitrogen. The proton NMR spectra of products (**288**) and (**289**) contain a single exchangeable NH proton and product (**290**) shows a new NH peak in the proton NMR spectrum, indicating that hydrolysis has occurred to give the secondary amino group observed in the proposed structure. It is also possible that the isomeric structures (**288A**) – (**290A**) were obtained, but these were ruled out because of the evidence outlined here.



(288A)



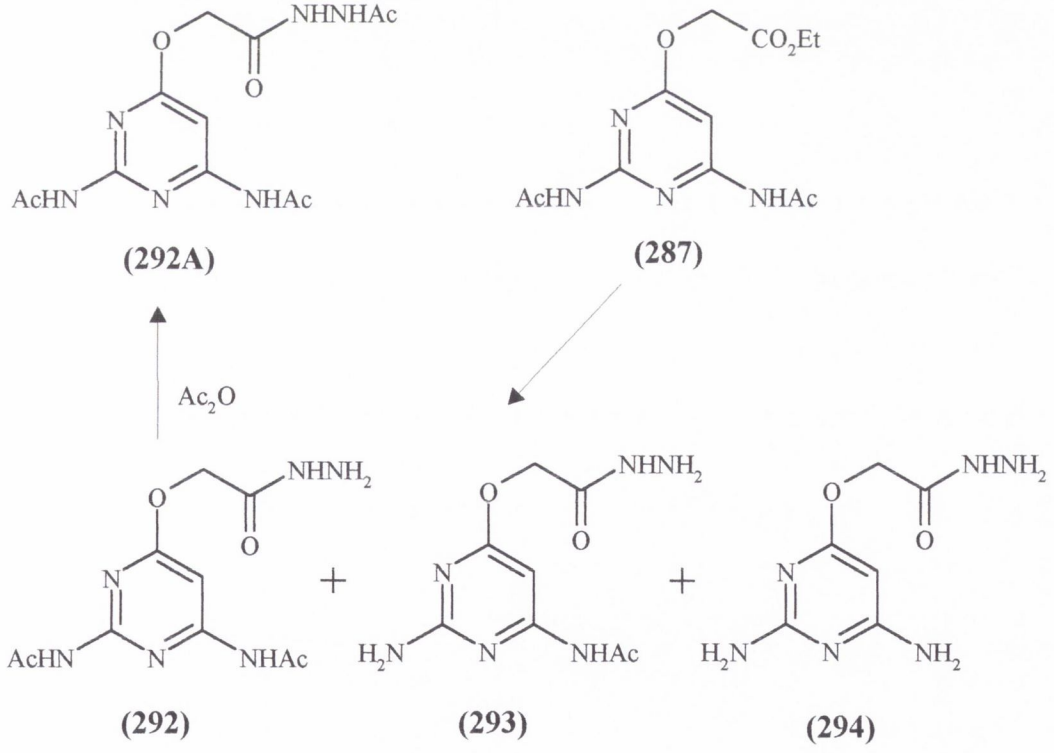
(289A)



(290A)

These results again demonstrate the versatility of acetamido-oxopyrimidines, which have been shown to undergo alkylation at oxygen and/or nitrogen, followed by cyclisation depending on the substrate used.

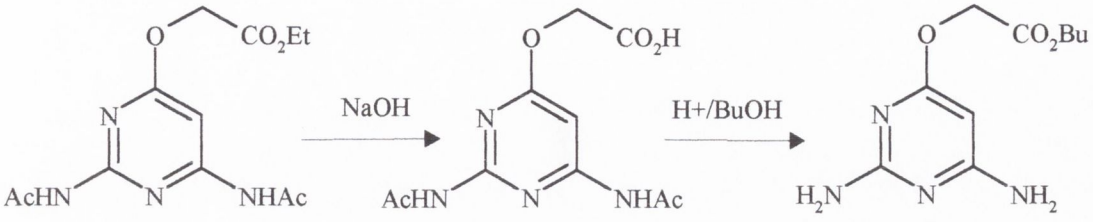
When the alkylation product 2,4-diacetamido-6-ethoxycarbonylmethoxy-pyrimidine (**287**) was treated with hydrazine in refluxing ethanol for 2 hours, there was obtained a mixture of hydrazide products which were shown to be (**292**), (**293**), and (**294**), in a ratio of 3:45:29 %. The fully hydrolysed product (**294**) is formed exclusively when the reaction time is extended beyond 6 hours. In addition the yield of unhydrolysed hydrazide (**292**) can also be maximised by reducing the reaction time to less than 10 minutes. Hydrolysis of the initially formed diacetamido hydrazide (**292**) occurs firstly at the 2-position to give the monoacetate major product (**293**). Evidence for this comes from the fact that the proton NMR spectrum of (**293**) shows a signal due to the 5-CH is shifted down field, which is characteristic for a 4-acetamidopyrimidine. Treatment of (**292**) with acetic anhydride gave the triacetate (**292A**)



(292A) **(287)** **(292)** **(293)** **(294)**

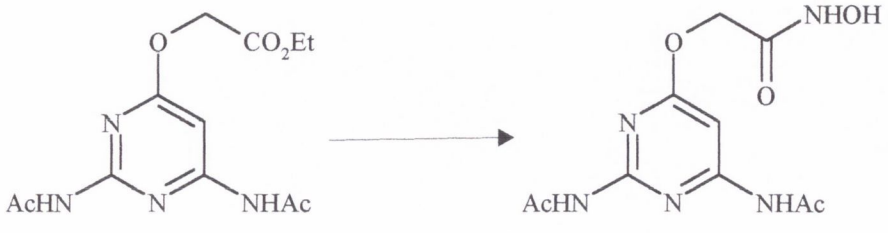
Treatment of 2,4-diacetamido-6-ethoxycarbonylmethoxypyrimidine (**287**) with dilute sodium hydroxide solution produced a highly insoluble product, possibly the acid (**295**), which was converted into a butyl ester (**296**) by treatment with 1-butanol containing concentrated sulphuric acid. The proton NMR spectrum of this product

shows that the product contains the required butyl side chain, and also that hydrolysis of both acetamido groups has occurred to give (**296**)

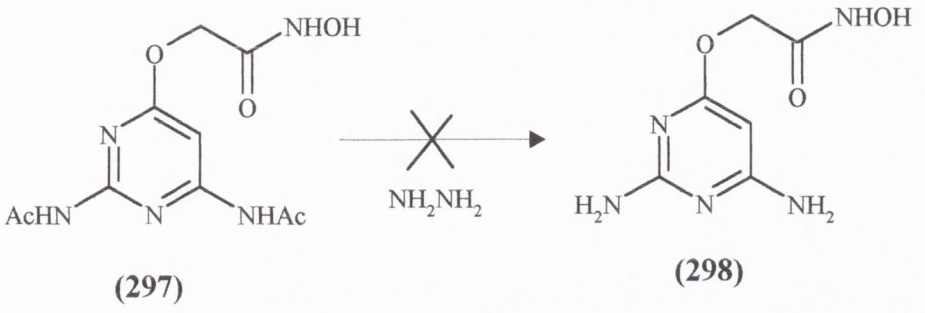


(287) **(295)** **(296)**

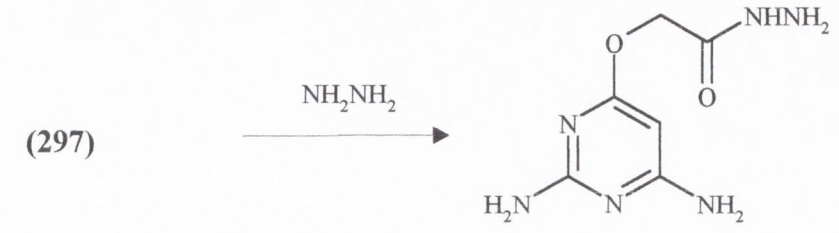
The hydroxamic acid product 2,4-diacetamido-6-*N*-hydroxycarbomylmethoxy-pyrimidine (**297**), was synthesised with some difficulty due to the insolubility of the ester (**287**) in ethanol, below room temperature. The hydroxamic acid product (**297**) was regularly contaminated with unreacted starting material (**287**) and an additional unknown product. It was not found possible to devise a suitable set of conditions that would lead to an optimum yield of the pure hydroxamic acid (**297**). The mixture did, however, give a strongly positive $FeCl_3$ test, indicating the presence of the *N*-hydroxy amido group. In an effort to prepare 2,4-diamino-6-*N*-hydroxycarbomylmethoxy-pyrimidine (**298**), the crude product (**297**) was treated with hydrazine. The reagent successfully hydrolysed both of the acetamido groups, but in addition also attacked the side chain carbonyl carbon to produce the hydrazide (**294**). This experiment demonstrated the incompatibility of hydrazine with the hydroxamic acid functional group in hydrolysis reactions of amides. Attempted acetylation of the crude hydroxamic acid (**297**) to give a possible substrate such as (**299**) for Iron III cyclisation studies was not successful.



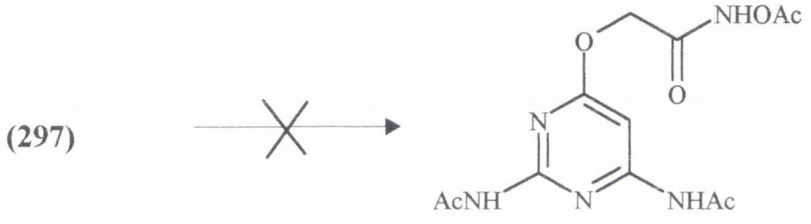
(287) **(297)**



(297) **(298)**

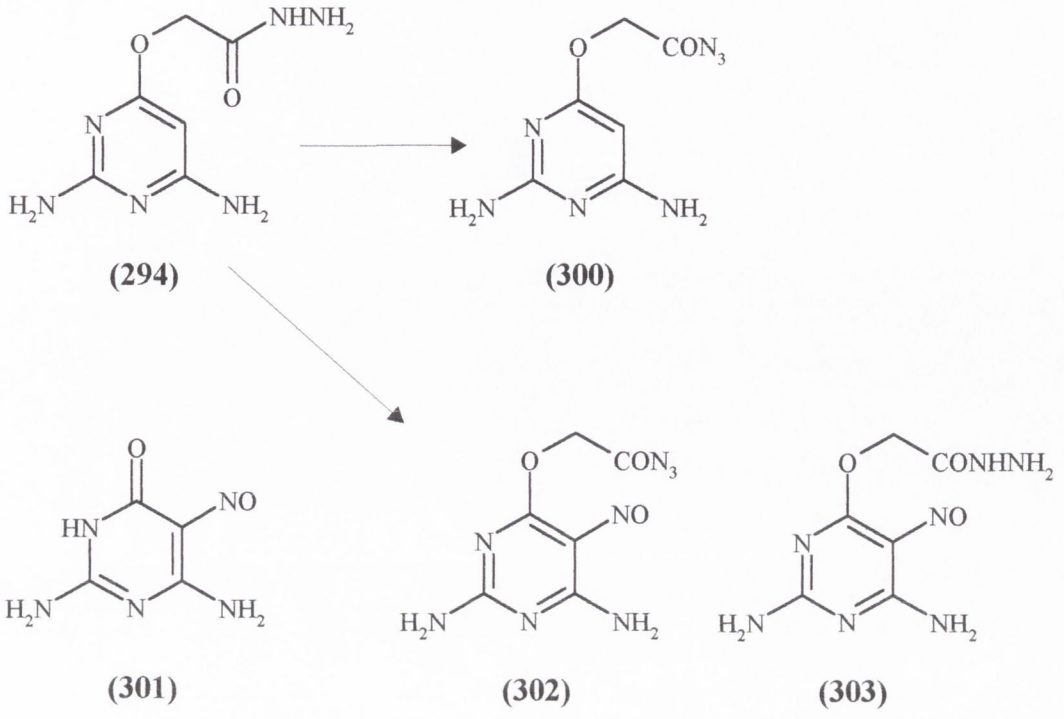


(294)



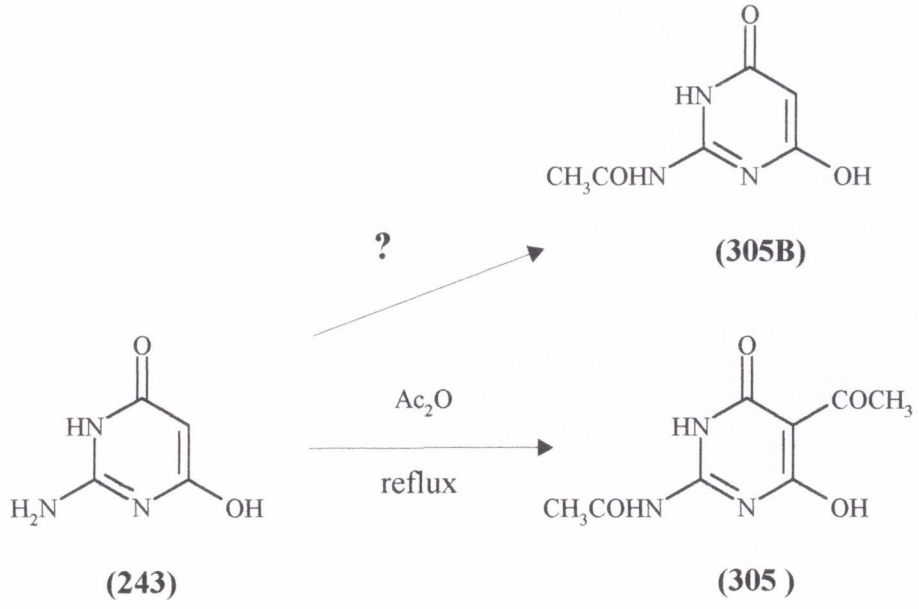
(299)

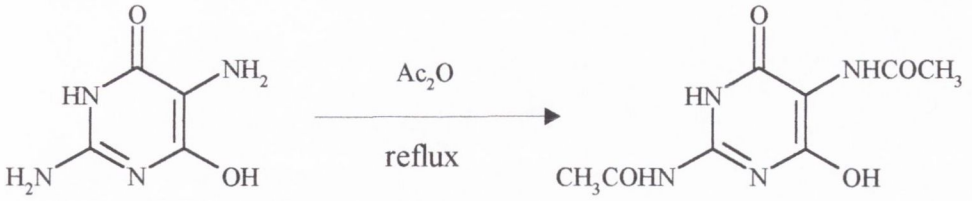
Efforts to prepare the azide (**300**) from the diamino hydrazide (**294**) by treatment with $NaNO_2$ in acetic acid, produced an impure purple solid product. Since 2,6-diamino-5-nitroso-4(3*H*)-pyrimidinone (**301**) is known to be a purple solid, it is possible that the product is therefore the 5-nitroso azide product (**302**), the 5-nitroso hydrazide (**303**), or a complex mixture, rather than the desired azide (**300**). The nitrosation reaction is possibly favoured over conversion to the azide, in the 2,6-diamino pyrimidine series due to the extra electron density at the 5-position caused by electron donation to the ring by the two amino groups.



3.7. Reactions of 4,6-dioxopyrimidines

When 2-amino-4(3*H*),6(1*H*)-pyrimidindione (**243**)[107] and 2,5-diamino-4(3*H*),6(1*H*)-pyrimidindione (**304**)[96] were treated with Ac_2O, there was obtained 2-acetamido-5-acetyl-4(3*H*),6(1*H*)-pyrimidindione (**305**), and 2,5-diacetamido-4(3*H*),6(1*H*)-

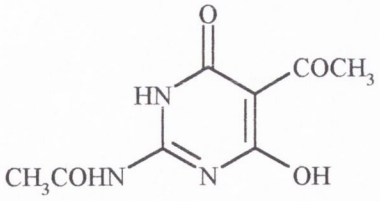




(304) **(306)**

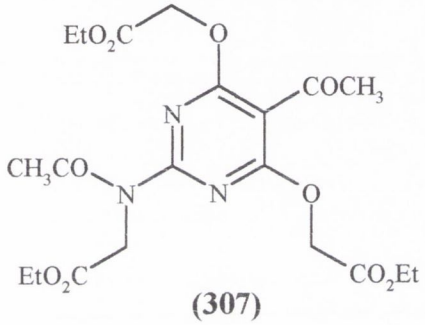
pyrimidindione (**306**) respectively. The unexpected acetylation of (**243**) at position 5 is evidence that 4,6-dioxopyrimidines have considerably enhanced electron density at this position. This acetylation reaction would need further investigation to ascertain if milder conditions could be used to produce the desired product (**305B**) directly. Substrates such as (**305B**), which appear to have high electron densities at position 5, would be useful starting materials in any future studies of intra molecular cyclisations onto this position.

As in previous cases, the products of acetylation (**305**) and (**306**) contain potentially nucleophilic oxygen atoms, which can be reacted with electrophiles. Thus treatment of (**305**) with ethyl bromoacetate gave a mixture of products which were shown to be (**307**) and (**308**). Similar treatment of (**304**) with ethylbromoacetate also gave a mixture of products, which were identified as (**309**) and (**310**). The structure of the unusual tri-alkylated product (**307**) was confirmed by its ^{13}C NMR spectrum and by comparison with a similar product. For example the earlier product (**273**), contains an *N*-alkyl and *O*-alkyl side chain. The methylene group adjacent to the *N*-atom in (**273**) has a chemical shift of 46.2 ppm whereas that next to an *O*-atom has a value of 63.0 ppm. In the product (**307**) there are corresponding peaks at 46.5 ppm and 63.0 ppm, which are probably due to the same two methylene groups as in (**273**). The mixed *N* and *O*-alkylation product (**310**) was also confirmed by a similar comparison of its mixed methylene groups. The ^{13}C chemical shifts of these and some related products are shown on page 101 (note that the proton NMR chemical shifts are given in brackets)



(305)

$BrCH_2CO_2Et/DMF/Na_2CO_3$



(307)

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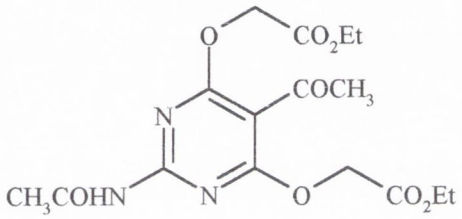
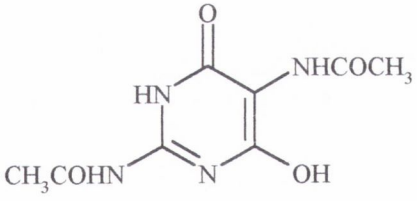
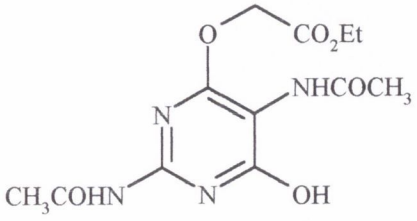


(308)



(306)

$BrCH_2CO_2Et/DMF/Na_2CO_3$



(309)

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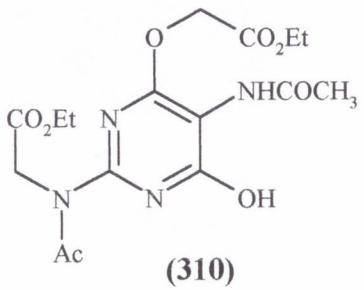
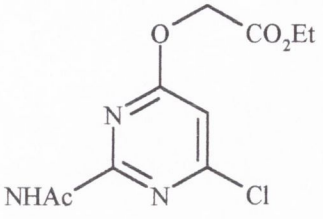


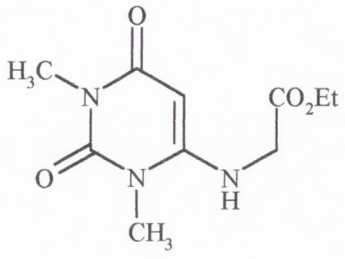
(310)

Chemical shifts of methylene protons in various pyrimidines



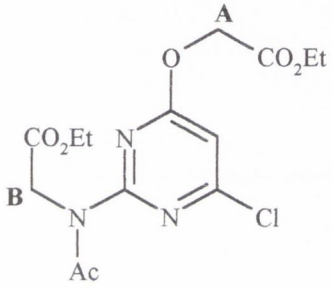
(272)

63.0 ppm (4.90)



(334)

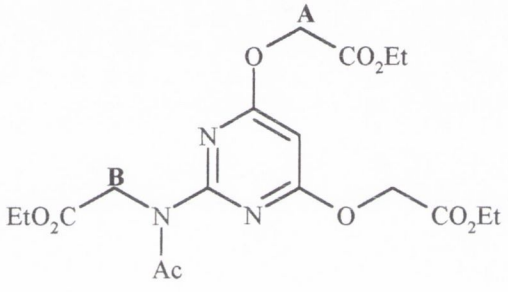
43.76 ppm (3.96)



(273)

A = 63.0 ppm (4.84)

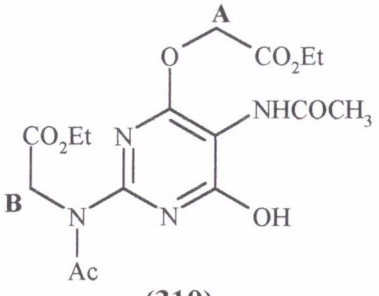
B = 46.2 ppm (4.74)



(307)

A = 63.0 ppm (4.87)

B = 46.5 ppm (4.67)

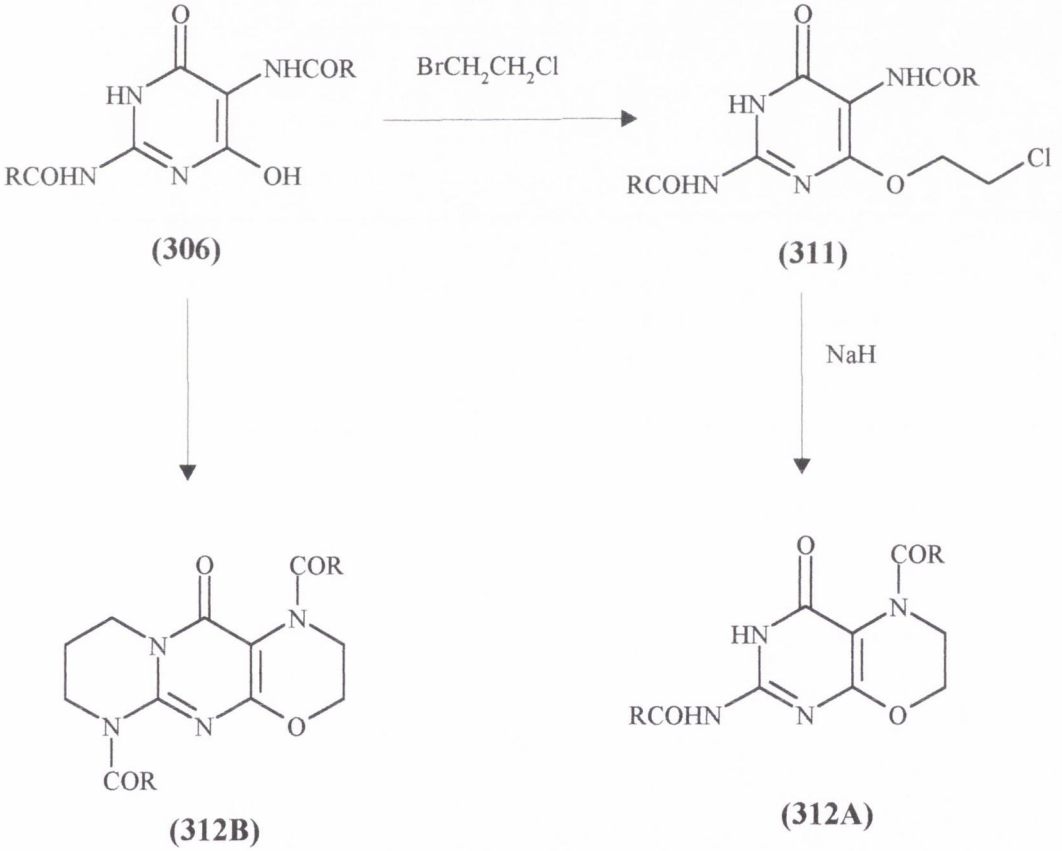


(310)

A = 64.0 ppm (5.15)

B = 47.3 ppm (4.7)

These alkylation reactions are another example of how a simple pyrimidine such as 2-amino-4(3*H*),6(1*H*)-pyrimidindione (**243**) can be converted, in two short steps, into highly functionalised products such as (**307**) and (**308**), which may be of use as model compounds for further studies. In addition to the aforementioned alkylation products, it may be possible to alkylate (**305**) or (**306**) with any chosen alkyl halide. For example the alkylation product (**311**) could be synthesised and might then react intramolecularly to give a cyclised product (**312A**). Alternatively the alkylation may follow a path similar to that which leads to the formation of (**288**) and (**289**) seen earlier, in this case giving (**312B**). In fact one would probably expect a number of novel multi alkylation/cyclised products.



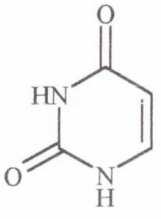
(306) **(311)**

(312B) **(312A)**

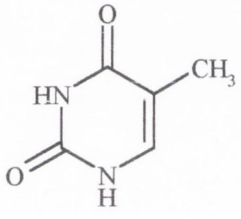
3.8. Reactions of 2,4-dioxopyrimidines

2,4-(1*H*, 3*H*)-pyrimidindione, normally called by the trivial name uracil (**313**), is the parent compound of an important class of naturally occurring pyrimidines which

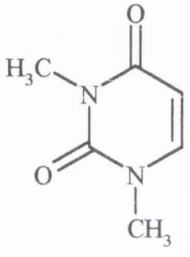
have been extensively studied.[108] Uracil itself is a constituent of RNA, while its 5-methyl derivative thymine (**314**), replaces it in DNA. There are uracils based drugs which act as anti-inflammatory,[109] anti-cancer agents,[110] thyroid inhibitors,[111] anti-hypertensives[112] and recently the reverse transcriptase inhibitors used in AIDS treatments, *e.g.* AZT (**316**)[113] and CNT (**317**). Condensed uracils form important molecules such as caffeine, riboflavin (Vit B_2) (**318**), and toxoflavin (an antibiotic). Because of its strongly polar groups, uracil itself shows only weak solubility in the normal solvents. Thus uracil is normally replaced by 1,3-dimethyluracil (**315**), which acts as a model compound.



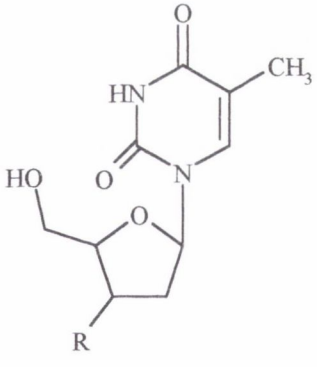
(313)



(314)

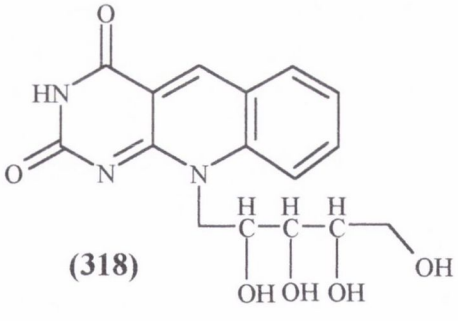


(315)



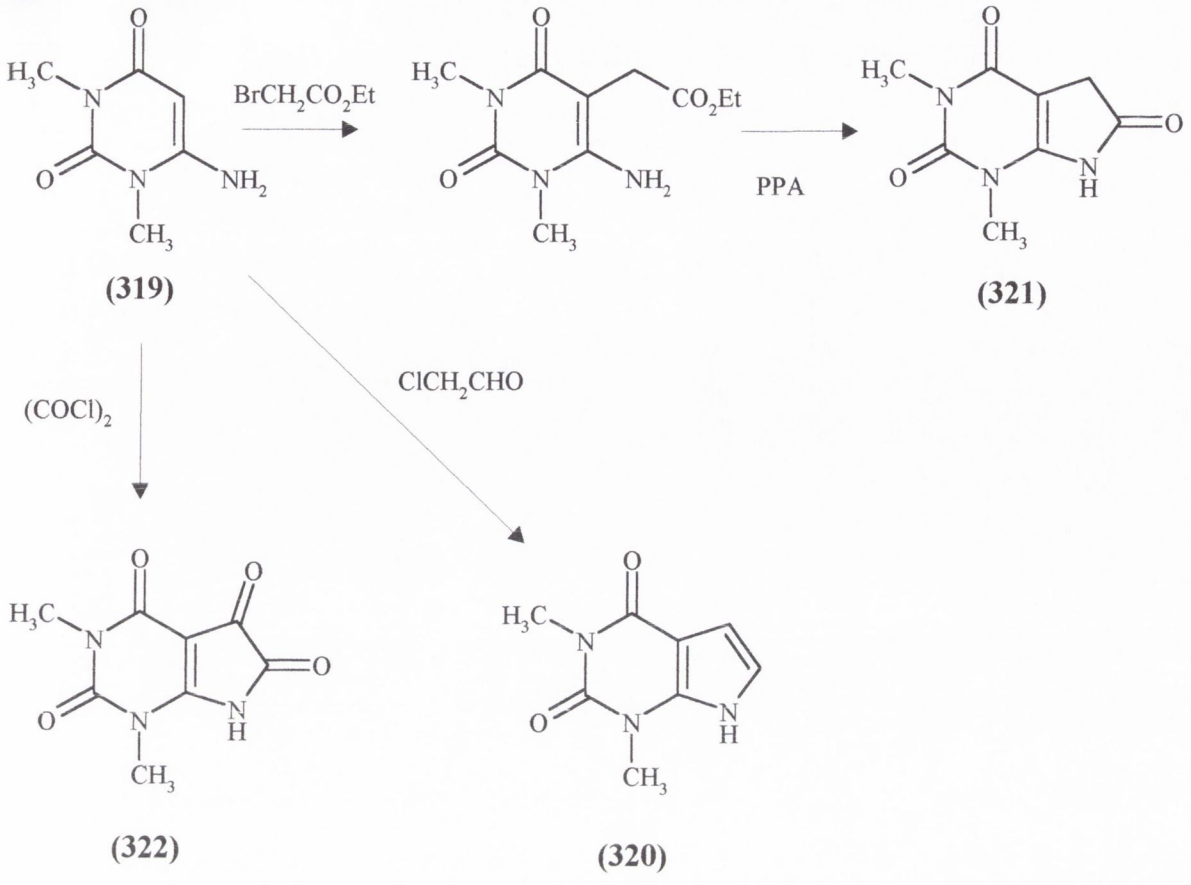
(316) R = N_3

(317) R = CN



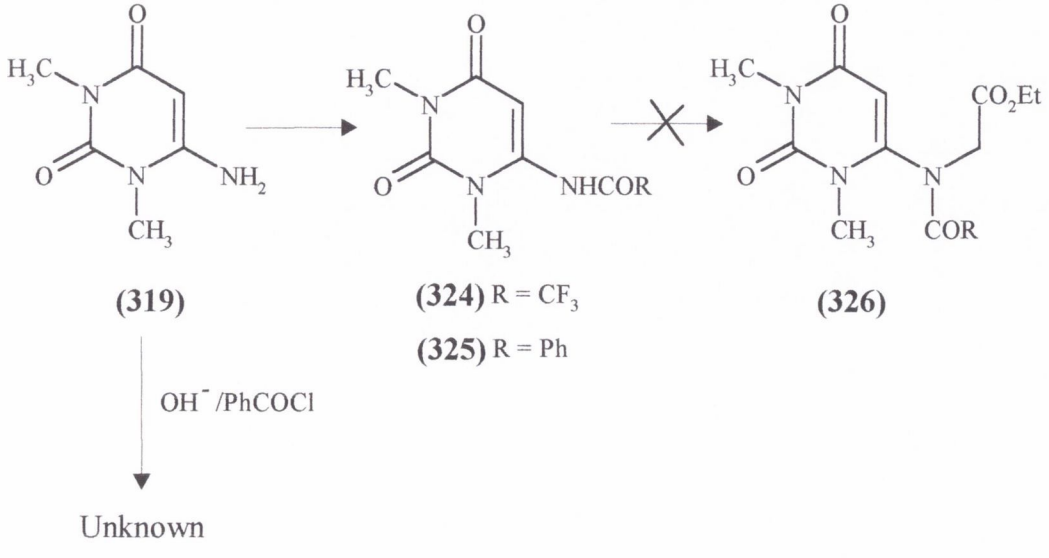
(318)

4-amino-1,3-dimethyl-uracil (**319**) is a cheap, commercially available chemical which has been used in the preparation of various heterocyclic compounds by treatment with α-halo aldehydes[114], α-halo esters[115] or oxalylchloride[116], to give (**320**), (**321**) and (**322**) respectively.

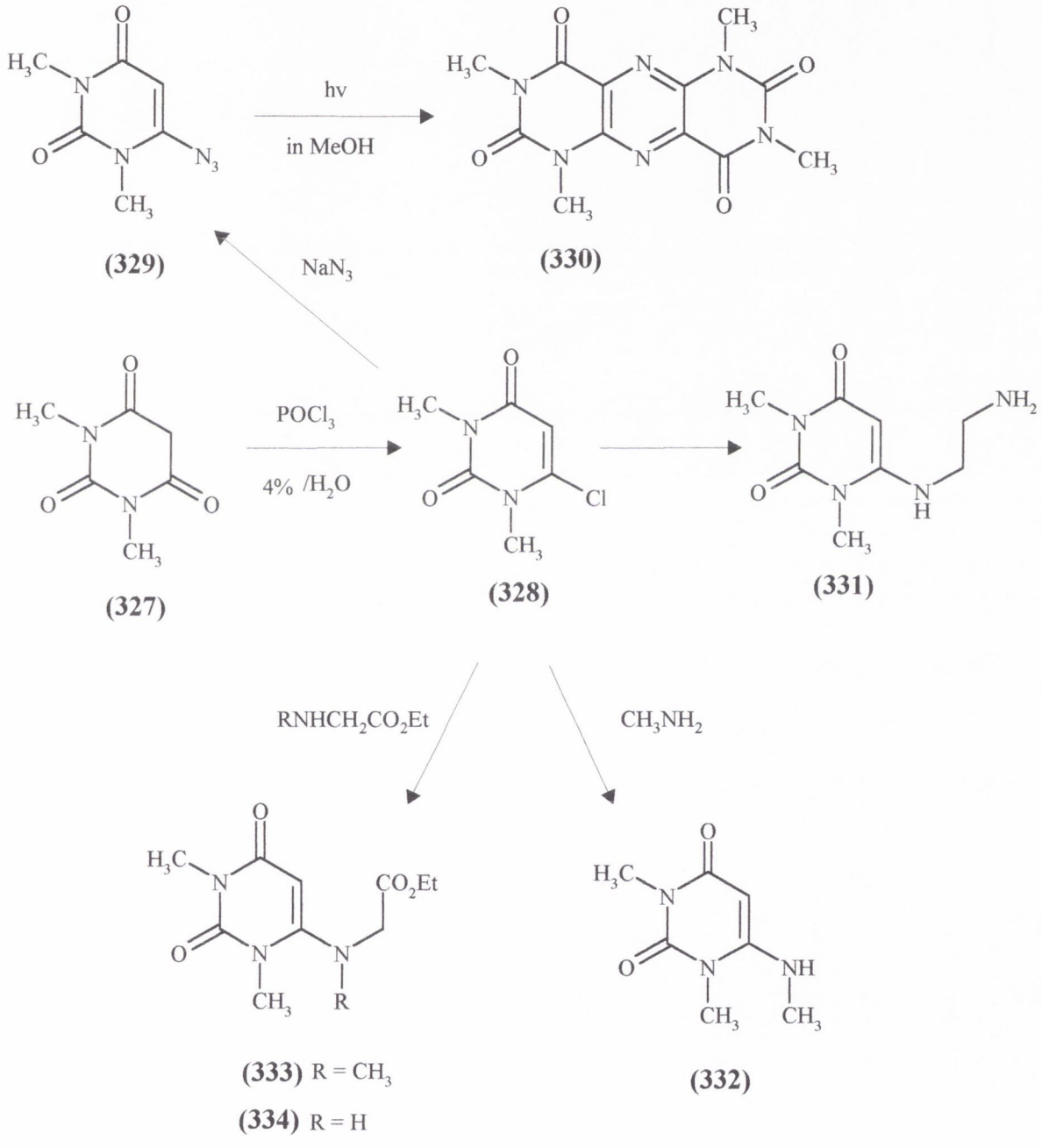


The 4-amino group in (**319**) is easily acylated to give, for example, the trifluoroacetamido derivative (**324**). All efforts to alkylate the amido nitrogen in (**324**) and thus produce (**326**) were proved unsuccessful.

In an effort to prepare 4-benzamido-1,3-dimethyluracil (**325**) by treatment of (**319**) with benzoyl chloride under Schotten Bauman conditions, a pure white crystalline product was isolated which, as yet remains unidentified.



4-Chloro-1,3-dimethyluracil (**328**) is easily prepared by treatment of the commercially available 1,3-dimethylbarbituric acid (**327**) with $POCl_3$ containing four percent water.[117] (**328**) has been converted to the azido product (**329**), which has been used to prepare various heterocyclics, such as (**330**).[25] In the present work the chlorine atom in (**328**) was easily replaced by various amino nucleophiles to give products (**331**) – (**334**).



(329) **(330)** **(327)** **(328)** **(331)**

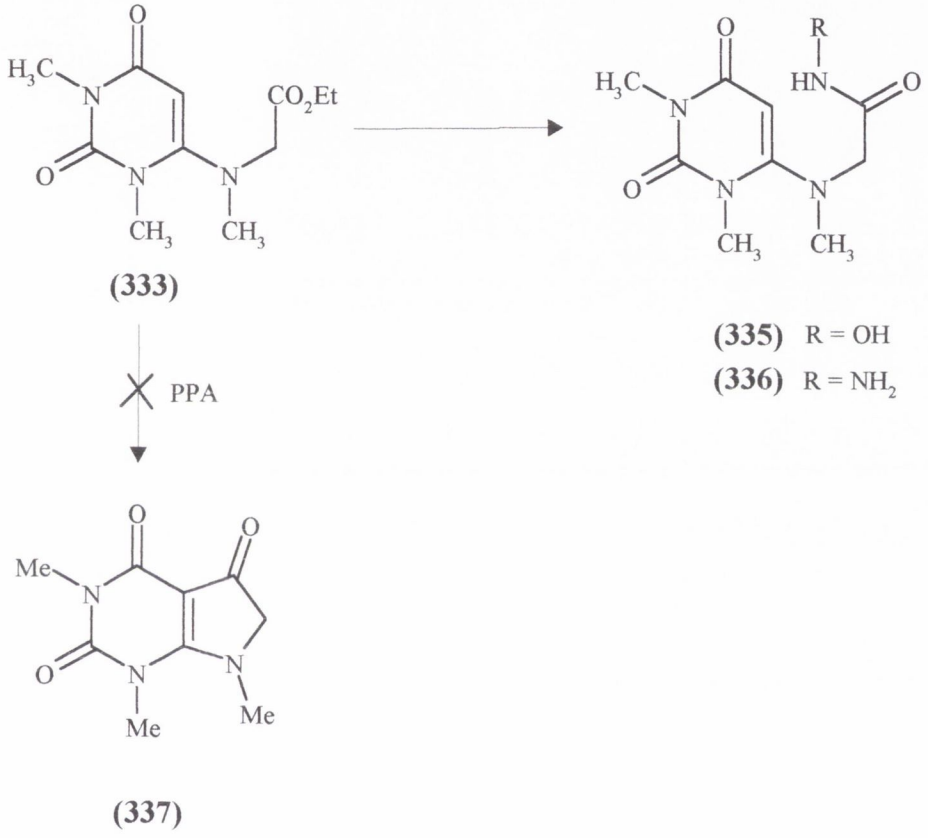
(333) R = CH_3

(334) R = H

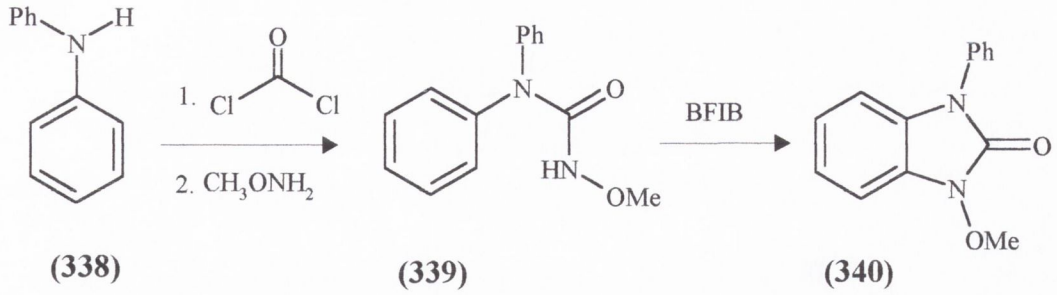
(332)

The product derived from sarcosine ethylester, namely 1,3-dimethyl-4-(ethoxy-carbonylmethyl-*N*-methyl)aminouracil (**333**), which has a fully *N*-protected nucleus,

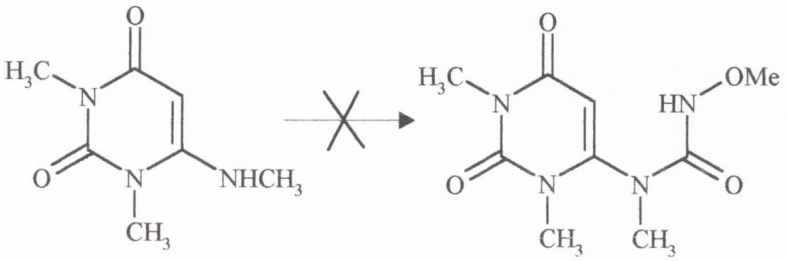
was converted into the corresponding hydroxamic acid (**335**) and hydrazide (**336**), by treatment with the appropriate reagent. It was noted that when the hydroxamic acid (**335**) was stored in a clear bottle at room temperature for long periods, it gradually deteriorated into a yellow gum like substance. An attempt was made to cyclise (**333**) to a pyrrolo[*2,3*-d]pyrimidine (**337**), using polyphosphoric acid (PPA) at however no useful product could be obtained from this experiment.



1,3-Dimethyl-4-methylaminouracil (**332**),[118] was prepared in order to test its suitability to a series of reactions described by Romero for the production of cyclic ureas.[65] In Romero's two step process, a substituted amide such as (**338**) is treated with phosgene or a phosgene equivalent such as carbonyl diimidazole (CDI), followed by methoxylamine to give the open chained urea product (**339**). Bis(trifluoroacetoxy)iodobenzene was then used in the oxidative cyclization of (**339**) to give an *N*-substituted 2-benzimidazolinone (**340**). However when (**332**) was treated with CDI/methoxylamine under the same conditions, there was no detectable reaction to produce (**341**) (TLC analysis).

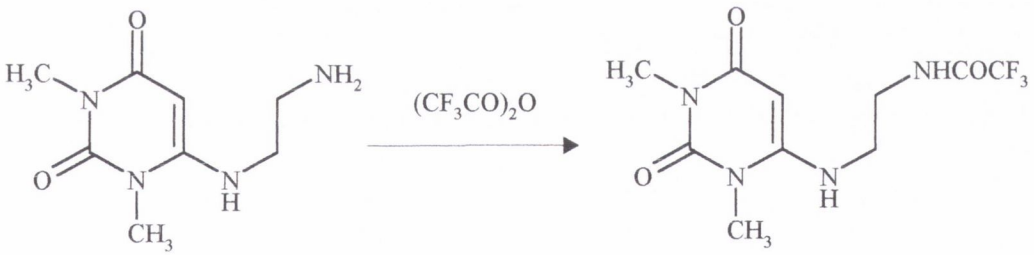


(338) **(339)** **(340)**



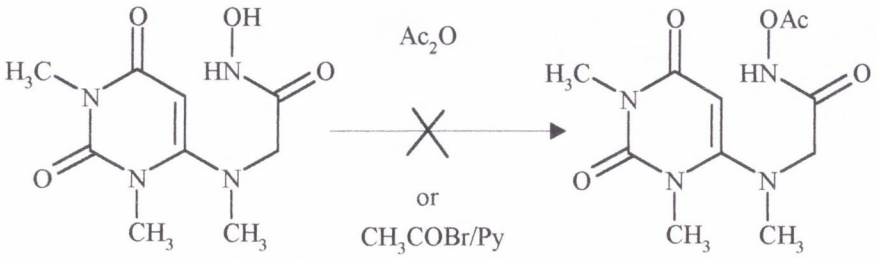
(332) **(341)**

The ethylenediamino substitution product (**331**) when treated with $(CF_3CO)_2O$, gave the acyl amino product (**342**).



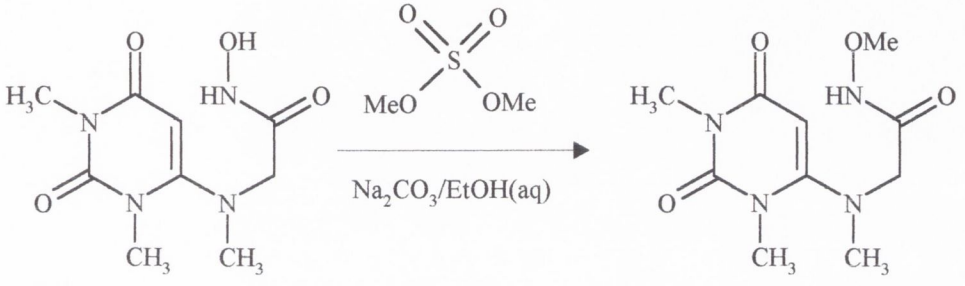
(331) **(342)**

All attempts to acetylate the hydroxamic acid (**335**) to prepare (**343**) resulted in the production of a mixture of products, which could not be purified.



(335) **(343)**

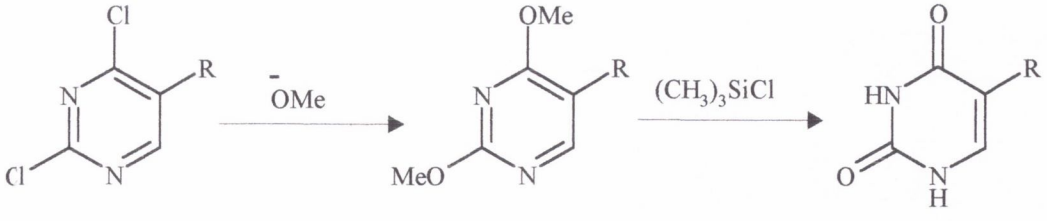
Methylation of (**335**) however, was more successful and the *O*-methyl hydroxamate (**344**) was prepared by treatment of (**335**) with dimethyl sulphate in basic aqueous ethanol. The product (**344**), which was obtained, was disappointingly insoluble in common organic solvents such as chloroform and THF, and no reactions were conducted on this substrate. This solubility might be improved by conversion of (**344**) to an *N*-chloro compound, similar to the substrate used by Kikugawa.[28]



(335) **(344)**

3.9. Reactions of 2,4-Dimethoxypyrimidines

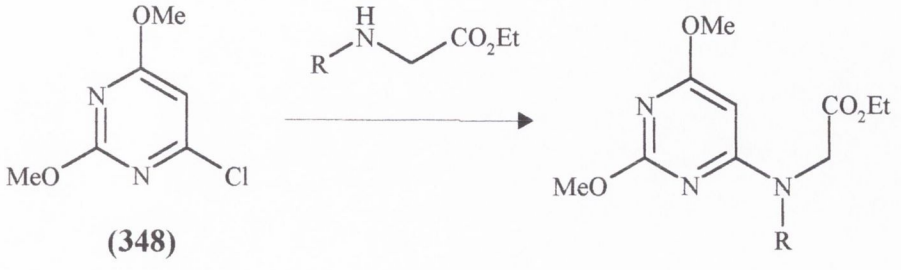
2,4-Dimethoxypyrimidines exhibit excellent solubility in common solvents and are therefore good replacements for the insoluble uracils. Interestingly, it is known that 2,4-dimethoxypyrimidines can readily be 'demasked' to give uracils, by treatment with trimethylchlorosilane as in the example of the conversion of (**346**) to (**347**)[119, 120]. When all reactions have been completed, they can be transformed into the biologically active uracil form.



(345) **(346)** **(347)**

4-Chloro-2,6-dimethoxypyrimidine (**348**) is a commercially available chemical. The chlorine atom in (**348**) is readily replaced by amino acid esters to give, for example, the substitution products (**349**) and (**350**). The *N*-methyl derivative, 2,4-

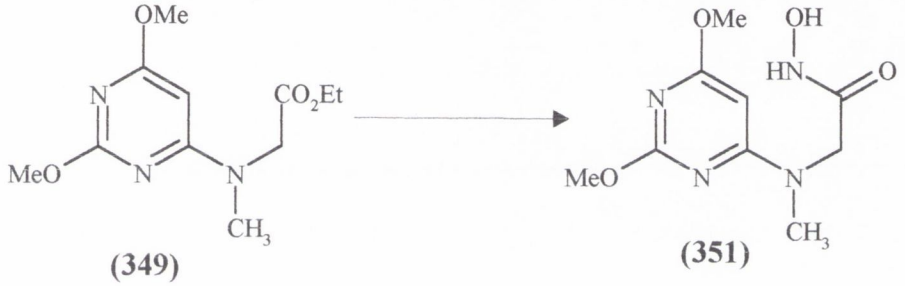
dimethoxy-6-(ethoxycarbonylmethyl-*N*-benzyl)aminopyrimidine (**349**), was chosen as the substrate for further reactions. For example (**349**) was converted into the corresponding hydroxamic acid (**351**).



(348)

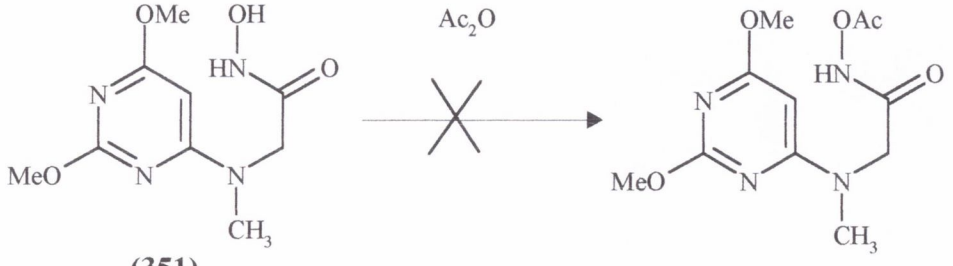
(349) R = CH_3

(350) R = CH_2Ph

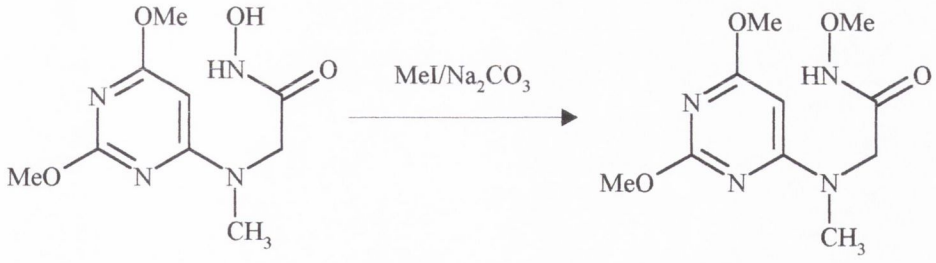


(349) **(351)**

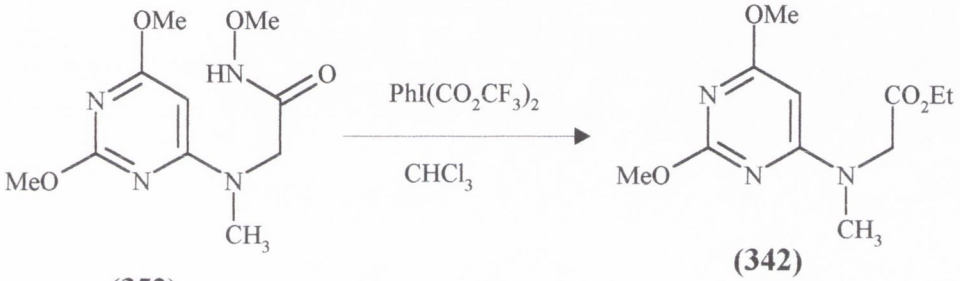
As with the earlier 1,3-dimethyluracil hydroxamic acid (**335**), the 2,4-dimethoxy hydroxamic acid (**351**) did not acetylate cleanly and no pure products were obtained using normal methods. Methylation of (**351**), however proved more successful, and the *O*-methyl hydroxamate product (**352**) obtained was very soluble in all common solvents. When (**352**) was treated with bis(trifluoroacetoxy)iodobenzene the only product obtained was the corresponding ethyl ester product (**349**),



(351)



(351) **(352)**



(352) **(342)**

This reaction is analogous to that discussed in chapter two for the 2-phenylpyrimidine (**188**), and the same mechanism is probably involved in both transformations.

3.0 Conclusions

A wide variety of new 2-phenylpyrimidines, containing functionalised side chains, were prepared. These included some unusual di-substituted products, which may find use in the synthesis of macrocyclics. The side chains were manipulated to contain various functional groups, including, hydroxyl, acid, anhydride, ester, amide, hydrazide, acyl azide, hydroxamic acids and their derivatives. The preparation and reactions of pyrimidine azides requires further investigation, as this may lead to some novel products. The hydroxamic derivatives were analogous to those prepared by earlier workers in the benzenoid field. In these earlier experiments, hydroxamic acid derivatives were induced to undergo cyclisation reactions when treated with either iron(III) chloride or a hypervalent iodine reagent. In each case, a nitrenium ion, a divalent electrophilic nitrogen species was proposed as an intermediate. Treatment of some pyrimidine hydroxamic acid derivatives with these reagents failed to give cyclised products. In the case of iron (III) catalysed reactions, the products were the corresponding ester and primary amide. The ester was formed by direct attack of alcohol on the carbonyl carbon atom of acylated hydroxamic acids. This carbon atom is rendered more electrophilic, by the strong inductive effect of the adjacent acylated nitrogen. The amide is proposed to have formed by reduction of an initially formed nitrenium ion. The pyrimidine ring in the test cases did not have sufficient electron density to trap the intermediate. It may be possible in future to synthesise alternative derivatives containing a more electron rich pyrimidine nucleus. Treatment of an *O*-methylhydroxamate with bis(trifluoroacetoxy)iodobenzene, lead to to isolation of the corresponding ester.

Also prepared, were a variety of 2-amino, 2-acetamido, 2,6-diamino, 2,6-diacetamido, 4,6-dioxo, 2,4-dioxo, and 2,4-dimethoxypyrimidines. Many of these products were unusual muti-alkylation products, containing up to three side chains, adjacent to both oxygen and nitrogen. Di-haloalkanes reacted with an acetamido pyrmidinone to give products in which alkylation and cyclisation had occurred in a single step. These reactions require intimate study to ascertain the scope of this interesting reaction. Some additional pyrimidine hydroxamic acids were synthesised, which could not be acylated to suitable derivatives. An *O*-methyl hydroxamic acid was prepared and reacted with bis(trifluoroacetoxy)iodobenzene to, again, give the corresponding ester.

Chapter four

Experimental Section

4-Amino-6-ethoxycarbonylmethoxy-2-phenylpyrimidine (132)

Method A

6-Amino-2-phenyl-4(3*H*)pyrimidinone (**130**) (2 g, 10.7 mmol) was dissolved in DMF (30 ml) and to this was added anhydrous sodium carbonate (2.32 g, 21.9 mmol) and the suspension stirred and heated for fifteen minutes. Ethyl bromoacetate (1.22 ml, 11 mmol) was added and the reaction mixture heated at 120° for 1.5 h. The solid sodium carbonate was filtered from the yellow solution and the filtrate evaporated to approximately 5-10 ml. The mixture was treated with water (50 ml), and a white product, which precipitated, was filtered. The product was recrystallised from aqueous ethanol (80 % ethanol) giving white needles of **(132)**, (2.2 g, 75 %) m.p. 103-106^{0}C (aq EtOH). (Found: C, 61.23; H, 5.54; N, 15.29; $C_{14}H_{15}N_3O_3$ requires C, 61.53; H, 5.53; N, 15.38 %) δ_H (300 MHz; d_6-DMSO) 1.20 (3H, t, J = 7, $CH_2\underline{CH_3}$), 4.17 (2H, q, J = 7, $\underline{CH_2}CH_3$), 4.93 (2H, s,CH_2), 5.82 (1H, s, 5-H), 6.85 (2H, s, NH_2), 7.47 (3H, m, Ph), 8.26 (2H, m, Ph) δ_C (75.5 MHz d_6-DMS0) +DEPT 14.1 ($CH_2\underline{CH_3}$) 60.4 ($\underline{CH_2}CH_3$) 62.3 (CH_2), 84.3 (5-CH), 127.5, 128.2, 130.4 (C-H Ph), 137.5, 162.1, 166.0, 168.3, 169.0 (q-C).

ν_{max} (nujol) 3428, 3334, 3233, 1742, 1642. λ_{max} (EtOH 95)/nm 236 (loge/dm^3 mol^{-1} cm^{-1}) (4.36), 260 (4.07), (0.1M NaOH) 216 (4.30), 234 (4.28), (0.1M HCl) 248 (4.17), 296 (4.0).

(132) Method B

To a flask containing iron(III) chloride (107 mg, 0.66 mmol) under a nitrogen atmosphere was added $CHCl_3$ (8 ml), and acetic acid (20 µl, 0.33 mmol). The mixture was stirred at room temp for 10 min, and to it was added a solution of 4-amino-6-*N*-acetoxycarbamoylmethoxy-2-phenylpyrimidine **(186)** (100 mg, 0.33 mmol) in $CHCl_3$ (15 ml). The mixture was refluxed under N_2 for 4 hr. Aqueous $NaHCO_3$ solution was then added and the mixture extracted with $CHCl_3$. The organic phase was dried ($MgSO_4$), passed through a plug of silica to remove residual iron salts and concentrated on a rotary evaporator. Addition of hexane followed by cooling gave **(132)** as a white solid (15 mg, 15 %). The product was identical to the specimen prepared in method A above

(132) Method C

4-Amino-6-*N*-methoxycarbamoylmethoxy-2-phenylpyrimidine (**188**) (274 mg 1 mmol) dissolved in $CHCl_3$ (8 ml) was added to a solution of bis(trifluoroacetoxy)iodobenzene (566 mg, 1.3 mmol) in $CHCl_3$ (10 ml) at 60^0C under an N_2 atmosphere. The reaction mixture, which had turned yellow upon the addition, was heated for 15 min. The mixture was poured into saturated $NaHCO_3$ solution and extracted with DCM. The organic phase was dried ($MgSO_4$), concentrated to an oil and loaded unto a plug of silica. Elution with EtOAc gave the product as a white solid (20 mg, 7%). The product was identical to specimens prepared in methods A and B above.

4-Amino-6-methoxycarbonylmethoxy-2-phenylpyrimidine (133)

6-Amino-2-phenyl-4(3*H*)-pyrimidinone (**130**) (2.0 g, 10.7 mmol) was dissolved in DMF (30 ml) and to this was added anhydrous sodium carbonate (2.34 g, 22 mmol) and the suspension stirred and gently heated for fifteen minutes. Methybromo acetate (1 ml, 10.5 mmol) was added to the mixture, and the reaction heated at 90°C for one hour. After filtration of the solid sodium carbonate and evaporation of two thirds of the solvent, the product was precipitated by the addition of H_2O (50 ml). The white product was recrystallised from 95 % MeOH/H_2O to give white needles (2.3 g, 83 %) m.p. 142°-146° C (MeOH 95/H_2O 5 %). (Found: C, 59.78; H, 5.03; N, 15.93; $C_{13}H_{13}N_3O_3$ requires; C, 60.23; H, 5.05; N, 16.21 %) δ_H (300 MHz d_6-DMSO), 3.71 (3H, s, CH_3), 4.96 (2H, s, CH_2), 5.80 (1H, s, 5-H), 6.86 (2H, s, NH_2), 7.48 (3H, m, Ph), 8.25 (2H, m, Ph). δ_C (75.5 MHz d_6- DMSO) + DEPT 51.7 (CH_3), 62.2 (CH_2), 84.3 (5-CH), 127.5, 128.3, 130.4 (C-H Ph), 137.5, 162.2, 166.0, 168.2, 169.5 (q-C) ν_{max} (nujol)/cm^{-1} 3502, 3390, 1740, 1609, 1553, 1279, 1232, 1195, 1082, 892, 834, 759, 706. λ_{max}(EtOH 95)/nm 238 (loge dm^3 mol^{-1} cm^{-1} 4.3), 262 (4.1).

4-Chloro-6-ethoxycarbonylmethylamino-2-phenylpyrimidine (135).

4-6-Dichloro-2-phenylpyrimidine **(134)** (500 mg, 2.2 mmol) was dissolved in 1-4 dioxan (15 ml) with heating. To this was added an aqueous solution (30 ml) of glycine ethyl ester (1.3 g, 12.6 mmol), (obtained by neutralising the equivalent

quantity of glycine ethyl ester hydrochloride salt with sodium bicarbonate in water). The mixture was refluxed for 3 h. Upon cooling a white solid separated from the solution. The product was recrystallised from ethanol to give white crystals of **(135)** (376 mg 58.5%); m.p.155.5-157.5°C (EtOH). (Found: C, 57.51; H, 4.82; N, 14.22; Cl, 11.88; $C_{14}H_{14}N_3O_2Cl$ requires C, 57.64; H, 4.84; N, 14.40; Cl, 12.15 %).

δ_H(300 MHz, d_6-DMSO) 1.22 (3H, t, $CH_2\underline{CH_3}$ J = 7), 4.16 (2H, q, $\underline{CH_2}CH_3$, J = 7), 4.22 (2H, d, CH_2,J = 5), 6.70 (1H, s, 5-H), 7.50 (3H, t, Ph), 8.26 (2H, m, Ph), 8.33 (1H, t, J = 5, NH). δ_C(75.5 MHz d_6-DMSO) 14.12 (CH_3), 42.58 (CH_2), 60.40 (CH_2), 102.04 (CH), 127.70, 128.40, 131.04 (CH, Ph), 136.4, 157.81, 163.08, 163.25, 170.08 (q-C). ν_{max} (nujol)/cm^{-1} 3375, 3115, 1731, 1604, 1569.

λ_{max} (EtOH 95)/nm 250 (loge/dm^3 mol^{-1} cm^{-1}) 4.28.

4-Amino-6-methoxy-2-phenylpyrimidine (140)

6-Amino-2-phenyl-4(3*H*)-pyrimidinone (**130**), (700 mg, 3.8 mmol) was dissolved in DMF (15 ml). The solution was heated at 100°C for ten minutes and anhydrous sodium carbonate (0.85 g, 8.0 mmol) was added. The suspension was heated for fifteen minutes. Methyl iodide (0.25 ml, 4.0 mmol) was added to the mixture, and the reaction heated at 140°C for 1 hr. A new product (TLC) was detected but it was necessary to add additional MeI (0.1 ml, 1.6 mmol) and to heat for a further 30 minutes in order to complete the reaction. The solid Na_2CO_3 was filtered from the mixture, and the DMF was evaporated to give oil. Water (50 ml) was added and the aqueous layer extracted with EtOAc. After drying, ($MgSO_4$) treatment with charcoal, evaporation of the excess solvent, and dilution with hexane, a white solid product was obtained (400 mg, 52 %) (EtOAc-Hex). δ_H (300 MHz d_6-DMSO) 3.17 (3H, s, CH_3), 5.18 (1H, s, 5H), 6.53 (2H, br.s, NH_2), 7.53 (5H, m, Ph). δ_C (75.5 MHz d_6-DMSO) + DEPT 32.6 (CH_3), 83.4 (5-C-H), 127.9, 128.3, 129.7 (C-H Ph), 135.2, 160.0, 162.10, 162.23 (q-C).

4-Amino-6-benzyloxy-2-phenylpyrimidine (141)

6-Amino-2-phenyl-4(3*H*)-pyrimidinone (**130**) (2.03 g, 10.85 mmol) was dissolved in DMF (30 ml). Anhydrous potassium carbonate (3.04 g, 21.9 mmol) was added and the suspension stirred vigorously and heated to 120°C for 10 min. Benzylchloride (1.1 ml, 9.55 mmol) was added and the mixture heated at 120°C for 40 min. The solid material was filtered and the filtrate evaporated to give a viscous orange oil. Water (50 ml) was added and the aqueous solution extracted with ethyl acetate and chloroform. The organic extracts were combined, dried ($MgSO_4$), and treated with charcoal. Further concentration gave a pale yellow oil, which was dissolved in ethyl acetate (3ml). The product was precipitated by addition of hexane dropwise to the solution in an ice bath, giving white crystals (1.3 g, 49 %), m.p. 89-92°C (EtOAc/Hex). δ_H (400MHz, d_6-DMSO) 5.47 (2H, s, 5-H) 6.72 (2H, s, NH_2) 7.38 (8H, m, Ph) 8.34 (2H, m, Ph). δ_C (100 MHz, d_6-DMSO) + DEPT 66.67 (CH_2) 84.38 (5-H) 127.50, 127.65, 127.90, 128.21, 128.40, 130.21 (C-H Ph) 137.38, 137.82, 162.57, 165.93, 169.25 (q-C)

4-Amino-6-(3-chloropropoxy)-2-phenylpyrimidine (142)

6-Amino-2-phenyl-4(3*H*)-pyrimidinone (**130**) (1 g, 5.35 mmol) and anhydrous K_2CO_3 (1.6 g, 11 mmol) were stirred together in DMF (20 ml) at 100^0C for 15 min. 1-Bromo-3-chloro-propane (0.5 ml, 5.2 mmol) was added and the reaction heated for a further 20 minutes. The solid carbonate was filtered and the DMF removed. The resulting oil was dissolved in H_2O (200 ml). The aqueous solution was frozen with an acetone/liq N_2 slush bath. Allowing the mixture to warm to room temp gave white prisms of product (600 mg, 43 %) m.p. 71-74^{0}C (EtOAc/Hex). (Found: C, 58.90; H, 5.38; N, 15.64; Cl, 12.30; $C_{13}H_{14}N_3OCl$ requires C, 59.20; H, 5.31; N, 15.94; Cl, 13.47 %). δ_H (400 MHz, $CDCl_3$), 2.17 (2H, quintet, $CH_2\underline{CH_2}CH_2$, J = 6.04), 3.63 (2H, t, $CH_2CH_2\underline{CH_2}Cl$, J = 6.5), 4.85 (2H, t, $\underline{CH_2}CH_2CH_2Cl$, J = 6.0), 4.74 (2H, br.s, NH_2), 5.60 (5-CH), 7.35 (3H, m, Ph), 8.27 (2H, m, Ph). δ_C (100 MHz, $CDCl_3$), 34.0, 43.0, 64.5 (CH_2), 87.2 (5-CH), 129.94, 130.05, 132.22, (CH, Ph), 139.6 165.8, 166.7, 172.02 (q-C)

ν_{max} (nujol)/cm^{-1} 3466, 3306, 3153, 1644, 1556, 1271.

4,6-Di(ethoxycarbonylmethoxy)-2-phenylpyrimidine (144)

This compound was obtained as described below for (**145**). The product was obtained as the faster eluting spot (8.0 g, 28 %) m.p.100-106^{0}C.

(Found: C, 60.30; H, 5.67; N, 7.94; $C_{18}H_{20}N_2O_6$ requires C, 59.99; H, 5.59; N, 7.77 %). δ_H (300 MHz d_6-DMSO) 1.22 (6H, t, 2 x CH_3, J = 7), 4.19 (4H, q, 2 x $\underline{CH_2}CH_3$, J = 7), 5.05 (4H, s, 2 x CH_2), 6.45 (1H, s, 5-H), 7.5 (3H, m, Ph), 8.2 (2H, q, Ph).

δ_C (75.5 MHz d_6-DMSO). + DEPT 14.07 (2 x CH_3), 60.62 (2 x CH_2CH_3), 63.24 (2 x CH_2), 88.92 (C-H 5 position), 127.67, 128.55, 131.47 (C-H Ph), 135.92, 161.73, 168.43, 169.9 (there are 2 sets of quaternary carbons).

ν_{max} (nujol)/cm^{-1} 1747, 1596, 1564, 1307, 1280, 1179, 1079, 1030.

λ_{max} (EtOH 95)/nm (loge dm^3 mol^{-1} cm^{-1}).

6-Ethoxycarbonylmethoxy-2-phenyl-4(3*H*)-pyrimidinone (145)

2-Phenyl-4(3*H*),6(1*H*)-pyrimidindione (**143**) (15 g, 0.08 mol) was dissolved in DMF (300 ml) with the aid of heat. To this was added Na_2CO_3 (18.75 g 17.5 mmol), and the mixture stirred and heated at 130^{0}C for 10 minutes. Ethyl bromoacetate (9.15 ml 0.082 mol) was added and the reaction was continued for 1 hr at 130^{0}C. The solid carbonate was filtered and the excess DMF removed until the solution was at a small volume (about 50 cm^3). Water (200 ml) was added slowly and the white precipitate which formed was collected and recrystallised from 95 % MeOH. The solid product (11.2 g) contained two compounds which were separated by flash chromatography (15 % EtOAc/85 % Hex) giving the above compound (**145**) as the slower eluting component (2.8 g, 13 %), m.p.172-177^{0}C (EtOAc-Hex). (Found: C, 61.24; H, 4.91; N, 10.30; $C_{14}H_{14}N_2O_4$ requires C, 61.31; H, 5.14; N, 10.21 %). δ_H (300 MHz, d_6-DMSO), 1.20 (3H, t, $CH_2\underline{CH_3}$, J = 6), 4.17 (2H, q, $\underline{CH_2}CH_3$ J = 6), 4.97 (2H, s, CH_2), 5.80 (1H, s, 5-H), 7.54 (3H, m, Ph), 8.20 (2H, m, Ph), 12.47 (1H, br.s, NH). δ_c (75.5 MHz, d_6-DMSO) + DEPT 14.09 (CH_3), 60.58 (CH_2), 63.10 (CH_2), 89.32 (5-CH),

12777, 128.63, 131.8 (C-H Ph), 132.1, 159.5, 168.5, 168.7 (NB: one peak represents two carbons) (q-C). ν_{max} (nujol)/ cm^{-1} 1752, 1654

4-Benzyloxy-6-trifluoroacetamido-2-phenylpyrimidine (152)

4-Amino-6-Benzyloxy-2-phenylpyrimidine (**141**) (750 mg, 2.7 mmol) was refluxed with trifluoroacetic anhydride (25 ml) and trifluoroacetic acid (1 ml) for 4 hr. The white solid product was filtered and dried to give (**152**) (500 mg, 58 %) m.p. 120-122^{0}C (EtOAc/Hex). δ_H (400 MHz, $CDCl_3$), 5.44 (1H, s, 5-CH), 5.5 (2H, s, CH_2), 7.2 (1H, s, NH), 7.32 (8H, m, Ph), 8.29 (2H, m, Ph). δ_C (100 MHz, $CDCl_3$) 71.3 (CH_2), 97.3 (5-CH), 130.8, 130.9, 131.2, 131.3, 131.8, 133.9 (CH Ph) 138.8, 139.0, 158.71, 166.6, 172.2, 173.8 (q-C), ν_{max} (nujol)/cm^{-1} 3347, 1723, 1600, 1567

4-Benzyloxy-6-ethoxycarbonylmethylamino-2-phenylpyrimidine (154)

4-Benzyloxy-6-trifluoroacetamido-2-phenylpyrimidine (**152**) (186 mg, 0.5 mmol) and NaH (0.12 g, 5 mmol) were heated together in dry DMF (5 ml) at 100^{0}C for 15 min. Ethylbromo acetate (0.22 ml, 2 mmol) was added and the reaction was refluxed for 2 days. The reaction was filtered, and excess DMF removed to furnish an oil, which was dissolved in EtOAc and treated with charcoal. Concentration of the solution, followed by addition of hexane and cooling gave a white fluffy solid product (50 mg, 22%) m.p. 145-147^{0}C (EtOAc/Hex). (Found: C, 69.49; H, 5.85; N, 11.42; $C_{21}H_{21}N_3O_3$ requires C, 69.42; H, 5.78; N, 11.57 %). δ_H (400 MHz, $CDCl_3$), 1.33 (3H, t, CH_3, J = 7.0), 4.21 (2H, d, CH_2), 4.28 (2H, q, CH_2, J = 7.04), 5.31 (1H, br.s, NH), 5.54 (2H, s, CH_2), 5.73 (1H, s, 5 CH), 7.42 (8H, m, Ph), 8.2 (2H, m, Ph) δ_C (100 MHz, $CDCl_3$) 13.75 (CH_3), 43.04 (CH_2), 61.0 (CH_2), 67.17 (CH_2), 84.7 (5-CH), 127.5, 127.6, 127.9, 127.75, 128.03, 129.9 (CH Ph), 136.8, 137.5, 162.9, 163.4, 169.5, 170.3 (q-C).

4-(3-Chloropropoxy)-6-trifluoroacetamido-2-phenylpyrimidine (156)

4-Amino-6-(3-chloropropoxy)-2-phenylpyrimidine (**142**) (140 mg, 0.5 mol) and trifluoroacetic anhydride (10 ml) were refluxed together for 1 hr. After cooling the

whie solid product was filtered and dried (110 mg, 61 %). m.p.135-138^{0}C. (EtOAc/Hex). (Found: C, 49.47; H, 3.65; N, 11.45; Cl, 9.55; F, 15.87; $C_{15}H_{13}N_3O_2ClF_3$ requires C, 50.07; H, 3.61; N, 11.68; Cl, 9.87; F, 15.85 %).

δ_H (400 MHz, $CDCl_3$), 2.19 (2H, quintet, $CH_2\underline{CH_2}CH_2$, J = 6.04), 3.65 (2H, t, $CH_2CH_2\underline{CH_2}Cl$, J = 6.5), 4.60 (2H, t, $\underline{CH_2}CH_2CH_2Cl$, J = 6.0), 7.25 (1H, s, NH), 7.31 (1H,s, 5H), 7.4 (3H, m, Ph), 8.28 (2H, m, Ph). δ_C (100 MHz, $CDCl_3$), 34 43, 42.0, 64.4(CH_2), 95.2 (5-CH), 129.94, 130.05, 132.22, (C-H Ph), 137.0 156.3, 156.7, 164.7, 172.) (q-C). ν_{max} (nujol)/cm^{-1} 3341, 1729, 1582, 1530, 1168.

4-Anino-6-carbamoylmethoxy-2-phenylpyrimidine (159)

4-Amino-6-ethoxycarbonylmethoxy-2-phenylpyrimidine (**132**) (880 mg, 3.22 mmd) was dissolved in ethanol (25 ml). To this solution was added ammonia soluton (11 ml of 0.88 NH_3) and the reaction mixture stirred overnight at room temperature. A white solid product separated from the reaction mixture. This material was filtered and recrystallised from aqueous ethanol to give a white powder (520 mg, 66 %), m.p.120-123^{0}C. (EtOH 90/H_2O 10 %) (Found: C, 58.91; H, 4.99; N, 22.5'; $C_{12}H_{12}N_4O_2$ requires; C, 59.01; H, 4.95; N, 22.94 %). δ_H (300 MHz, d_6-DMSO), 4.77 (2H, s, CH_2), 5.80 (1H, s, 5-H), 6.80 (2H, br.s, NH_2), 7.29 (1H, s, CONH), 7.49 (3H, s, Ph), 7.56 (1H, s, CONH), 8.31 (2H, s, Ph). δ_c (75.5 MHz d_6-DMSO) + DEPT 63.66 (CH_2), 84.60 (5-C-H), 127.68, 128.19, 130.30 (C-H Ph), 137.65, 162.28, 165.82, 168.59, 170.16 (q-C).

ν_{max}(nujol)/cm^{-1} 3633, 3464, 3421, 3335, 3166, 1682, 1648, 1591.

λ_{max}(EtOH 95)/nm 236 (loge dm^3 mol^{-1} cm^{-1}) (4.32), 260 (4.03).

4-Amino-6-hydrazinocarbonylmethoxy-2-phenylpyrimidine (160)

Method A

4Amino-6-ethoxycarbonylmethoxy-2-phenyl pyrimidine (**132**) (1 g, 3.66 mmol) was dissolved in ethanol (15 ml) containing hydrazine hydrate (12 ml) and the mixtue stirred overnight at room temperature. The product which precipitated from the soution was collected and dried (680 mg, 72 %) m.p. 182-185 (EtOH). (Found:

C, 55.63; H, 5.05; N, 26.66; $C_{12}H_{13}N_5O_2$ requires; C, 55.59; H, 5.05; N, 27.01 %). δ_H (300 MHz d_6-DMSO), 4.33 (2H, br.s, NH-$\underline{NH_2}$), 4.84 (2H, s, CH_2), 5.8 (1H, s, 5H), 6.82 (2H, s, NH_2), 7.48 (3H, m, Ph), 8.32 (2H, m, Ph), 9.38 (1H, s, $\underline{NH}$-NH_2). δ_c (75.5 MHz d_6-DMSO) + DEPT 63.07 (CH_2), 84.70 (5-C-H), 127.75, 128.25, 130.34 (C-H Ph), 137.64, 162.37, 165.84, 167.30, 168.56 (q-C).

ν_{max} (nujol)/cm^{-1} 3440, 3310, 1676, 1635, 1591, 1560 1214, 837. λ_{max} (EtOH 95)/nm 236 (loge dm^3 mol^{-1} cm^1 4.26), 262 (4.04)

(160) Method B

Product (**160**) was also obtained as the major product during the attempted preparation of 4-acetamido-6-hydrazinocarbamoylmethoxy-2-phenylpyrimidine (**163**) by reaction of the corresponding 4-acetamido ester (**171**) with hydrazine hydrate (Page 34). Thus after removal of (**163**) by filtration, the filtrate was diluted with water (50 ml). (**160**) precipitated and was collected and dried (280 mg, 68 %). This sample was identical with the specimen prepared in method A above.

4-Amino-6-*N*-propylcarbamoylmethoxy-2-phenypyrimidine (161)

4-Amino-6-etoxycarbonylmethoxy-2-phenyl pyrimidine (**132**) (600 mg, 2.2 mmol) was dissolved in n-propylamine (10 ml). The reaction was stirred at room temperature overnight and then the excess amine was removed leaving the product as a yellow oil. The oil when left to stand overnight solidified and the solid product was recrystallised from aqueous methanol (390 mg, 62 %) m.p. 114-117° C (aq MeOH) (Found: C, 63.00; H, 6.32; N, 19.30; $C_{15}H_{18}N_4O_2$ requires; C, 62.92; H, 6.34; N, 19.57%). δ_H (300 MHz d_6-DMSO) 0.86 (3H, t, CH_3, J = 7.5), 1.51 (2H, m, $CH_2\underline{CH_2}CH_3$, J = 7.3), 3.26 (2H, t, $\underline{CH_2}CH_2CH_3$, J = 6.8), 4.92 (2H, s, CH_2), 5.14 (2H, s, NH_2), 5.78 (1H, s, 5H), 6.47 (1H, br.s, NH), 7.41 (3H, m, Ph), 8.32 (2H, m, Ph). δ_c (75.5 MHz d_6-DMSO) +DEPT 11.17 (CH_3), 22.69 (CH_2), 40.70 ($\underline{CH_2}$), 64.64 (CH_2), 85.22 (5-C-H), 128.04, 128.20, 130.59 (C-H Ph), 137.10, 163.92, 165.17, 168.35, 168.72 (q-C).

ν_{max} (nujol)/ cm^{-1} 3443, 3290, 1658, 1627, 1595, 1572 and 1201. λ_{max} (EtOH 95)/nm 238 (loge dm^3 mol^{-1} cm^{-1}) (4.32), 262 (4.11)

4-Amino-6-(*N*-2-methylpropylcarbamoylmethoxy)-2-phenylpyrimidine (162)

4-Amino-6-etoxycarbonylmethoxy-2-phenylpyrimidine **(132)** (1 g, 3.66 mmol) was dissolved in isobutylamine (7 ml) and the mixture stirred for two days at room temperature. The excess solvent was removed (rot. vap.) and the resulting oily residue was allowed to solidify to a crystalline mass, which was recrystallised from ethanol. (870 mg, 79 %) m.p.112°C (EtOH). (Found: C, 64.28; H, 6.78; N, 18.49; $C_{16}H_{20}N_4O_2$ requires C, 63.98; H, 6.71; N, 18.65 %). δ_H (300 MHz, d_6-DMSO), 0.81 (6H, d, CH_3, J = 6.7), 1.72 (1H, m, $CH_2\underline{CH}(CH_3)_2$, J = 6.7), 2.96 (2H, t, CH_2 J = 6.3), 4.81 (2H, s, CH_2), 5.81 (1H, s, CH), 6.80 (2H, br.s, NH_2), 7.45 (3H, m, Ph), 8.08 (1H, t, J=6.7, NH), 8.3 (2H, m, Ph). δ_C (75.5 MHz, d_6-DMSO) + DEPT 20.00 (2 x CH_3), 28.08 ($\underline{CH}(CH_3)_2$), 45.78 ($\underline{CH_2}CH(CH_3)_2$, 63.93 ($CH_2$), 84.56 (5-CH), 127.64, 128.04, 130.22 (C-H Ph), 137.58, 162.24, 165.77, 167.83, 168.56 (q-C).

ν_{max} (nujol)/ cm^{-1} 3445, 3299, 1659, 1626, 1594, 1572.

λ_{max} (EtOH 95)/nm 228 (loge dm^3 mol^{-1} cm^{-1}) (4.4), 298 (3.66), 246 (4.22,).

4-Acetamido-6-hydrazinocarbonylmethoxy-2-phenylpyrimidine (163)

4-Acetamido-6-ethoxycarbonylmethoxy-2-phenylpyrimidine (**171**) (500 mg, 1.6 mmol) and hydrazine hydrate (5 ml) were refluxed together in ethanol (30 ml) for 30 min. The reaction mixture was concentrated, and cooled in an ice bath. The white solid, which precipitated, was collected and dried to give (**163**) (110 mg, 21 %) m .p. 194-200°C (EtOH) (Found: C, 55.38; H, 5.12; N, 22.93; $C_{14}H_{15}N_5O_3$ requires C, 55.81; H, 4.98; N, 23.26 %). δ_H (400 MHz d_6-DMSO) 2.17 (3H, s, CH_3), 4.28 (2H, br.s, NH_2), 4.90 (2H, s, CH_2), 7.46 (1H, s, 5H), 7.52 (3H, m, Ph), 8.32 (3H, m, Ph), 9.41 (1H, br.s, NH), 10.80 (1H, br.s, NH). δ_C (100 MHz d_6-DMSO) + DEPT 24.18 (CH_3), 63.71 (CH_2), 92.53 (5-H), 127.8, 128.5, 131.0 (CH Ph), 136.64, 159.07, 162.34, 166.6, 169.71, 170.6 (q-C).

ν_{max} (nujol)/cm^{-1} 3257, 3167, 1734, 1670, 1570.

4-Amino-6-*N*-(2-hydroxyethyl)carbamoylmethoxy-2-phenylpyrimidine (165)

4-Amino-6-ethoxycarbonylmethoxy-2-phenylpyrimidine (**132**) (300 mg, 1.1 nmol) and ethanolamine (0.6 ml, 9.9 mmol). Were refluxed together in ethanol (10 nl) for 2 hr. The reaction mixture was cooled and concentrated to an oil. Water (5ml) was added and the mixture frozen. The frozen mixture was allowed to warm to room temperature, when (**165**) was isolated as a white solid (120 mg, 38 %) m.p.138-140^{0}C (EtOH). (Found: C, 58.03; H, 5.65; N, 19.23; $C_{14}H_{16}N_4O_3$ requires C, 58.32; H, 5.59; N; 19.43 %). δ_H (300 MHz d_6-DMSO), 3.23 (2H, q, NH-$\underline{CH_2}$ J = 5.8), 3.45 (2H, t, CH_2, J= 6.0), 4.80 (2H, s, CH_2), 5.81 (1H, s, 5-H), 6.79 (2H, br.s, NH_2), 7.5 (3H, m, Ph), 8.09 (1H, br.s, NH), 8.3 (2H, m, Ph). δ_C (80 MHz d_6-DMSO) +DEPT 41.30 (CH_2), 59.90 (CH_2), 64.07 (CH_2), 84.69 (5-C-H), 127.82,128.35, 130.48 (C-H Ph), 137.66, 162.44, 165.95, 168.28, 168.65 (q-C).

ν_{max} (nujol)/cm^{-1} 3300, 3150, 1640, 1598, 1210, 1050, 985, 820, 755, 710. λ_{max} (EtOH 95)/nm 238 (loge dm^3 mol^{-1} cm^{-1} 4.24), 262 (4.08).

4,6-Di(hydrazinocarbonylmethoxy)-2-phenylpyrimidine (167)

4,6-Di(ethoxycarbonylmethoxy)-2-phenylpyrimidine (**144**) (0.5 g, 1.39 mmol) was refluxed in ethanol (25 ml) containing hydrazine hydrate (5 ml) for 10 minutes. The mixture was cooled and the white solid product (**167**) was collected and dried (250 mg, 57 %), m.p.>199-200^{0}C (MeOH 50/H_2O 50). (Found: C, 47.85; H, 5.12; N, 23.87; $C_{14}H_{16}N_6O_4.1H_2O$ requires C, 48.0; H, 5.14; N, 24.0 %).

δ_H (400 MHz d_6-DMSO) 4.32 (4H, br.s, 2 x NH_2), 4.90 (4H, s, 2 x CH_2), 6.29 (1H, s, 5-H) 7.51 (3H, m, Ph) 8.30 (2H, m, Ph), 9.37 (2H, br.s, 2 x NH). δ_C (100 MHz $CDCl_3$) + DEPT 63.90 (2 x CH_2) 89.30 (5-CH) 128.52, 128.05, 131.21 (C-H Ph) 136.34, 162.18, 166.63, 170.05. (q-C). (There are 2 sets of equivalent q-C)

ν_{max} (nujol/cm^{-1}) 3313, 3213, 1670, 1594, 1572, 1171, 1050.

4,6-Di(*N*-(2-hydroxyethyl)carbamoylmethoxy)-2-phenylpyrimidine (168)

4,6-Di(ethoxycarbonylmethoxy)-2-phenylpyrimidine (**144**) (0.5 g, 1.39 mmol) was refluxed in ethanol (25 ml) containing ethanolamine (1.5 ml) for 4 hr. The reaction was concentrated to a thick yellow oil, which was dissolved in H_2O (50 ml). The aqueous solution was frozen using an acetone/liq N_2 slush bath, and allowed to warm up to room temperature. The solid product was filtered to give (**168**) (100 mg, 20 %), m.p. >48 ^{0}C. (EtOH). δ_H (400 MHz d_6-DMSO) 3.21 (4H, q, 2 x $\underline{CH_2}$OH), 3.43 (4H, t, 2 x NH$\underline{CH_2}$), 4.87 (4H, s, 2 x CH_2), 6.30 (1H, s, 5-H) 7.51 (3H, m, Ph), 8.15 (2H, m, Ph), 9.85 (2H, d, 2 x NH), δ_C (100 MHz $CDCl_3$) + DEPT) 41.24 (2 x CH_2) 59.80 (2 x CH_2) 64.80 (2 x CH_2) 89.05 (5CH) 128.03, 128.5, 131.23 (C-H Ph) 136.32, 162.07, 167.42, 170.0. (q-C). There are 2 sets of equivalent q-C.

ν_{max} (nujol/cm^{-1}) 3266, 1654, 1596, 1560, 1497, 1263, 1175.

4-Amino-6-*N*-hydroxycarbamoylmethoxy-2-phenylpyrimidine (169)

Hydroxylamine hydrochloride (1.36 g, 19.6 mmol) in ethanol (30 ml) was neutralised by an equivalent molar quantity of sodium ethoxide in ethanol (30 cm^3). The precipitated sodium chloride was filtered. 4-Amino-6-ethoxycarbonylmethoxy-2-phenylpyrimidine (**132**) (1 g, 3.66 mmol) was dissolved in ethanol (120 cm^3) and the solution was cooled for fifteen minutes in an ice water bath. To this was added the solution of hydroxylamine in ethanol described above and the mixture stirred for five minutes. A solution of sodium ethoxide (15.6 mmol) in ethanol (40 ml) was added in one portion and the reaction mixture stirred for thirty minutes while maintaining the reaction vessel in the ice bath. When the reaction was complete (TLC), the mixture was acidified (pH 5) with conc. hydrochloric acid. The product slowly precipitated and was recrystallised from 80% MeOH/H_2O giving white needles (660 mg, 69 %) m.p. 148-150^{0}C (MeOH-H_2O) (Found: C, 55.16; H, 4.60; N, 21.64; $C_{12}H_{12}N_4O_3$ requires C, 55.38; H, 4.65; N, 21.53 %). δ_H (300 MHz d_6-DMSO), 4.79 (2H, s, CH_2), 5.78 (1H, s, 5-H), 6.81 (2H, s, NH_2), 7.49 (3H, m, Ph), 8.31 (2H, m, Ph), 9.32 (1H, s, -$\underline{NH}$-OH), 10.83 (1H, s, NH-$\underline{OH}$). δ_C (75.5 MHz d_6-DMSO) +DEPT

62.4 (CH_2), 84.5 (5-C-H), 127.7, 128.2, 130.3 (C-H Ph), 137.6, 162.3, 164.8, 165.8, 168.5 (q-C).

ν_{max}(nujol)/cm-1 3486, 3355, 3227, 1661, 1631, 1602, 1562, 1203 cm^{-1} λ_{max} (EtOH 95)/nm 236 (loge dm^3 mol^{-1} cm^1 4.27), 262 (3.99), (0.1M NaOH) 228 (4.35), (0.1M HCl) 248 (4.15), 296 (3.99).

4,6-Di(*N*-hydroxycarbomylmethoxy)-2-phenylpyrimidine (170)

4,6-Di(ethoxycarbonylmethoxy)-2-phenylpyrimidine (**144**) (1 g, 2.28 mmol) was dissolved in ethanol (100 ml) and cooled in an ice bath. To this was added a solution of free hydroxylamine (22.77 mmol) in ethanol (60 ml) and stirring continued at ice bath temperature for 10 minutes. The reaction was acidified with conc. HCl to pH 4-5 and cooled. The NaCl was removed and the filtrate concentrated to give a white solid which was recrystallised from MeOH, (690 mg, 91%) m.p. 210^{0}C (MeOH) (Found: C, 49.87; H, 4.49; N, 16.33; $C_{14}H_{14}N_4O_6$ requires C, 50.30; H, 4.19; N, 16.77 %). δ_H (400 MHz d_6 DMSO) 4.87 (4H, s, 2 x CH_2), 6.27 (1H, s, 5-H), 7.51 (3H, m, Ph), 8.35(2H, m, Ph), 8.98 (2H, br.s, 2xNH), 10.98 (2H, s, 2 x OH).

δ_C (100 MHz d_6 DMSO) + DEPT 62.64 (CH_2), 63.22 (CH_2), 89.10 (5-H), 128.19, 128.50, 131.23, (C-H Ph), 136.30, 162.24, 164.28, 170.06 (q-C) Note there are 2 sets of equivalent quaternary carbons.

ν_{max} (nujol/cm^{-1}) 3311, 3183, 1685, 1670, 1640, 1595, 1571.

4-Acetamido-6-ethoxycarbonylmethoxy-2-phenylpyrimidine (171)

Method A (acetylation of 2-amino ester)

4-Amino-6-ethoxycarbonylmethoxy-2-phenylpyrimidine (**132**) (1 g, 3.66 mmol) and acetic anhydride (12 ml) were heated at 100^{0}C for 1.5 h. Cooling afforded a white solid, which was filtered, washed with hexane, dried. and recrystallised from EtOH-Hexane to give **(171)** (740 mg, 64%) m.p. 154-156^{0}C. (Found: C, 61.07; H, 5.48; N, 13.33; $C_{16}H_{17}N_3O_4$ requires C, 60.95; H, 5.40; N, 13.33 %).

δ_H (300 MHz, d_6-DMSO): 1.18 (3H, t, $CH_2\underline{CH_3}$, J = 7.05), 2.18 (3H, s, $COCH_3$), 4.17 (2H, q, $C\underline{H_2}CH_3$, J = 7.02), 5.02 (2H, s, CH_2), 7.45 (1H, s, 5-H), 7.50 (3H, m, Ph), 8.29

(2H, m, Ph), 10.84 (1H, s, NH). δ_C (75.5MHz, d_6-DMSO): 14.46 (CH_3), 24.56 (CH_3), 60.97 (CH_2), 63.42 (CH_2), 92.45 (5-CH), 127.64 128.47, 131.09 (CH Ph), 136.44, 159.32, 162.17, 168.40, 169.44, 170.68 (q-C).

ν_{max} (nujol/cm^{-1} 3162, 1758, 1680, 1570, 1224.

(171) Method B (triacetate and ethanol)

Triacetate (**183**) (100 mg, 0.26 mmol) was refluxed in ethanol (5 ml) for 1 day. Removal of the alcohol afforded an oil, which was dissolved in ethyl acetate (2 ml). Addition of hexane and cooling gave (**171**) as a white solid (32 mg, 39 %) which was identical to the specimen prepared in method A

(171) Method C (triacetate and $FeCl_3$ in $CHCl_3$)

In a 50 ml flask was placed anhydrous iron (III) chloride (422 mg, 2.6 mmol), chloroform (5 ml), acetic acid (75 µl, 1.3 mmol) and the mixture was stirred for 15 min. To this was added a solution of triacetate (**183**) (0.5g, 1.3 mmol) in chloroform (10 ml). A reflux condenser fitted with a $CaCl_2$ drying tube was connected to the reaction flask and the solution refluxed for 12 hr. The cooled reaction mixture was poured into saturated aqueous sodium bicarbonate solution and the mixture extracted with $CHCl_3$. The extract was concentrated and residual iron salts were removed by drying ($MgSO_4$) and passing the $CHCl_3$ extract through a plug of silica. The solvent was concentrated, diluted with hexane, and cooled to give (**171**) as a white solid (170 mg, 41.5%). The product was identical to specimens prepared in methods A and B above. NOTE: When the plug of silica was eluted with EtOAc, the amide (**196**) was isolated 60 mg (see

(171) Method D

Triacetate (183) with $FeCl_3$ in THF containing ethanol.

In a 50 ml flask was placed anhydrous iron (III) chloride (422 mg, 2.6 mmol), dry THF (5 ml) acetic acid (75 µl, 1.3 mmol) and the mixture was stirred for 15 min. To this was added a solution of triacetate (**183**) (0.5 g, 1.3 mmol) in dry THF (10 ml), and ethanol (0.3 ml). A $CaCl_2$ drying tube was connected to the reaction flask and the

solution refluxed for 1 day. The cooled reaction mixture was poured into saturated aqueous sodium bicarbonate solution and the mixture extracted with $CHCl_3$. The extract was concentrated and any residual iron salts were removed by drying ($MgSO_4$) and passing the $CHCl_3$ extract through plug of silica. The solvent was further concentrated. Addition of hexane and cooling gave (**171**) as a white solid (130 mg, 32 %) which was identical to the specimens prepared in methods A and B and C above.

4-Acetamido-6-(*N*-hydroxycarbamoylmethoxy)-2-phenylpyrimidine (172)

4-Acetamido-6-ethoxycarbonylmethoxy-2-phenylpyrimidine (**171**) (1 g, 3.17 mmol) was dissolved in ethanol (100 ml) and the solution stirred in an ice bath. Hydroxylamine hydrochloride (1.18 g, 16.92 mmol) dissolved in ethanol (50 ml) was neutralised by an equivalent amount of sodium ethoxide (390 mg Na in EtOH) in ethanol (50 ml). The sodium chloride was filtered to give a solution of free hydroxylamine. This solution was added to the solution of ester (**171**) and the mixture stirred at ice bath temperature for 15 minutes. A solution of sodium ethoxide (13.5 mmol) in ethanol (30 ml) was then added and the solution stirred for another 30 minutes. The reaction was acidified with conc. HCl to pH5 and filtered through celite. Evaporation of the ethanol to a small volume and addition of ethyl acetate yielded a white solid (0.9 g, 94 %). m.p. 174°C. (EtOH). (Found: C, 53.10; H, 4.53; N, 17.47; $C_{14}H_{14}N_4O_4$ $1H_2O$ requires: C, 52.50; H, 5.0; N, 17.50 %). δ_H (300 MHz, d_6-DMSO): 2.17 (3H, s, CH_3), 4.97 (2H, s, CH_2), 7.43 (1H, s, 5-H), 7.51 (3H, m, Ph), 8.34 (2H, s, Ph), 9.4 (2H, br.s, OH and NH), 10.82 (1H, s, NH). δ_C (75.5MHz, d_6-DMSO): 24.18 (CH_3), 63.11 (CH_2), 127.88, 128.47, 131.01 (CH Ph), 136.40, 159.07, 162.10, 168.35,169.41, 170.63 (q-C).

ν_{max} (nujol)/cm^{-1} 3170, 1743, 1664, 1568, 1194.

4-Amino-6-carboxymethoxy-2-phenylpyrimidine (173)

4-Amino-6-etoxycarbonylmethoxy-2-phenylpyrimidine (**132**) (510 mg, 1.87 mmol) was mixed with sodium hydroxide (0.25M, 10 ml), and the mixture refluxed for 2 hr. The hot solution was filtered, removing unreacted starting material (100

mg). The clear filtrate was acidified with HCl (2M) to pH 5-6 and left to stir at room temperature overnight. The white solid, which precipitated, was filtered, washed with water and acetone, and dried. The product was recrystallised from methanol. (250 mg, 68 %) m.p. 226°C (MeOH). (Found: C, 58.51; H, 4.58; N, 17.20; $C_{12}H_{11}N_3O_3$ requires C, 58.77; H, 4.52; N, 17.13 %). δ_H (300 MHz d_6-DMSO) 4.88 (2H, s, CH_2), 5.79 (1H, s, 5-H), 6.80 (2H, s, NH_2), 7.49 (3H, m, Ph), 8.27 (2H, q, Ph), 12.8 (1H, br.s, CO_2H). δ_C (75.5 MHz d_6-DMSO) + DEPT 62.2 (CH_2), 84.5 (C-H 5 position), 127.7, 128.4, 130.5 (C-H Ph), 137.6, 162.3, 166.0, 168.6, 170.5 (q-C). ν_{max} (nujol)/cm^{-1} 1686, 1610, 730. λ_{max} (EtOH 95)/nm (loge dm^3 mol^{-1} cm^{-1})

4,6-Di(carboxymethoxy)-2-phenylpyrimidine (174)

4,6-Di(ethoxycarbonylmethoxy)-2-phenylpyrimidine (**144**) (0.5 g, 1.39 mmol) was mixed with NaOH 1M (20 ml, 0.02 mol) and the mixture was refluxed for 1.5 hr. The reaction mixture was cooled, filtered and acidified with HCl (1M) to pH 5. The white precipitate was collected and recrystallised from aqueous methanol. (320 mg, 76%) m.p. > 200°C (Dec) (aq MeOH). (Found: C, 54.97; H, 4.11; N, 8.91; $C_{14}H_{12}N_2O_6$ requires C, 55.26; H, 3.95; N, 9.21 %) δ_H (300 MHz d_6 DMSO) 4.95 (4H, s, 2xCH_2), 6.40 (1H, s, 5-H), 7.45 (3H, m, Ph), 8.25 (2H, m, Ph), 13.10 (2H, br s, 2 x OH). δ_C (75.5 MHz d_6-DMSO) + DEPT 63.02 (CH_2 x 2), 88.91 (5-CH), 127.89, 128.65, 131.42 (CH Ph), 136.30, 161.90 (q-C), 169.30 (2 x q-C), 170.13 (2 x q-C) ν_{max} (nujol)/cm^{-1} 1718, 1564, 1171.

4-Amino-6-propoxycarbonylmethoxy-2-phenylpyrimidine (175)

4-Amino-6-carboxymethoxy-2-phenylpyrimidine (**173**) (200 mg, 0.8 mmol) was refluxed in propan-1-ol containing conc. H_2SO_4 (10 drops), for 45 min. The alcohol was removed and the oil dissolved in $NaHCO_3$ solution. The aqueous solution was extracted with EtOAc, dried ($MgSO_4$), concentrated, diluted with hexane and cooled, giving white plates of product (170 mg, 74 %) m.p. 122-125°C (EtOAc/Hex). (Found: C, 62.33; H, 6.02; N, 14.44; $C_{15}H_{17}N_3O_3$ requires C, 62.72; H, 5.92; N, 14.63 %). δ_H (400 MHz $CDCl_3$) 0.92 (3H, t, $CH_2CH_2\underline{CH_3}$, J = 7.5), 1.72 (2H, m, $CH_2\underline{CH_2}CH_3$, J =

7.5), 4.17 (2H, t, $\underline{CH_2}CH_2CH_3$, J = 6.5), 4.87 (2H, br s, NH_2), 4.97 (2H, br s, CH_2), 5.86 (1H, s, 5H), 7.44 (3H, m, Ph), 8.30 (2H, m, Ph). δ_C (100 MHz $CDCl_3$) + DEPT 9.8 (CH_3), 62.2 (CH_2), 66.25 (CH_2), 85.22 (5-CH), 127.62, 127.72, 130.0 (CH Ph), 137.0, 163.0, 165.55, 168.71, 168.8 (q-C).

ν_{max} (nujol)/cm^{-1} 3424, 3330, 3326, 1736, 1644, 1553, 1194.

4,6-Di(propoxycarbonylmethoxy)-2-phenylpyrimidine (176)

Method A (esterification of diacid (174))

4,6-Di(carboxymethoxy)-2-phenylpyrimidine (**174**) (304 mg, 1 mmol) was refluxed in propan-1-ol (5 ml) containing conc. sulphuric acid (10 drops) for 1.5 hr. The solvent was removed and the oily residue dissolved in saturated $NaHCO_3$ solution. The solution was extracted with EtOAc, dried ($MgSO_4$) and concentrated. Addition of hexane and cooling gave the product (**176**) as a white fluffy solid (230 mg, 60 %) m.p.51-53^{0}C (EtOAc/Hex). (Found: C, 61.0; H, 6.17; N, 7.09; $C_{20}H_{24}N_2O_6$ requires C, 61.86; H, 6.19; N, 7.22 %). δ_H (400 MHz $CDCl_3$) 0.91 (6H, t, 2 x CH_3, J = 7.04), 1.67 (4H, m, 2 x $CH_2\underline{CH_2}CH_3$ J = 7.0), 4.16 (4H, t, 2 x $\underline{CH_2}CH_2CH_3$, J = 6.5), 5.0 (4H, s, 2 x CH_2), 6.30 (1H, s, 5-H), 7.45 (3H, m, Ph), 8.28 (2H, m, Ph).

δ_C (100 MHz $CDCl_3$) + DEPT 10.16 (2 x CH_3), 21.50 (2 x CH_2), 62.76 (2 x CH_2), 66.33 (2 x CH_2), 89.0 (5-CH), 127.74, 127.83, 130.55 (C-H Ph), 136.17, 162.20, 168.32, 169.65 (q-C) (note there are 2 sets of equivalent quaternary carbons)

ν_{max} (nujol/cm^{-1}) 1744, 1594, 1081

(176) Method B (tetraacetate (194) and propanol)

4,6-Di(*N*-acetyl-*N*-acetoxycarbamoylmethoxy)-2-phenylpyrimidine (**194**) (110 mg, 0.22 mmol) and propan-1-ol (10 ml) were refluxed together for 19 hrs. The solvent was removed and the oil dissolved in EtOAc. The solution was treated with charcoal, concentrated, and diluted with hexane and cooled for 2 days. The product was filtered as white crystals (35 mg, 41 %), m.p. 49-52 ^{0}C. The product obtained was identical in every respect to the specimen prepared in method A above

4-Acetamido-6-carboxymethoxy-2-phenylpyrimidine (177)

4-Amino-6-carboxymethoxy-2-phenylpyrimidine (**173**) (2.0 g, 8.2 mmol) and acetic anhydride (40 ml) were heated together at 110^0C for 1.5 hr. The excess anhydride was removed (rot vap) and the oily residue was stirred with H_2O (100 ml) for 5 min. The aqueous solution was then extracted with ethyl acetate, dried ($MgSO_4$) and treated with charcoal. The solution was concentrated and purified by flash chromatography (MeOH/DCM 1:9). This gave the white solid product as the slower eluting component (530 mg, 24 %) m.p.155-158^{0}C (EtOH). δ_H (400 MHz, d_6-DMSO), 2.15 (3H, s, CH_3), 4.64 (2H, s, CH_2), 7.33 (1H, s, 5H), 7.49 (3H, m, Ph), 8.30 (3H, m, Ph), 10.70 (1H, s, NH), 12 80 (1H, br s, CO_2H). δ_C (100 MHz, d_6-DMSO) + DEPT 24.16 (CH_3), 65.33 (CH_2), 92.46 (5-CH), 127.8, 128.32, 130.65 (CH Ph), 137.11, 158.74, 162.19, 168.3, 170.47, 170.80 (q-C)

ν_{max} (nujol/cm^{-1}) 1690, 1565. UV/λ_{max}/nm 214, 238, 265.

4-Acetamido-6-(2,4-dioxopentoxy)-2-phenylpyrimidine(178)

The procedure for the preparation of (**177**) was followed and the white solid product was obtained as the faster eluting component, (660 mg, 25 %) m.p. >210^{0}C Dec. (EtOH). (Found: C, 58.16; H, 4.96; N 13.25; $C_{16}H_{15}N_3O_5$ requires C, 58.36; H, 4.56; N, 12.76 %). δ_H (400 MHz, $CDCl_3$) 2.22 (3H, s, CH_3), 3.80 (3H, s, CH_3), 5.03 (2H, s, CH_2), 7.46 (3H, m, Ph), 7.60 (1H, s, 5-H), 8.18 (1H, s, NH), 8.29 (2H, m, Ph)

δ_C (100 MHz, $CDCl_3$) + DEPT 24.27 (CH_3), 51.67 (CH_3), 62.58 (CH_2), 92.74 (5-CH), 127.53, 127.96, 130.52 CH Ph), 136.21, 157.90, 162.60, 168.65, 168.70, 169.56 171.0, (q-C). ν_{max} (nujol/cm^{-1}) 3348, 1749, 1684, 1576.

UV/λ_{max}/nm 214, 238.

4-Acetamido 6-*N*-acetoxy-*N*-acetyl-carbamoylmethoxy-2-phenylpyrimidine (183)

"Triacetate" method A

4-Amino-6-*N*-hydroxycarbamoylmethoxy-2-phenylpyrimidine (**169**) (900 mg, 3.46 mmol) was mixed with freshly distilled acetic anhydride (12 ml) and the mixture heated for 30 min. The solution when allowed to cool produced a white solid, which

was filtered washed with water and dried. NB, if the product did not precipitate from the cold reaction mixture the following work up was used. The excess anhydride was removed (rot vap) and the resulting oil was stirred with H_2O (50 ml) for 15 min. The aqueous mixture was extracted with EtOAc, dried, diluted with hexane, and cooled to give (**183**) (820 mg, 69 %). m.p. 148^{0}C (EtOAc-Hex). (Found: C, 56.01; H, 4.61; N, 14.29; $C_{18}H_{18}N_4O_6$ requires C, 55.96; H, 4.66; N, 14.51 %) δ_H (300 MHz d_6-DMSO) 2.11 (3H, s, CH_3), 2.31 (3H, s, CH_3), 2.36 (3H, s, CH_3), 5.42 (2H, d, CH_2) 7.42 (3H, m, Ph) 7.59 (1H, s, 5-CH), 8.24 (2H, m, Ph) 8.41 (1H, s, NHCOCH$_3$) δ_C (80 MHz d_6-DMSO) + DEPT 17.81 (CH_3), 23.30 (CH_3), 24.62 (CH_3), 64.96 (CH_2), 93.10 (5-CH), 128.04, 128.35, 130.90 (C-H Ph), 136.55, 158.42, 163.04, 165.39, 167.0, 169.26, 169.85 (q-C).(Note one peak represents two equivalent carbons)

ν_{max} (nujol/cm^{-1}) 3331, 1804, 1730, 1683, 1570, 1170.

(183) Method B

4-Acetamido-6-*N*-hydroxycarbamoylmethoxy-2-phenyl pyrimidine (**172**) (0.3 g, 0.99 mmol) was mixed with acetic anhydride (3 ml) and gently heated. Undissolved solid was filtered from the hot solution and the excess anhydride evaporated to give a yellow oil, which was then dissolved in ethyl acetate. Addition of hexane and cooling gave a cream solid (240 mg, 63 %). m.p. 145-148°C. The sample was identical to that prepared in method A above.

2-Amino-4-*N*-acetoxycarbamoylmethoxy-2-phenylpyrimidine (186) ("monoacetate")

2-Amino-4-*N*-hydroxycarbamoylmethoxy-2-phenylpyrimidine (**169**) (0.5 g, 1.92 mmol) was heated with acetic anhydride (6 ml) at 100^{0}C for such time as was necessary to produce the product (continuous monitoring by TLC) in a reasonable quantity before the acetylation proceeded further to the triacetate (**183**) stage. Cooling the reaction mixture produced a white solid product, which was filtered and dried. Flash chromatography (EtOAc 50/Hex 50) of the solid removed the triacetate impurity to give the required product (**186**) (200 mg, 34 %) m.p. 176^{0}C (EtOAc-Hex) (Found: C, 55.40; H, 4.67; N, 18.34; $C_{14}H_{14}N_4O_4$ requires: C, 55.63; H, 4.63; N, 18.54

%). δ_H (400 MHz, d_6-DMSO) 2.17 (3H, s, CH_3), 4.92 (2H, s, CH_2), 5.78 (1H, s, 5-H), 6.77 (2H, s, NH_2), 7.46 (3H, m, Ph), 8.30 (2H, m, Ph), 12.03 (1H, br s, NHOAc). δ_C (100 MHz, d_6-DMSO) 18.01 (CH_3), 64.98 (CH_2), 84.55 (5-CH), 127.8, 128.2, 137.5 (C-H Ph), 137.5, 162.4, 165.4, 165.9, 168.3, 168.33 (q-C). ν_{max} (nujol/cm^{-1}) 3496, 3385, 1776, 1702, 1625, 1551, 1194.

4-Acetamido-6-*N*-acetoxycarbamoylmethoxy-2-phenylpyrimidine (187) ("Diacetate")

4-Acetamido-6-*N*-hydroxycarbamoylmethoxy-2-phenylpyrimidine (**172**) (300 mg, 1 mmol) was dissolved in dry pyridine under a nitrogen atmosphere. The solution was cooled in an ice bath, and acetyl bromide (78 µl, 1.05 mmol) was added slowly with stirring and the reaction mixture was maintained at 0^0C for 30 min and then at room temperature for 45 min. It was then diluted with HCl (1M, 100 ml) and extracted with ethyl acetate. The combined organic extracts were washed with aqueous NH_4Cl solution, aqueous NaCl solution and finally with water, dried ($MgSO_4$) and concentrated to a small volume. Addition of 40-60 petroleum ether followed by cooling gave (**187**) as a white powder (150 mg, 44%) m.p.155-158^{0}C (EtOAc/Hex). (Found: C, 55.18; H, 4.73; N, 15.87; $C_{16}H_{16}N_4O_5$ requires C, 55.81; H, 4.65; N, 16.28 %). δ_H (400 MHz, d_6-Acetone) 2.16 (3H, s, CH_3), 2.26 (3H, s, CH_3), 5.15 (2H, s, CH_2), 7.47 (1H, s, 5-H), 7.51 (3H, m, Ph), 8.40 (1H, s, NHAc), 8.89 (2H, m, Ph), 11.9 (1H, s, NHOAc). δ_C (100 MHz, d_6 Acetone) 16.64 (CH_3), 23.1 (CH_3), 63.0 (CH_2), 92.0 (5-CH), 127.6, 127.8, 130.4 (C-H Ph), 136.5, 158.9, 162.5, 167.6, 169.4, 169.5 (q-C). (As for the triacetate, there is one set of equivalent q-carbons) ν_{max} (nujol/cm^{-1}) 1796, 1684, 1570, 1522, 1175, 975, 842.

4-Amino-6-(*N*-methoxy-*N*-methylcarbamoylmethoxy)-2-phenylpyrimidine. (189)

4-Amino-6-*N*-hydroxycarbomylmethoxy-2-phenylpyrimidine (**169**) (3.0 g, 11.54 mmol) was dissolved in ethanol/water (50/50, 180 ml) containing sodium carbonate (3.67 g, 34.62 mmol) and the suspension stirred for 20 minutes. Dimethylsulphate (3.0 ml, 31.70 mmol) was added and the solution stirred overnight. The inorganic

solids were filtered, and the filtrate was concentrated to an aqueous solution and extracted with chloroform, dried ($MgSO_4$), and concentrated to give a yellow oil. The oil was dissolved in ethyl acetate, (3 ml) diluted with hexane, and cooled to give a white solid (1.032g). This material, which was a mixture of two products was separated by flash chromatography using (90% ethyl acetate/10% Et_3N) for the faster component (**188**) and MeOH for the above named slower component (**189**) (363 mg, 11 %) m.p 155-160^{0}C. (Found: C, 58.22; H, 5.63; N, 19.20; $C_{14}H_{16}N_4O_3$ requires: C, 58.32; H, 5.59; N, 19.43 %) δ_H (300 MHz d_6-DMSO) 3.16 (3H, s, CH_3), 3.83 (3H, s, CH_3), 5.18 (2H, s, CH_2), 5.77 (1H, s, 5-H), 6.78 (2H, br s, NH_2), 7.46 (3H, m, Ph), 8.24 (2H, m, Ph). δ_C (75.5 MHz d_6-DMSO) + DEPT 32.07 (CH_3), 61.40 (CH_3), 61.78 (CH_2) 84.42 (5-C-H), 127.52, 128.19, 130.23 (C-H Ph), 137.68, 162.16, 165.82, 168.63 168.80 (q-C).

ν_{max} (nujol)/cm^{-1} 3436, 3338, 1630, 1598, 1578, 1547, 1378.

λ_{max} (EtOH 95)/nm 236 (loge dm^3 mol^{-1} cm^{-1}) (4.28), (0.1M NaOH), 232 (4.40), (0.1M HCl) 248 (4.17), 296 (3.99).

4-Amino-6-*N*-methoxycarbamoylmethoxy-2-phenylpyrimidine (188)

This compound was prepared as for (**189**) above, and appeared as the faster component of the mixture (243 mg, 7 %). (**188**) was also obtained as the exclusive product when the procedure for the preparation of (**189**) and (**188**) was followed but using one mole equivalent of dimethylsulphate. m.p. 148-150^{0}C (Found C, 56.86; H, 5.23; N, 20.20; $C_{13}H_{14}N_4O_3$ requires C, 56.93; H, 5.14; N, 20.43 %). δ_H (300 MHz d_6-DMSO), 3.59(3H, s, CH_3), 4.73 (2H, s, CH_2), 5.77 (1H, s, 5-H), 6.81 (2H, br s, NH_2), 7.45 (3H, m, phenyl), 8.30 (2H, m, Ph), 11.48 (1H, br s, CONHOMe). δ_c (75.5 MHz, d_6-DMSO) plus DEPT, 62.43 (CH_2), 63.31 (CH_3), 84.56 (5-CH), 127.7, 128.2, 130.4, (C-H, Ph), 137.51, 162.27, 164.93, 165.85, 168.38 (q-C).

ν_{max} (nujol)/cm^{-1} 3452, 1662, 1636.

,

4-Acetamido-6-(N^2,N^2-diacetylhydrazinocarbonylmethoxy)-2-phenylpyrimidine (191)

4-Amino-6-hydrazinocarbonylmethoxy-2-phenylpyrimidine (**160**) (300 mg, 1.16 mmol) was mixed with acetic anhydride (5 ml) and heated at 100^0C for 1.5 hr. The anhydride was partially removed and the remaining liquid cooled to produce a white solid product (220 mg, 49 %) m.p. 190-192^0C (EtOH). (Found: C, 55.45; H, 4.96; N, 17.90; $C_{18}H_{19}N_5O_5$ requires C, 56.10; H, 4.93; N, 18.18 %). δ_H (400 MHz d_6-DMSO) 2.18 (3H, s, CH_3), 2.20 (6H, s, 2 x CH_3), 5.14 (2H, s, CH_2), 7.52 (3H, m, Ph), 7.53 (1H, s, 5-H), 8.35 (2H, m, Ph), 10.80 (1H, s, NH), 10.84 (1H, s, NH). δ_C (100 MHz d_6 DMSO) + DEPT 24.18 (CH_3), 24.5 (2 x CH_3), 63.5 (CH_2), 92.46 (5-H), 127.85, 128.45, 131.10 (C-H Ph), 136.40, 159.22, 162.42, 167.58, 169.46, 170.71, 170.86 (q-C). NB one of these represents 2 peaks

ν_{max} (nujol/cm^{-1}) 3450, 3229, 1730, 1690, 1571, 1517.

4-Acetamido-6-(N^2-acetylhydrazinocarbonylmethoxy)-2-phenylpyrimidine (191B)

A solution of 4-acetamido-6-(N^2,N^2-diacetylaminocarbomylmethoxy)-2-phenyl-pyrimidine **(191)** (320 mg, 0.83 mmol) in $CHCl_3$ (20 ml) was added to a solution of $FeCl_3$ (304 mg, 1.87 mmol) and CH_3CO_2H (54μL, 0.94 mmol) in $CHCl_3$ (10 ml), and the mixture was refluxed for 1 h under a nitrogen atmosphere. The solution was concentrated to a small volume and poured into a saturated $NaHCO_3$ solution, before being extracted with EtOAc (1 litre). The solution was dried ($MgSO_4$), concentrated and diluted with hexane to give a white solid which was a mixture of (**191B**) and (**172**), (160 mg). The solid material was extracted with boiling DCM and filtered. The filtered solid was shown to be pure (**191B**) (70 mg). The DCM extract was brought to dryness yielding (**172**) (40 mg).

(Found: C, 55.04; H, 5.01; N, 19.50; $C_{16}H_{17}N_5O_4$ requires C, 55.98; H, 4.96; N, 20.41 %). δ_H (400 MHz d_6-DMSO) 1.8 (3H, s, CH_3), 2.17 (3H, s, CH_3), 5.0 (2H, s, CH_2), 7.46 (1H, s, 5H), 7.52 (3H, m, Ph), 8.36 (2H, m, Ph), 9.84 (1H, s, NH), 10.16 (1H, s, NH), 10.80 (1H, s, NH). δ_C (100 MHz d_6 DMSO) + DEPT 20.45, 24.18 (CH_3), 63.30 (CH_2), 92.4 (5-CH), 136.6, 159.1, 162.4, 166.2, 168.0, 169.6, 170.6 (q-C).

ν_{max} (nujol/cm^{-1}) 3201, 1675, 1597.

4-Acetamido-6-*N*-methoxy-*N*-acetylcarbamoylmethoxy-2-phenylpyrimidine.(192)

4-Amino-6-*N*-methoxycarbomylmethoxy-2-phenylpyrimidine (**188**) (100 mg, 0.36 mmol) was mixed with acetic anhydride (0.5 ml) and heated at 100^{0}C for 1.5 h. The reaction mixture was cooled and the precipitated solid was filtered, dissolved in ethyl acetate and treated with charcoal. The solution was concentrated and the product diluted with hexane giving a white solid (38 mg, 29 %) m.pt.127-130^{0}C (EtOAc/Hex). (Found: C, 56.65; H, 4.93; N, 15.47; $C_{17}H_{18}N_4O_5$ requires C, 56.98; H, 5.03; N, 15.64 %). δ_H (400 MHz $CDCl_3$) 2.18 (3H, s, CH_3), 2.46 (3H, s, CH_3), 3.92 (3H, s, CH_3), 5.42 (2H, s, CH_2), 7.43 (3H, m, Ph), 7.63 (1H, s, 5-H), 8.21 (2H, m, Ph), 8.30 (1H, s, NH). δ_C (100 MHz $CDCl_3$) + DEPT 23.80 (CH_3), 24.64 (CH_3), 64.17 (CH_3), 65.27 (CH_2), 93.25 (5-C-H), 127.87, 128.33, 130.90 (C-H Ph), 136.8, 158.44, 162.95, 167.20, 168.0, 169.20, 171.0 (q-C).

ν_{max} (nujol/cm^{-1}) 3168, 1734,1570.

4,6-Di(*N*-acetoxycarbamoylmethoxy)-2-phenylpyrimidine (193)

4,6-Di(*N*-hydroxycarbomylmethoxy)-2-phenylpyrimidine (**170**) (50 mg, 0.15 mmol) was mixed with acetic anhydride (2ml) and heated at 90-100^{0}C. After the starting material had dissolved, there was immediate precipitation of the product (**193**). Cooling and filtering gave the title compound (40 mg, 64%) m.p. 205-208^{0}C (EtOAc-Hex) (Found: C, 50.95; H, 4.42; N, 12.87; $C_{14}H_{14}N_4O_6$ requires C, 51.67; H, 4.30; N, 13.40 %). δ_H (400 MHz d_6 DMSO), 2.17 (6H, s, 2xCH_3), 5.03 (4H, s, 2xCH_2), 6.35 (1H, s, 5-H), 7.53 (3H, m, Ph), 8.38 (2H, m, Ph), 12.12 (2H, br s, 2 x NH). δ_C (100 MHz d_6 DMSO) + DEPT 18.35 (2 x CH_3), 63.16 (2 x CH_2), 89.54 (5,C-H), 128.63, 128.81, 131.68 (C-H Ph), 136.51, 162.65, 165.22, 168.64, 170.24 (q-C) there are three sets of equivalent quaternary carbon atoms.

ν_{max} (nujol/cm^{-1}) 3132, 1806, 1790, 1681, 1599, 1572.

4,6-Di(*N*-acetyl-*N*-acetoxycarbamoylmethoxy)-2-phenylpyrimidine (194)

4,6-Di(*N*-hydroxycarbamoylmethoxy)-2-phenylpyrimidine (**170**) (140 mg, 0.42 mmol) was mixed with acetic anhydride (6 ml) and heated at 90-100^{0}C. After the starting material had dissolved there was precipitation of the diacetate (**193**), which upon further heating dissolved to give a clear solution. The reaction was heated for 30 min, concentrated to an oil, and stirred with water (50 ml) at room temperature for 15 min. The aqueous mixture was extracted with EtOAc, dried (Na_2SO_4), concentrated, and the product precipitated by the addition of hexane with overnight cooling. (150 mg, 71%) m.p. 120-122^{0}C (EtOAc-Hex). (Found: C, 51.95; H, 4.53; N, 10.93; $C_{14}H_{14}N_4O_6$ requires: C, 52.59; H, 4.38; N, 11.15 %). δ_H (400 MHz $CDCl_3$) 2.33 (6H, s, 2 x CH_3), 2.38 (6H, s, 2 xCH_3), 5.42 (4H, d, 2 x CH_2), 6.29 (1H, s, 5-H), 7.45 (3H, m, Ph), 8.28 2H, m, Ph). δ_C (100 MHz $CDCl_3$) + DEPT 17.35 (2 x CH_3), 22.86 (3 x CH_3), 64.57 (2 x CH_2), 88.97 (5-CH) 127.82, 127.93, 130.50 (C-H Ph), 136.10, 162.37, 165.05, 166.60, 168.4, 169.51 (q-C) there are 4 sets of equivalent quaternary carbon atoms.

ν_{max} (nujol/cm^{-1}) 1813, 1803, 1743, 1730, 1600, 1575. 1183.

4,6-Di(N^2-N^2-diacetamidohydrazinomethoxy)-2-phenylpyrimidine (195)

4,6-Di(hydrazinocarbamoylmethoxy)-2-phenylpyrimidine (**167**) (29) (100 mg, 0.31 mmol) was refluxed with acetic anhydride (5 ml). After initial dissolution of the starting material, there was immediate precipitation of the product. The reflux was continued for 1 hr. After cooling, the white solid product was collected and washed with EtOH, to give (**195**) (90 mg, 70 %), m.p. > 285 ^{0}C Dec (EtOH). (Found: C, 51.51; H, 4.77; N, 19.56; $C_{18}H_{20}N_6O_6$ requires C, 51.92; H, 4.81; N, 20.19 %).

δ_H (400 MHz d_6-DMSO) 1.86 (6H, s, 2 x CH_3), 4.99 (4H, s, 2 x CH_2), 6.32 (1H, s, 5-H), 7.51 (3H, m, Ph), 8.39 (2H, m, Ph), 9.85 (2H, br s, 2 x NH), 10.14 (2H, br s, 2 x NH). δ_C (100 MHz $CDCl_3$) + DEPT 20.44 (2 x CH_3) 63.45 (2 x CH_2) 89.13 (5-C-H) 128.39, 128.5, 136.25 (C-H Ph) 136.25, 162.0 166.14, 167.88, 170.0. (q-C). There are 3 sets of equivalent q-C).

ν_{max} (nujol/cm^{-1}) 3205, 3064, 1684, 1593, 1497, 1276.

4-Acetamido-6-carbamoylmethoxy-2-phenylpyrimidine (196)

Method A

Ammonia solution (5 ml of 0.88 NH_3) was added to an ethanolic solution of 4-acetamido-6-ethoxycarbonylmethoxy-2-phenylpyrimidine (**171**) (200 mg, 0.64 mmol) and the mixture stirred overnight at room temperature and then in an ice bath for 1h. (**196**) was obtained as a white solid (120 mg, 66 %) m.p. 185-190^{0}C (EtOH). (Found: C, 58.46; H, 5.03; N, 19.10; $C_{14}H_{14}N_4O_3$ requires C, 58.74; H, 4.89; N, 19.58 %). δ_H (400 MHz, d_6-acetone) 2.27 (3H, s, CH_3), 4.95 (2H, s, CH_2), 6.64 (1H, br s, NH), 7.33 (1H, br s, NH), 7.49 (3H, m, Ph), 7.54 (1H, s, 5-H), 8.38 (2H, m, Ph), 9.82 (1H, br s, NH). δ_C (100 MHz, d_6-acetone) 23.1 (CH_3), 64.1 (CH_2), 92.1 (5-CH), 127.5, 127.8, 130.3 (C-H Ph), 136.6 158.9, 162.4, 169.1, 169.5, 169.7 (q-C).

ν_{max} (nujol/cm^{-1}) 1796, 1684, 1570, 1522, 1175, 975, 842.

(196) Method B

4-Amino-6-carbamoylmethoxy-2-phenylpyrimidine **(159)** (200 mg, 0.82 mmol) was heated with acetic anhydride (4 ml) at 100^{0}C for 1 h. On cooling, **(196)** was obtained as a white solid (150 mg, 64%). The product was identical to the specimen prepared in method A above

(196) Method C (triacetate and $FeCl_3$ in THF)

To a dry flask containing iron(III) chloride (422 mg, 2.6 mmol) under nitrogen was added dry THF (5 ml), and acetic acid (75µl, 1.3 mmol). The mixture was stirred at room temp for 10 min, and to it was added a solution of triacetate (**183**) (500 mg, 1.3 mmol) in dry THF (20 ml). The mixture was refluxed under N_2 for 1 day. Aqueous $NaHCO_3$ solution was then added and the mixture extracted with ethyl acetate. The organic phase was dried ($MgSO_4$), passed through a plug of silica to remove residual iron salts and concentrated on a rotary evaporator. Addition of hexane and cooling gave (**196**) (100 mg, 40%). The product was identical to the specimens prepared in methods A and B above

(196) Method D (diacetate and $FeCl_3$ in DCM)

To a dry flask containing iron(III) chloride (141 mg, 0.88 mmol) under nitrogen was added dry CH_2Cl_2 (5 ml), and acetic acid (25 µl, 0.44 mmol). The mixture was stirred at room temp for 10 min, and to it was added a solution of diacetate (**187**) (150 mg, 0.44 mmol) in dry CH_2Cl_2 (20 ml). The mixture was refluxed under N_2 for 3 days. Aqueous $NaHCO_3$ solution was then added and the mixture extracted with ethyl acetate. The organic phase was dried ($MgSO_4$), passed through a plug of silica to remove residual iron salts and concentrated on a rotary evaporator. Addition of hexane followed by cooling gave (**196**) (30 mg, 24 %) identical to the specimens in methods A and B and C described previously.

(196) Method E (as a minor product from the reaction of triacetate (183) with $FeCl_3$ in $CHCl_3$)

See the preparation of (**171**) method C.

4-Acetamido-6-propoxycarbonylmethoxy-2-phenylpyrimidine (197)

Method A (acetylation of propylester (175)

4-Amino-6-propoxycarbonylmethoxy-2-phenylpyrimidine (**175**) (100 mg, 0.35 mmol) and acetic anhydride (3 ml) were heated together at 100^0C for 2 hr. The excess anhydride was removed (rot vap) and the resulting oil was stirred with water (50 ml) for 30 min. The aqueous mixture was extracted with EtOAc, dried ($MgSO_4$), and treated with charcoal. The solution was concentrated, diluted with hexane and cooled to give a white solid product (42 mg, 36 %) m.p.96-100^0C (EtOAc/Hex) (Found: C, 62.06; H, 5.89; N, 12.95; $C_{17}H_{19}N_3O_4$ requires; C, 62.01; H, 5.80; N, 12.77 %). δ_H (400 MHz $CDCl_3$), 0.90 (3H, t, $CH_2CH_2\underline{CH_3}$, J = 7.5), 1.67 (2H, m, $CH_2\underline{CH_2}CH_3$, J = 7), 2.21 (3H, s, CH_3), 4.17 (2H, t, $\underline{CH_2}CH_2CH_3$, J = 7), 5.01 (2H, s, CH_2), 7.45 (3H, m, Ph), 7.60 (1H, s, 5-H), 8.2 (1H, s, NH), 8.31 (2H, m, Ph). δ_C (100 MHz $CDCL_3$) +DEPT 9.77 (CH_3), 21.46 (CH_2), 24.26 (CH_3), 62.73 (CH_2), 66.35 (CH_2), 92.72 (5-CH), 127.53, 127.91, 130.5, (CH- Ph), 136.22, 157.88, 162.54, 168.3, 168.7, 169.63 (q-C)

ν_{max} (nujol)/cm-1 3231, 3166, 1756, 1686, 1570.

(197) Method B (from triacetate and $FeCl_3$ in THF containing propanol)

Triacetate (**183**) (0.5 g, 1.3 mmol), anhydrous $FeCl_3$ (422 mg, 2.6 mmol), acetic acid (75 μL, 1.3 mmol) and propanol (1 ml) were refluxed together in dry THF for 16 hr. The cooled reaction mixture was poured into saturated aqueous sodium bicarbonate solution and the mixture extracted with $CHCl_3$ and EtOAc. The extract was concentrated to a brown oil and any residual iron salts were removed by passing the residue through a plug flash silica, and eluting with $CHCl_3$ to give the title compound as a white solid (102 mg, 24 %) m.p.93-95^{0}C (EtOAc-Hex). The product was identical to that obtained in methods A above

(197) Method C (triacetate (183) and propanol)

Triacetate (**183**) (200 mg, 0.52 mmol) was refluxed with propan-1-ol (5 ml) for 2 days. The solvent was removed and the residue recrystallised from EtOAc/Hex to give (**183**) as a white solid (100 mg, 58 %). Identical to the specimens prepared in methods A, B, and C above.

4-Carbamoylmethyamino-6-chloro-2-phenylpyrimidine (207).

Glycinamide hydrochloride (2 g, 0.018 mol) was dissolved in water (25 ml) and neutralised with an equivalent amount of sodium bicarbonate solution to give a solution containing 53.6 mg/ml of free Glycinamide. 4-6-Dichloro-2-phenylpyrimidine (**134**) (510 mg, 2.25 mmol) was dissolved in 1-4 dioxan (20 ml) with heating and to this was added the glycinamide solution (12 ml, 0.087 mol). The reaction mixture was refluxed for 5 h and cooled. The mixture when concentrated produced a solid product, which was recrystallised from aqueous ethanol to give (**207**) (490 mg, 83 %). (Found: C, 54.75; H, 4.29; N, 20.55; Cl, 13.03; $C_{12}H_{11}N_4OCl$ requires C, 54.86; H, 4.19; N, 21.33; Cl, 13.52 %). δ_H (300 MHz d_6-DMSO) 4.0 (2H, d, CH_2), 6.6 (1H, s, 5-H), 7.18 (1H, s, CONH), 7.53 (3H, m, Ph), 7.60 (1H, s, CONH), 8.3 (2H, m, Ph), 8.06 (1H, t, NH). .δ_C (75.5 MHz d_6-DMSO) 43.1 (CH_2), 66.4 (CH_2), 102.3 (5-CH), 127.85, 128.5, 131.0 (CH-Ph), 136.7, 157.5, 163.2, 163.4, 171.0 (q-C).

ν_{max} (nujol)/cm^{-1} 3374, 3144, 1676, 1592, 1576.

4-Chloro-6-methoxycarbonylmethyl-*N*-methylamino-2-phenylpyrimidine (208)

4.6-Dichloro-2-phenylpyrimidine (**134**) (0.5 g, 2.2 mmol) was dissolved in 1,4-dioxane (15 ml). To this was added a solution of sarcosine methyl ester (12.6 mmol) in H_2O (20 ml), obtained by neutralising the HCl salt with $NaHCO_3$ solution. The reaction mixture was refluxed for 1 hr. The excess solvent was removed and the residue redissolved in H_2O (100 ml) and extracted with ethyl acetate. After drying ($MgSO_4$), the organic phase was concentrated and the product precipitated by the addition of hexane with cooling to give (**208**) (350 mg, 55 %) m.p. (EtOAc/Hex)

δ_H (400 MHz, $CDCl_3$) 3.17 (3H, s, CH_3), 3.76 (3H, s, CH_3), 4.45 (2H, s, CH_2), 6.44 (1H, s, 5-H), 7.40 (3H, m, Ph), 8.34 (2H, m, Ph). δ_C (400 MHz; $CDCl_3$ +DEPT) 36.64 (CH_3), 51.0 (CH_2), 51.8 (CH_2), 99.0 (5-C-H), 127.8, 127.9, 130.4 (C-H Ph), 136.45, 160.16, 162.53, 163.2, 169.7 (q-C)

4-Chloro-6-ethoxycarbonylmethyl-*N*-benzylamino-2-phenylpyrimidine (209)

4.6-Dichloro-2-phenylpyrimidine (**134**)(2.5 g, 11 mmol) was dissolved in DMF (50 ml) and to this was added Et_3N (3.5 ml, 25 mmol) and *N*-benzyl glycine ethyl ester (2.1 ml, 11 mmol). The mixture was heated at approximately 130^0C for 3 hr. The DMF was removed (rot. vap.) and the brown oil was purified by flash chromatography (EtOAc 60/Hex 40). The combined fractions were concentrated to an oil and dissolved in EtOH (60 ml). Addition of NH_3 solution (30 ml, 0.88 NH_3) and vigorous stirring caused precipitation of the product as a white solid (1.86 g, 44 %) m.p. 75^0C (EtOAc-Hex). (Found: C, 65.96; H, 5.24; N, 10.90; Cl, 9.03; $C_{21}H_{20}N_3O_2Cl$ requires C, 66.05; H, 5.24; N, 11.01; Cl, 9.3 %).

δ_H (400 MHz; $CDCl_3$) 1.29 (3H, t, CH_3 J = 7), 4.24 (2H, q, CH_2 J = 7), 4.37 (2H, br s, CH_2), 4.80 (2H, br s, CH_2), 6.47 (1H, s, 5-H), 7.4 (8H, m, Ph), 8.41 (2H, m, Ph)

δ_C (400 MHz; $CDCl_3$ +DEPT) 13.80 (CH_3), 49.76 (CH_2), 52.75 (CH_2), 53.07 (CH_2), 99.3 (5-CH), 126.53, 127.45, 127.82, 128.0, 128.55, 130.5 (CH Ph), 136.43, 160.32, 162.8, 163.4, 169.2, 171.0 (q-C)

ν_{max}(nujol)/cm^{-1} 1736, 1588, 1560.

4-carboxymethyl-*N*-benzylamino-6-chloro 2-phenylpyrimidine (212)

4-Chloro-6-ethoxycarbonylmethyl-(*N*-benzyl)amino-2-phenylpyrimidine (**209**) (200 mg, 0.52 mmol) and NaOH solution (25 mmol) were refluxed together for 3 hr. The hot reaction mixture was filtered through celite, cooled and acidified to pH 1-2 with conc. HCl. The precipitated product was dried over P_2O_5 in a dessicator to give (**212**) as a white solid (76 mg, 41 %) m.p.>175^{0}C Dec.

δ_H (400 MHz, d_6-DMSO) 4.44 (2H, d, CH_2), 4.83 (2H, d, CH_2), 6.77 (1H, s, 5H), 7.4 (8H, m, Ph), 8.28 (2H, m, Ph), 12 76 (1H, br s, CO_2H). δ_C (400 MHz; d_6-DMSO) + DEPT, 50.33 (CH_2), 52.27 (CH_2), 99.7 (5-H), 126.55, 127.0, 127.3, 128.3, 130.75 (CH Ph), 136.05, 159.0, 162.3, 163.5, 162.5, 170.0, 174.3 (q-C)

ν_{max}(nujol)/cm^{-1} 1702, 1560.

6-Carboxymethyl-*N*-benzylamino-2-phenyl-4(3*H*)pyrimidinone (213)

4-Chloro-6-ethoxycarbonylmethyl-*N*-benzylamino-2-phenylpyrimidine (**209**) (2 g, 5.24 mmol) was refluxed with NaOH solution (200 ml, 10% soln) for 24 hr. After cooling, the reaction was acidified with Conc. HCl (pH 2-3). The filtered white solid was dried in the oven, finely powdered, and extracted with boiling methanol (200 ml). The filtered methanolic solution was concentrated, diluted with DCM, and cooled, producing a white solid product (1.02 g, 58 %) m.p. >215^{0}C (H_2O). (Found: C, 65.48, H, 4.89, N, 12.04, $C_{19}H_{17}N_3O_3$ 1H_2O requires C, 64.58, H, 5.38, N, 11.89 %).

δ_H (400 MHz, d_6-DMSO) 4.38 (2H, br s, CH_2), 4.70 (2H, br s, CH_2), 5.20 (1H, s, 5-H), 7.28 (5H, m, Ph), 7.52 (3H, m, Ph), 8.12 (2H, m, Ph), 12.30 (2H, br s, NH and CO_2H). δ_C (400 MHz, d_6-DMSO +DEPT) 50.74 (CH_2), 53.10 (CH_2), 84.35 (5-CH), 127.0, 127.6, 128.4, 128.5, 131.1, 133.0, (CH phenyl), 136.50, 137.6, 156.2, 162.0, 164.3, 171.4 (q-C) ν_{max}(nujol)/cm^{-1}

6-Methoxycarbonylmethyl-*N*-benzylamino-2-phenyl-4(3*H*)-pyrimidinone (215)

6-Carboxymethyl-(*N*-benzylamino)-2-phenyl-4(3*H*)-pyrimidinone (**213**) (1.25 g, 3.73 mmol) was refluxed with methanol containing Conc. H_2SO_4 (1.5 ml) for 2.5 hr. The reaction was concentrated to remove methanol, diluted with H_2O (100 ml), and

stirred vigorously for 15 min while cooling. The precipitated solid was filtered and dried to give (**215**) (1.2 g, 92 %) m.p. 182-188^{0}C (EtOH). (Found: C, 68.48; H, 5.49; N, 11.99; $C_{20}H_{19}N_3O_3$ requires C, 68.76; H, 5.44; N, 12.03 %).

δ_H (400 MHz, d_6-DMSO) 3.67 (3H, s, CH_3), 4.44 (2H, br s, CH_2), 4.74 (2H, br s, CH_2), 5.22 (1H, s, 5 CH), 7.35 (8H, m, Ph), 8.1 (2H, m, Ph), 11.86 (1H, br s, NH).

δ_C (100 MHz; d_6-DMSO) +DEPT 50.5 (CH_2), 51.75 (CH_3), 53.0 (CH_2), 84.5 (5 CH), 126.5, 127.0, 127.7, 128.3, 128.5, 131.6 (CH Ph), 132.9, 137.4, 156.4, 162.0, 164.4, 170.4 (q-C).

ν_{max}(nujol)/cm^{-1}1745, 1657, 1565, 1212, 974

6-*N*-methylcarbamoylmethyl-*N*-benzylamino-2-phenyl-4(3*H*)-pyrimidinone (216)

6-Methoxycarbonylmethyl-*N*-benzylamino-2-phenyl-4(3*H*)-pyrimidinone **(215)** (100 mg, 0.28 mmol) was heated with 40 % aqueous methylamine solution (10 ml). The solid initially dissilved and after 15 min, a white precipitate formed, which was filtered and recrystallised from EtOH.(80 mg, 80 %) m.p.>288^{0}C

δ_H (400 MHz, d_6-DMSO) 2.70 (3H, br s, $NHCH_3$), 3.9 (3H, s, CH_3), 4.5 (2H, br s, CH_2), 4.7 (2H, br s, CH_2), 5.26 (1H, s, 5 CH), 7.35 (8H, m, Ph), 7.95 (1H, br s, $\underline{NH}CH_3$), 8.1 (2H, m, Ph), 11.92 (1H, br s, NH).

δ_C (100 MHz; d_6-DMSO) +DEPT 27.0 (CH_3), 50.5 (CH_2), 53.0 (CH_2), 84.5 (5 CH), 126.5, 127.0, 127.7, 128.3, 128.5, 131.6 (CH Ph), 132.0, 138.2, 157.3, 162.0, 164.8, 171.6 (q-C).

6-Methoxycarbonylmethyl-*N*-benzylamino-4-methoxy-2-phenylpyrimidine (217)

6-Methoxycarbonylmethyl-*N*-benzylamino-2-phenyl-4(3*H*)-pyrimidinone (**215**) (2.1 g, 6 mmol) and anhydrous K_2CO_3 (2.11 g, 15.3 mmol) were stirred together in DMF (30 ml) at 100^{0}C for 10 minutes. Methyl iodide (530 μL, 8.4 mmol) was added to the suspension and the reaction continued for 10 minutes. The DMF was removed and the oily residue mixed with H_2O (100 ml) and extracted with EtOAc. The extract was dried, concentrated, diluted with hexane and cooled overnight to give a white crystalline product (1.16 g, 73 %) m.p. 96-100^{0}C (EtOH). Analytically pure (**217**)

could be obtained by flash chromatographic purification of the product (EtOAc 3/Hex 5), which rid it of small traces of the starting material (**215**) and an unknown side product. (Found: C, 69.36; H, 5.85; N, 11.55; $C_{21}H_{21}N_3O_3$ requires C, 69.42; H, 5.78; N, 11.57 %). δ_H (400 MHz, d_6-DMSO) 3.64 (3H, s, CH_3), 3.92 (3H, s, CH_3), 4.47 (2H, br s, CH_2), 4.80 (2H, br s, CH_2), 5.88 (1H, s, 5 CH), 7.41 (8H, m, Ph), 8.31 (2H, m, Ph). δ_C (100 MHz d_6-DMSO) +DEPT 50.6 (CH_2), 51.67 (CH_3), 53.0 (CH_2), 53.20 (CH_3), 83.9 (5 CH), 127.1, 127.7, 128.25, 128.4, 128.5, 130.5, (CH Ph), 133.0, 137.5, 161.7, 163.5, 170.26, 174.0, (q-C).

ν_{max}(nujol)/cm^{-1} 1740, 1596, 1575, 1548, 1195.

6-Methoxy-4-*N*-methycarbamoylmethyl-*N*-benzylamino-2-phenylpyrimidine (218)

6-Methoxycarbonylmethyl-*N*-benzylamino-4-methoxy-2-phenylpyrimidine (**217**) (300 mg, 0.82 mmol) was mixed with a 40 % aqueous solution of methylamine (30 ml) and the mixture heated to reflux. Sufficient methanol was added to the reaction to dissolve all solid material, and the reflux continued for a further 20 min. Evaporation of half of the solvents and cooling gave a white solid product (200 mg, 68 %) m.p.190-192^{0}C (EtOH). (Found: C, 69.33; H, 6.07; N, 15.28; $C_{21}H_{22}N_4O_2$ requires C, 69.61; H, 6.08; N, 15.47 %). δ_H (400 MHz, d_6-DMSO) 2.64 (3H, d, NH$\underline{CH_3}$), 3.93 (3H, s, CH_3), 4.18 (2H, br s, CH_2), 4.84 (2H, br s, CH_2), 5.82 (1H, s, 5-CH), 7.36 (8H, m, Ph), 7.92 (1H, d, NH), 8.33 (2H, m, Ph).). δ_C (100 MHz; d_6-DMSO) +DEPT 25.93 (CH_3) 50.7 (CH_2), 53.2 (CH_2), 55.54 (CH_3), 84.0 (5-CH), 127.02, 127.44, 128.16, 128.66, 128.91, 130.84 (CH Ph), 133.5, 138.0, 161.2, 164.2, 171.0, 173.5.0 (q-C).

ν_{max}(nujol) cm^{-1} 3309, 1657, 1598, 1553, 1200

6-Carboxymethyl-*N*-benzylamino-6-ethoxy-2-phenylpyrimidine(219)

4-Chloro-6-ethoxycarbonylmethyl-(*N*-benzylamino)-2-phenylpyrimidine (**209**) (3 g, 7.86 mmol) was refluxed in ethanol containing sodium ethoxide (0.26 mole) for 2 days. The reaction was filtered of sodium chloride, and the filtrate acidified with 5M

HCl (pH 3-4). The mixture was evaporated to dryness and diluted with hot methanol. The solid NaCl was filtered and the filtrate was concentrated and purified by flash chromatography (EtOAc 50/hex 50), giving the title compound as a white solid (500, mg, 17 %). , m.p. 168-172^{0}C (EtOH). The column also yielded a mixture of the product and starting material (unseparated) as well as pure starting material (600 mg). (Found: C, 68.43, H, 5.73, N, 11.37, $C_{21}H_{21}N_3O_3$ requires C, 69.42, H, 5.75, N, 11.57 %). δ_H (400 MHz; d_6-DMSO) 1.42 (3H, t, CH_3, J = 7.0), 4.38 (2H, s, CH_2), 4.51 (2H, q, CH_2, J = 7.5), 4.74 (2H, s, CH_2), 5.80 (1H, s, 5-H), 7.36 (8H, m, Ph), 8.37 (2H, m, Ph), 12 40 (1H, br s, CO_2H. δ_c (100 MHz; d_6-DMSO)+DEPT 14.2 (CH_3), 50.51 (CH_2), 52.84 (CH_2), 61.70 (CH_2), 84.0 (5-CH), 126.44, 127.22, 127.71, 127.83, 128.5, 130.14 (CH Ph), 135.9, 137.1, 162.5, 163.5, 170.3, 173.6 (q-C).

ν_{max}(nujol)/cm$^-$ 1701, 1594, 1553, 1192, 1045

4-Ethoxy-6-propoxycarbonylmethyl-*N*-benzylamino-2-phenylpyrimidine (220)

6-Carboxymethyl-*N*-benzylamino-6-ethoxy-2-phenylpyrimidine (**219**) (100 mg, 0.275 mmol) was refluxed in propan-1-ol (10 ml) containing Conc. H_2SO_4 (10 drops) for 1 hr. The excess propanol was removed and the residue mixed with H_2O (50 ml) and extracted with EtOAc. The extract was dried ($MgSO_4$), concentrated, diluted with hexane and cooled. The precipitated product was dried to give (**220**) (65 mg, 58 %) m.p. 79-82^{0}C (EtOAc/Hex). (Found: C, 70.42; H, 6.72; N, 10.15; $C_{24}H_{27}N_3O_3$ requires C, 71.11; H, 6.66; N, 10.37 %).

δ_H (400 MHz; $CDCl_3$) 0.91 (3H, t, $OCH_2CH_2\underline{CH_3}$, J = 7.5), 1.40 (3H, t, $OCH_2\underline{CH3}$ J = 7.0), 1.65 ($OCH_2\underline{CH_2}CH_3$, J = 7.5), 4.1 (2H, t, $O\underline{CH_2}CH_2CH_3$, J = 7.0), 4.30 (2H, br s, CH_2), 4.47 (2H, q, OCH_2CH_3, J = 7.0), 4.80 (2H, br s, CH_2), 5.75 (1H, s, 5-CH), 7.37 (8H, m, Ph), 8.41 (2H, m, Ph). δ_c (400 MHz; $CDCl_3$) + DEPT 9.9 (CH_3), 14.2 (CH_3), 22.0 (CH_3), 50.10, 53.0, 61.8, 66.7 (4 x CH_2), 84.0 (5-CH), 126.6, 127.0, 127.6, 127.7, 128.3, 129.7 (CH Ph), 136.6, 137.7, 162.1, 163.6, 170.14 173.2 (q-C)

4-*N,N*-dimethylamino-2-phenyl-4(3*H*)-pyrimidinone (223)

6-Chloro-2-phenyl-4(3*H*)-pyrimidinone (**205**) (500 mg, 2.4 mmol) was refluxed with Et_3N (1 ml, 7.2 mmol), and *N*-benzylglycine ethyl ester (0.9 ml, 4.8 mmol) in DMF (20 ml) at 150^{0}C overnight. The black mixture was cooled and a light brown solid was filtered and recrystallised from MeOH containing charcoal, to give (**223**) as a white solid (130 mg, 25 %) m.p. >250^{0}C Dec (MeOH).

δ_H (400 MHz, d_6-DMSO) 3.17 (6H, s, 2 x CH_3), 5.37 (1H, s, 5-CH), 7.5 (3H, m, Ph), 8.26 (2H, m, Ph), 12.8 (1H, s, NH). δ_C (100 MHz, d_6-DMSO) + DEPT, 37.1 (2 x CH_3), 83.3 (5-CH), 127.4, 128.3, 131.06 (CH Ph), 132.4, 15, 162.7, 165.4 (q-C).

ν_{max} (nujol)/cm^{-1} 1655, 1596.

6-(2-Hydroxyethyl)amino-2-phenyl-4(3*H*)-pyrimidinone (224)

6-Chloro-2-phenyl-4(3*H*)-pyrimidinone (**205**) (1.03 g, 5 mmol) and ethanolamine (4 ml) were refluxed together in methoxyethanol (25 ml) for 4hr. Removal of the excess solvent afforded a brown viscous oil, which was dissolved in brine solution (100 ml). This aqueous solution was then extracted with EtOAc, dried ($MgSO_4$), concentrated to one third of its volume and cooled. The yellow precipitate, which formed was dried to give (**224**) (500 mg, 43 %) m.p. 195-197^{0}C (EtOH). δ_H (400 MHz, d_6-DMSO), 3.3 (2H, d, CH_2), 3.56 (2H, d, CH_2), 4.74 (1H, br s, OH), 5.5 (1H, s, 5-H), 6.9 (1H, br s, NH), 7.78 (3H, m, Ph), 8.1 (2H, m, Ph), 11.72 (1H, br s, NH). δ_C (100 MHz, d_6-DMSO + DEPT) 43.8 (CH_2), 59.5 (CH_2), 84.0 (5-H), 127.5, 128.5,131.3 (C-H Ph), 133.0, 156.8, 162.9, 164.0 (q-C)

ν_{max} (nujol)/cm^{-1} 1630

6-(2-Hydroxyethyl-*N*-methyl)amino-2-phenyl-4(3*H*)-pyrimidinone (225)

6-chloro-2-phenyl-4(3*H*)-pyrimidinone (**205**) (0.5 g, 2.43 mmol), triethylamine (2 ml) and *N*-methylethanolamine (1.5 ml) were refluxed together in ethoxyethanol (15 ml) for 3hr. Following the removal of the excess solvent (rot vap), the residue was dissolved in water and cooled overnight. A yellow solid product was collected (300 mg, 59 %) m.p. 185-188^{0}C (EtOH). δ_H (400 MHz, d_6-DMSO), 3.05 (3H, s, CH_3),

3.61 (4H, br s, 2 x CH_2), 4.72 (1H, br s, OH), 5.17 (1H, s, 5-H), 7.52 (3H, m, Ph), 8.13 (2H, m, Ph), 11.81(1H, br s, NH). δ_C (100 MHz, d_6-DMSO + DEPT), 36.75 (CH_3), 51.71 (CH_2), 58.2 (CH_2), 82.8 (5-H), 127.6, 128.5, 131.3, (CH-Ph), 133.2, 155.8, 162,0, 164.1 (q-C).

ν_{max} (nujol)/cm^{-1} 1654

4-Benzyloxy-6-(2-hydroxyethyl)amino-2-phenylpyrimidine (226)

6-(2-Hydroxyethyl)amino-2-phenyl-4(3*H*)-pyrimidinone **(224)** (230 mg, 1 mmol) was dissolved in DMF (6 ml) and to this was added anhydrous K_2CO_3 (304 mg, 2.2 mmol) and the suspension heated at 120^{0}C for 15 min. Benzyl chloride (110 µl, 0.95 mmol) was added and the mixture heated for a further 15 min. Removal of the DMF (rot vap) afforded an orange oil which was purified by flash chromatography (EtOAc 70/Hex 30) to give (**226**) as a pale yellow solid (117 mg, 36%) m.p.91-95^{0}C (EtOAc-Hex). (Found: C, 70.81; H, 5.99; N, 12.82; $C_{19}H_{19}N_3O_2$ requires C, 71.03; H, 5.92; N, 13.08 %). δ_H (400 MHz, $CDCl_3$), 3.5 (1H, s, OH), 3.54 (2H, t, CH_2), 3.83 (2H, t, CH_2), 5.28 (1H, br s, NH), 5.53 (2H, s, CH_2), 5.7 (1H, s, 5-H), 7.43 (8H, m, Ph), 8.1 (2H, m, Ph). δ_C (100 MHz, $CDCl_3$ + DEPT), 43.83 (CH_2), 63.02 (CH_2), 67.20 (CH_2), 84.0 (5-H), 127.51, 127.64, 127.67, 127.84, 128.05, 129.98 (C-H Ph), 136.7, 137.35, 163.04, 164.43, 169.52 (q-C).

ν_{max} (nujol)/cm^{-1} 1610, 1572.

4-Benzyloxy-6-(2-hydroxyethyl-*N*-methyl)amino-2-phenylpyrimidine (227)

6-(2-Hydroxyethyl-*N*-methyl)amino-2-phenyl-4(3*H*)-pyrimidinone (**225**) (1.15 g, 4.7 mmol) and anhydrous K_2CO_3 (1.62 g, 11.75 mmol) were heated together in DMF (25 ml) for 15 min. Benzyl chloride (0.62 ml, 5 mmol) was added and the mixture heated at 120^{0}C for 1 hr. Removal of the DMF gave an oil which was purified by flash chromatography (EtOAc 30/Hex 70) giving the product as white crystals (820 mg, 52 %) m.p. 72-76^{0}C (EtOAc-Hex). (Found: C, 70.77; H, 6.25; N, 12.33; $C_{20}H_{21}N_3O_2$ requires C, 71.64; H, 6.27; N, 12.53 %).

δ_H (400 MHz, $CDCl_3$), 3.1 (3H, s, CH_3), 3.88 (1H, s, OH), 3.9 (2H, s, CH_2), 3.91 (2H, s, CH_2), 5.56 (2H, s, CH_2), 5.79 (1H, s, 5-H), 7.42 (8H, m, Ph), 8.4 (2H, m, Ph). δ_C (100 MHz, $CDCl_3$ + DEPT), 36.63 (CH_3), 52.52 (CH_2), 61.98 (CH_2), 67.18 (CH_2), 83.28 (5-H), 127.5, 127.62, 127.67, 127.86, 128.05, 130.0 (CH Ph), 136.8, 137.42, 162.35, 164.37, 169.75 (q-C)

ν_{max} (nujol)/cm^{-1} 1593, 1573.

4-Benzyloxy-*N*-methylamino-2-phenylpyrimidine (235)

Method A

To an ice-cold suspension of Cr_2O_3 (0.3 g, 3 mmol) in dry DCM (5.5 ml) was added, acetic anhydride (0.28 ml, 3 mmol) and pyridine (0.48 ml, 6 mmol). The mixture was allowed to stir at room temperature for 20 minutes. To this was added a solution of 4-benzyloxy-6-(2-hydroxyethyl-*N*-methyl)amino-2-phenylpyrimidine (**227**) (335 mg, 1 mmol) in dry DCM (3 ml). The mixture was stirred under a nitrogen atmosphere at room temperature overnight. The reaction was diluted with DCM (20 ml) and filtered through celite. The filtrate was concentrated and purified by loading the sample unto a plug of silica and eluting with EtOAc 25%/ Hex 75%, giving the product as white needles (52 mg, 16 %) m.p. 105-107^{0}C (EtOAc/Hex). δ_H (300 MHz, $CDCl_3$) 3.29 (3H, s, CH_3), 5.59 (2H, s, CH_2), 6.20 (1H, s, 5-CH), 7.43 (8H, m, Ph), 8.43 (2H, m, Ph), 9.90 (1H, s, NH). δ_C (75.5 MHz, $CDCl_3$) + DEPT 27.9 (CH_3), 68.3 (CH_2), 89.92 (5-CH), 126.7, 128.25, 128.31, 128.42, 128.60, 131.15, (CH-Ph)136.32, 136.83, 161.90, 163.22, 170.66 (q-C).

(235) Method B

4-Benzyloxy-6-chloro-2-phenylpyrimidine (**237**) (150 mg, 0.5 mmol) was refluxed with an ethanolic solution of methylamine (20 ml of a 30 % $MeNH_2$ soln) in ethanol (10 ml) for 2 days. After all volatile material had been removed, the resulting oil was dissolved in EtOH (5 ml) and diluted with H_2O while stirring. The precipitated product was collected and dried. (120 mg, 82 %). The product was identical to the specimen prepared in Method A above.

4-Benzyloxy-6-chloro-2-phenylpyrimidine (237)

6-Chloro-2-phenyl-4(3*H*)-pyrimidinone (**205**) (1.11 g, 5 mmol) and anhydrous Na_2CO_3 (1.73 g, 12.5 mmol) and benzyl chloride (0.58 ml, 5 mmol), were heated together in DMF (30 ml) at 120^{0}C for 15 min. The DMF was removed and the resulting oil was mixed with H_2O. The aqueous solution was extracted with EtOAc, dried ($MgSO_4$), concentrated, diluted with hexane and cooled. The product was collected as a yellow solid (840 mg, 57 %) m.p.75-78^{0}C (EtOAc/Hex). (Found: C, 68.62; H, 4.49; N, 9.34; Cl, 11.72; $C_{17}H_{13}N_2OCl$ requires C, 68.80; H, 4.38; N, 9.44; Cl, 11.97 %). δ_H (300 MHz, $CDCl_3$) 5.57 (2H, s, CH_2), 6.71 (1H, s, 5-H), 7.46 (8H, m, Ph) 8.46 (2H, m, Ph). δ_C (75.5 MHz, $CDCl_3$+ DEPT) 68.70 (CH_2), 105.40 (5-CH), 127.6, 128.21, 128.35, 128.4, 128.59, 131.40 (CH- Ph), 135.85, 136.10, 161.06, 164.45, 169.95 (q-C).

ν_{max} (nujol)/cm^{-1} 1549, 1326, 1146, 1002

4-Benzyloxy-6-ethylenediamino-2-phenylpyrimidine (238)

4-Benzyloxy-6-chloro-2-phenylpyrimidine (**237**) (1.04 g, 3.5 mmol), ethylenediamine (0.3 ml, 4.5 mmol), and Et_3N (0.9 ml, 6.55 mmol) were heated together in DMF (30 ml) at 100^{0}C for 45 min. The excess DMF was removed and the semi crystalline solid was dissolved in H_2O (100 ml), and extracted with EtOAc. The extract was dried ($MgSO_4$), concentrated, diluted with hexane, and chilled to give a yellow solid product (360 mg, 32 %) m.p.120^{0}C (EtOH).

δ_H (400 MHz, d_6-DMSO) 3.36 (4H, d, 2 x CH_2), 5.47 (2H, s, CH_2), 5.81 (1H, s, 5-CH), 7.37 (8H, m, Ph), 8.06 (2H, s, NH_2), 8.33 (2H, m, Ph) 8.25 (1H, s, NH).

δ_C (100 MHz, d_6-DMSO + DEPT) 35.1 (2 x CH_2), 65 (5-CH), 125.93, 125.95, 126.14, 126.4, 126.5, 128.5, (CH Ph), 135.5, 135.6, 159.53, 160.4, 162.9 (q-C).

ν_{max} (nujol)/cm^{-1} 3338, 1647, 1610, 1557, 1516, 1206.

2-Amino-4-chloro-6-ethoxycarbonylmethylaminopyrimidine (245)

Glycine ethyl ester hydrochloride (4.61 g, 33 mmol) was added to a solution of 2-amino-4-6-dichloropyrimidine (**244**) (5.37 g, 3.3 mmol) in DMF (70 ml). and

dissolved with heating. Triethylamine (13 ml, 94 mmol) was added and the mixture heated at 140° for 1.5 h. The reaction mixture was cooled and the precipitated triethylamine-hydrochloride was filtered. The filtrate was evaporated to a small volume (5-10 ml) of solution. Water (30 ml) was added, and the mixture extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and treated with charcoal before being concentrated. H_2O (40 ml) was added slowly with stirring and the mixture frozen. The frozen mixture was allowed to warm to room temperature when the precipitated product was collected and dried. The product was recrystallised from ethyl acetate/Hexane giving white crystals (5.23 g, 68.5 %) m.p. 132-139°C (EtOAc-Hex). (Found: C, 41.7; H, 4.83; N, 24.15; Cl, 15.54; $C_8H_{11}N_4O_2Cl$ requires C, 41.66; H, 4.81; N, 24.3; Cl, 15.37 %). δ_H (300 MHz d_6-DMSO), 1.21 (3H, t, CH_3, J = 7.0), 4.05 (2H, q, $\underline{CH_2}CH_3$, J = 7.0), 4.15 (2H, d, NH-$\underline{CH_2}$), 5.9 (1H, s, 5H), 6.5 (2H, br s, $\underline{NH_2}$), 7.5 (1H, br s, N-H). δ_c (75.5 MHz d_6-DMSO) + DEPT 14.11 (CH_3), 41.7 (CH_2), 60.5 (CH_2), 92.9 (5-C-H), 157.5, 162.4, 162.7, 170.4 (q-C).

ν_{max} 3514, 3365, 3303, 3172, 1733, 1644, 1587, 1220, 1165. λ_{max} (EtOH 95)/nm 211 (loge $dm^3\ mol^{-1}\ cm^{-1}$ 4.5), 282 (4.0), 233 (4.1).

2-Amino-4-chloro-6-(methoxycarbonylmethyl-N-methylamino)pyrimidine (246)

2-Amino-4,6-dichloropyrimidine (**244**)(1.45 g, 8.8 mmol), Et_3N (8.4 ml, 60 mmol) and sarcosine methyl ester hydrochloride (6.1 g, 43.7 mmol) were heated together in DMF (70 ml) for 1 hr at 120^{0}C. After removal of the excess DMF (rot vap), the residue was dissolved in H_2O (100 ml) and extracted with EtOAc. The organic phase was dried ($MgSO_4$), and purified by flash chromatography which removed traces of the starting material. The separation gave the required product as a white solid (1.1 g, 58 %) m.p. 112-115^{0}C (EtOAc-Hex). (Found: C, 40.47;H, 4.59; N, 23.97; Cl, 15.59; $C_8H_{11}N_4O_2Cl$ requires C, 41.64; H, 4.77; N, 24.39; Cl, 16.39 %).

δ_H (400 MHz $CDCl_3$), 3.04 (3H, s, CH_3), 3.74 (3H, s, CH_3), 4.30 (2H, s, CH_2), 5.05 (2H, s, NH_2), 5.94 (1H, s, 5-H). δ_c (100 MHz $CDCL_3$) + DEPT 36.3 (CH_3), 50.31 (CH_2), 51.65 (CH_3), 91.82 (5-CH), 159.74, 161.4, 163.4, 169.7 (q-C).

ν_{max} (nujol)/cm^{-1} 3498, 3296, 3160, 1740, 1636, 1542.

2-Amino-4-chloro-6-carbamoylmethylaminopyrimidine (247)

To a solution of 2-amino-4-6 dichloropyrimidine (**244**)(3 g, 18.3 mmol) in DMF (50 ml) was added, glycinamide hydrochloride (2.21 g, 20 mmol) and the salt dissolved with the aid of heat, ethanol (10 ml), and H_2O (2 ml). Triethylamine (8.4 ml, 60 mmol) was added and the mixture heated at 140^0C for five hours. The ethanol was removed and the cooled solution filtered of triethylamine hydrochloride. Evaporation of most of the DMF and addition of water and by cooling caused precipitation of a white product (1.5 g, 44.8 %) m. p. > 205 ° C. (Dec) (EtOAc-Hex). (Found: C, 36.07; H, 4.10; N, 35.21; Cl, 18.31; $C_6H_8N_5OCl$ requires C, 35.75; H, 3.99; N, 35.74; Cl, 17.60 %). δ_H (300 MHz, d_6-DMSO) 3.83 (2H, br s, CH_2), 5.8 (1H, br s, 5-H), 6.4 (2H, br s, NH_2), 7.1 (1H, s, NH), 7.4 (2H, br s, $CO\underline{NH_2}$). δ_C (75.5 MHz, d_6-DMSO) + DEPT) 43.0 (CH_2), 93.1 (5-CH), 152.7, 162.7, 164.0, 171.2 (q-C).

ν_{max} (nujol)/cm^{-1} 3447.9, 3311.3, 1673.6, 1652, 1575, 1255.

2-Amino-4-chloro-6-ethoxycarbonylmethyl(-*N*-benzyl)aminopyrimidine (248)

2-Amino-4,6-dichloropyrimidine (244)(500 mg, 3 mmol) was dissolved in DMF (30 ml) and to this was added Et_3N (1.4 ml, 10 mmol) and the solution heated. N-benzyl-glycine ethyl ester (3.2 mmol, 0.6 ml) was added and the reaction heated at 130^0C for 3 hr. The excess DMF was removed (rot vap) and the brown oil was mixed with H_2O (100 ml) and extracted with EtOAc. The extract was dried ($MgSO_4$), treated with charcoal and concentrated. Dilution with hexane and stirring produced a heavy precipitate of product. (370 mg, 38 %) m.p. 140^0C. (EtOAc-Hex). (Found: C, 55.88; H, 5.25; N, 17.24; Cl, 10.80; $C_{15}H_{17}N_4O_2Cl$ requires C, 56.16; H, 5.30; N, 17.47; Cl, 11.08 %). δ_H (400 MHz d_6-DMSO), 1.18 (3H, t, CH_3, J = 7), 4.10 (2H, q, CH_2, J = 7), 4.31 (2H, br s, CH_2), 4.69 (2H, br s, CH_2), 5.95 (1H, s, 5-H), 6.53 (2H, br s, NH_2), 7.26 (5H, m, Ph). δ_c (80.0 MHz d_6-DMSO) + DEPT 14.06 (CH_3), 49.21 (CH_2), 60.92 (CH_2), 90.87 (CH, 5-H), 127.12, 128.50 128.80, (CH, Ph), 137.41, 159.21, 162.31, 163.72, 169.43 (q-C).

ν_{max} (nujol)/cm^{-1} 3491, 3293, 3158, 1734, 1628, 1576, 1212

2-amino-4-chloro-6-[methoxycarbonyl(2-methyl)ethyl-*N*-methylamino]-pyrimidine (249)

2-Amino-4,6-dichloropyrimidine (**244**)(500 mg, 3 mmol) was dissolved in DMF (20 ml) and to this was added Et_3N (9 mmol, 1.25 ml) and the mixture heated at 90-100^{0}C for a short while. To this was added propanoic acid, 3-(methylamino)-2-methyl, methyl ester (1 ml) and the reaction continued at 100^{0}C for 1.5 hr. The reaction was cooled, producing crystals of $Et_3N.HCl$, which were filtered. The filtrate was concentrated and H_2O (50 ml) was added. The aqueous solution was extracted with ethyl acetate (50 ml). The organic phase was dried ($MgSO_4$), treated with charcoal and concentrated. Addition of hexane and cooling gave a white solid product (625 g, 68 %) m.p.100-103^{0}C (EtOAc/Hex). (Found: C, 46.77, H, 5.90, N, 21.21, Cl, 12.90, $C_{10}H_{15}N_4O_2Cl$ requires C, 46.42, H, 5.80, N, 21.66, Cl, 13.73 %).

δ_H (400 MHz d_6-DMSO), 1.05 (3H, d, CH_3), 2.90 (1H, m, CH), 2.94 (3H, s, CH_3), 3.57 (3H, s, CH_3), 3.60 (2H, d, CH_2), 5.90 (1H, s, 5-H), 6.39 (2H, br s, NH_2).

δ_c (100MHz d_6-DMSO) + DEPT 14.41 (CH_3), 36.03 (CH_3), 37.44 (CH_3), 59.90 (CH), 52.08 (CH_2), 90.37 (5-CH), 158.99, 162.31, 163.50, 174.84 (q-C)

ν_{max} (nujol)/cm^{-1} 3324, 3150, 1734, 1654, 1173, 1576.

2-Amino-4-carboxymethylamino-6-chloropyrimidine (251)

2-Amino-4-chloro-6-ethoxycarbonymethylaminopyrimidine (**245**) (300 mg, 1.3 mmol) was mixed with sodium hydroxide solution (10 ml of 1.25 M soln) and the mixture refluxed for 4.5 hr. The solution was filtered hot, cooled, and then acidified to pH 4 with dilute HCl (2M). The white precipitate was collected, washed with water, extracted with boiling methanol and refiltered. Evaporation of the methanol solution afforded a white solid (130 mg, 49 %) m. p. > 210 ° C (Dec) (EtOH 50/H_2O 50) (Found: C, 35.41; H, 3.58; N, 27.39; Cl, 17.44; $C_6H_7N_4O_2Cl$ requires C, 35.57; H, 3.48; N, 27.65 Cl; 17.51 %). δ_H (300 MHz, d_6-DMSO) 3.9 (2H, s, CH_2), 5.8 (1H, s, 5-H), 6.4 (2H, br s, NH_2), 7.45 (1H, br s, NH), 12.4 (1H, br s, CO_2H). δ_C (75.5 MHz, d_6-DMSO) + DEPT 41.7 (CH_2), 92.9 (5-CH), 157.2, 162.8, 164, 171.8 (q-C).

ν_{max} (nujol)/cm^{-1} 3510, 3340, 1670, 1624, 1534, 1360 and 1182 . λ_{max} (EtOH 95)/nm 212 (loge dm^3 mol^{-1} cm^{-1} 4.4), 283 (3.93), 236, (4.02, shoulder).

Unknown hydrolysis product (252)

2-Amino-4-chloro-6-ethoxycarbonylmethylaminopyrimidine (**245**) (1.12 g, 4.84 mmol) was mixed with sodium hydroxide solution (2M, 35 ml) and the reaction mixture refluxed for 12 h. The solution was filtered hot and acidified with HCl (1M) to pH 5-6. The precipitated product was filtered and dried. The product was contaminated with small amounts of two other compounds, however due to its extreme insolubility in all solvents (sparingly soluble in DMSO only), it was not possible to isolate a pure sample of the product or obtain satisfactory spectroscopic data.

2-Amino-4-ethoxy-6-ethoxycarbonylmethylaminopyrimidine H_2SO_4 salt (253)

(**252**) 670 mg in ethanol (60 ml) containing conc. H_2SO_4 (0.6 ml) was refluxed for 2 h. The hot solution was filtered and the solution evaporated to approximately one third its original volume yielding a white solid precipitate. The product was recrystallised from ethanol (190 mg) m.p.>200°C (EtOH).

(Found: C, 35.28; H, 5.38; N, 16.35; S, 10.09; $C_{10}H_{18}N_4O_7S$ requires C 35.50; H, 5.32; N, 16.56; S, 9.47 %). δ_H (300 MHz, d_6-DMSO) 1.2 (6H, 2 x t, 2 x CH_3), 3.76 (2H, q, $\underline{CH_2}CH_3$), 4.1 (2H, q, $\underline{CH_2}CH_3$), 4.2 (2H, s, NH-$\underline{CH_2}$), 5.3 (1H, br s, 5-H), 7.4 (1H, br s, NH), 8.36 (2H, br s NH_2), 11.9 (1H, br s, H_2SO4). δ_C (75.5 MHz, d_6-DMSO) + DEPT 14.0 (CH_3), 15.1 (CH_3), 42.24 (CH_2), 60.7 (CH_2), 61.3 (CH_2), 75.8 (5-CH), 154.5, 163.5, 169.5, 171.0 (q-C).

ν_{max} 3250 (broad), 1734, 1696, 1636, 1534, 1337, 1242 cm^{-1}

2-Amino-4-methoxy-6-methoxycarbonylmethylamino pyrimidine H_2SO_4 salt (254)

The unknown hydrolysis product (**252**) (1.4 g) was refluxed in methanol (125 ml) containing conc. H_2SO_4 (0.75 ml) for 2 h. The slightly turbid solution was filtered through celite and the resulting clear solution evaporated to approximately 20-30 ml

and cooled. A white solid precipitated from the solution, which was dried and recrystallised from methanol (600 mg). m.p. 185-188^{0}C (Dec) (MeOH)
(Found: C, 30.67; H, 4.49; N, 17.96; S, 10.63; $C_8H_{14}N_4O_7S$ requires C 30.96; H, 4.52; N, 18.06; S, 10.32 %). δ_H (300 MHz, d_6-DMSO), 3.4 (3H, s, CH_3), 3.68 (3H, s, CH_3), 4.14 (2H, s, CH_2), 5.32 (1H, s, 5-H), 7.47 (2H, br s, NH_2), 8.4 (1H, br s, NH), 10.0 (1H, br s, H_2SO_4). δ_c (75.5 MHz, d_6-DMSO) + DEPT 42.2 (CH_2), 52.0 (CH_3), 53.0 (CH_3), 76.1 (5-C-H), 154.3, 161.3, 165.3, 170.0 (q-C).

ν_{max} (nujol)/cm^{-1} 3317, 3188, 1747, 1714, 1656, 1536

2-Amino-6-carbamoylmethylamino-4(3*H*)-pyrimidinone monohydrate (255)

2-Amino-4-methoxy-6-methoxycarbonylmethylaminopyrimidine H_2SO_4 salt (**254**) (512 mg, 1.64 mmol), ammonia solution (8 ml of 0.88 NH_3,) and methanol were refluxed together for 2hr. Cooling produced a greenish solid, which was recrystallised from methanol (210 mg, 64 %) m.p. >250^{0}C. (Found: C, 35.80; H, 5.47; N, 34.55; $C_6H_9N_5O_21H_2O$ requires C, 35.82; H, 5.47; N, 34.82 %). δ_H (400 MHz d_6 DMSO) 3.63 (2H, d, CH_2), 4.44 (1H, s, NH), 6.2 (2H, br s, NH_2), 6.37 (1H, s, 5H), 7.03 (1H, s, NH), 7.22 (1H, s, NH), 9.8 (1H, s, lactam NH)

δ_C (100 MHz d_6 DMSO) + DEPT 43.3 (CH_2), 76.4 (5-H), 155.4, 162.9, 164.0, 171.5 (q-C)

ν_{max} (nujol/cm^{-1}) 3420, 3150, 1654, 1290.

2-Amino-6-*N*-methylcarbamoylmethylamino-4(3*H*)-pyrimidinone mono hydrate (256)

2-Amino-4-methoxy-6-methoxycarbonylmethylaminopyrimidine H_2SO_4 salt (**254**) (500mg, 1.6 mmol), methylamine solution (8ml of 40% aq soln,), and methanol (10 ml) were refluxed together for 0.5 h. The solution was concentrated to an oily semi solid. Addition of ethanol and cooling gave a white solid (300 mg, 88 %) m.p.gradual>200^{0}C. (EtOH). (Found: C, 39.25; H, 6.07; N, 33.35; $C_7H_{11}N_5O_2$ $1H_2O$ requires C, 39.07; H, 6.05; N, 32.56 %) δ_H (400 MHz d_6 DMSO) 2.58 (3H, s, CH_3), 3.84 (2H, s, CH_2), 4.44 (1H, s, NHCH_3), 6.24 (2H, s, NH_2, 2-position), 6.49 (1H, s, 5-

H), 7.69 (1H, s, NHCH$_2$), 9.85 (1H, s, lactam NH). δ_C (100 MHz d_6 DMSO) + DEPT 25.54 (CH_3), 44.34 (CH_2), 76.29 (5-H), 155.04, 163.08, 164.23, 169.92 (q-C). ν_{max} (nujol/cm^{-1}) 3399, 3294, 1684, 1639, 1598, 1522.

2-Amino-6-hydrazinocarbonylmethylamino-4(3*H*)-pyrimidinone (257)

2-Amino-4-methoxy-6-methoxycarbonylmethylaminopyrimidine H_2SO_4 salt (**254**) (1g, 3.2 mmol) was suspended in methanol (30 ml) containing hydrazine hydrate (10 ml), and heated until full dissolution of the solid occurred. The reaction was stirred at room temperature overnight. The white solid precipitate was collected and dried (500 mg, 85 %) m.p. (MeOH-H_2O 50/50)

δ_H (400 MHz d_6 DMSO) 3.60 (2H, d, CH_2), 3.66 (2H, br s, NHNH$_2$), 3.70 (1H, br s, NHNH$_2$), 4.27 (1H, s, NH), 6.31 (2H, s, NH_2 2 position), 6.46 (1H, s, 5-H), 9.80 (1H, s, lactam NH). δ_C (100 MHz d_6 DMSO) + DEPT 44.03 (CH_2), 75.93 (5-H), 154.95, 162.89, 164.10, 171.52 (q-C)

2-Amino-6-ethylenediamino-4(3*H*)-pyrimidinone (263)

2-Amino-6-chloro-4(3*H*)-pyrimidinone (**258**) (456 mg, 3 mmol), Et_3N (1.25 ml, 9 mmol) and ethylenediamine (0.2 ml, 3.2 mmol) were heated together in DMF (30 ml) at 120^{0}C for 3-4 hours. The reaction mixture when cooled yielded a white solid precipitate of (263) (110 mg, 22 %) m.p.> 250^{0}C (MeOH 90/H_2O 10). Analysis of the filtrate (TLC) indicated a mixture of starting material and product, which were not separated. δ_H (300 MHz d_6-DMSO) 2.11 (2H, q, CH_2), 2.92 (2H, s, NH_2), 3.17 (2H, t, CH_2), 4.54 (1H, s, 5H), 6.2 (2H, br s, NH_2 2 position), 8.03 (2H, br s 2 x NH). δ_C (75.5 MHz d_6-DMSO) + DEPT 30.65 (CH_2), 37 (CH_2), 75.5 (5-CH), 154.17, 161.3, 162.93, (q-C).

ν_{max} (nujol)/cm^{-1} 3412, 3306, 1598, 1330, 964, 777

6-Chloro-2-pivaloylamido-4(*3H*)-pyrimidinone (266)

2-Amino-6-chloro-4(3*H*)-pyrimidinone (**258**) (3 g, 20.9 mmol) and DMAP (360 mg, 3 mmol) were refluxed together in pivalic anhydride (20 ml) for 10 hr. The

excess anhydride was removed by distillation under reduced pressure and the residue dissolved in EtOAc. The organic solution was treated with charcoal, concentrated and diluted with hexane. This gave a white solid precipitate of product (2.1 g, 44 %) m.p. 217-219^{0}C (EtOAc-Hex). δ_H (400 MHz d_6-DMSO) 1.23 (9H, s, 3 x CH_3), 6.21 (1H, s, 5-H), 11.44 (1H, br s, NH), 12.13 (1H, br s, NH). δ_C (100 MHz d_6-DMSO) 26.05 (3 x CH_3), 107.1 (5-CH), 151.56, 157.92, 159.8, 181.64 (q-C).

2-Amino-6-(acetaldehydediethylacetal)amino-4(3*H*)-pyrimidinone (267)

2-Acetamido-6-chloro-4(3*H*)-pyrimidinone (**264**) (100 mg, 0.53 mmol) and amino acetaldehyde diethylether (0.2 ml) in ethanol (4 ml) were heated together in a sealed tube at 160^{0}C for 16 hr. The reaction mixture was treated with charcoal, concentrated to an oil and dissolved in ethyl acetate. Addition of hexane and cooling gave a light brown solid product (20 mg, 16%). δ_H (400 MHz, d_6-DMSO), 1.13 (6H, t, 2 x CH_3), 3.17 (2H, s, CH_2), 3.47 (2H, q, CH_2), 3.63 (2H, q, CH_2), 4.52 (2H, br s, 5-H and NH), 6.20 (2H, br s, NH_2), 9.89 (1H, br s, NH) δ_C (100 MHz, d_6-DMSO) + DEPT 15.30 (2 x CH_3), 43.6 (2 x CH_2), 61.48 (CH_2), 100.4 (5-CH), 139.5, 155.0, 164.25 (q-C)

2-Acetamido-6-chloro-4-benzyloxypyrimidine (269)

2-Acetamido-6-chloro-4(3*H*)-pyrimidinone (**264**) (3 g, 16.1 mmol) was dissolved in DMF (75 ml). To this was added anhydrous K_2CO_3 (4.9 g, 35.5 mmol) and the suspension heated at 100^{0}C for 15 min. Benzyl chloride (1.5 ml, 16.1 mmol) was added and the reaction heated at 100^{0}C for 2.5 h. The DMF was removed (rot vap) and the residue dissolved in H_2O (100 ml), and extracted with EtOAc. The extract was dried, concentrated, diluted with hexane and cooled in a freezer for 2 days. The white precipitate was filtered to give (**269**) (1.5 g, 34 %) m.p. 100^{0}C (EtOAc/Hex). (Found: C, 55.92; H, 4.31; N, 14.94; Cl, 12.67; $C_{13}H_{12}N_3O_2Cl$ requires C, 56.21; H, 4.32; N, 15.13; Cl, 12.79 %). δ_H (300 MHz d_6-DMSO) 2.23 (3H, s, CH_3), 5.44 (2H, s, CH_2), 6.76 (1H, s, 5-H), 7.37 (3H, m, Ph), 7.49 (2H, m, Ph), 10.72 (1H, s, NH). δ_C

(100 MHz d_6-DMSO). 24.93 (CH_3), 68.4 (CH_2), 101.3 (5-CH), 128.3, 128.44, 128.55 (CH, Ph), 135.75, 156.91, 160.10, 169.2, 173.0 (q-C)

ν_{max} (nujol/cm^{-1}) 3159, 1677, 1574, 1314, 1009.

2-Acetamido-*N*-benzyl-4-chloro-6-benzyloxypyrimidine (270)

The procedure for the preparation of 2-acetamido-4-chloro-6-benzyloxypyrimidine (**269**) was followed. After the filtration of (**269**), the hexane rich filtrate was concentrated and refrigerated for a further 2 days, eventually yielding a white crystalline product (430 mg, 7 %) m.p. 76-78^{0}C (EtOAc-Hex).

(Found: C, 64.3; H, 4.80; N, 11.66; Cl, 9.96; $C_{20}H_{18}N_3O_2Cl$ requires C, 65.31,; H, 4.89; N, 11.43; Cl, 9.66 %). δ_H (400 MHz, d_6-DMSO), 2.51 (3H, s, CH_3), 5.18 (2H, s, CH_2), 5.40 (2H, s, CH_2), 6.90 (1H, s, 5-H), 7.19 (5H, m, Ph), 7.35 (5H, m, Ph). δ_C (100 MHz, d_6-DMSO) + DEPT 26.10 (CH_3), 48.21 (CH_3), 68.87 (CH_2), 102.4 (5-CH), 127.18, 127.41, 128.42, 128.62, 128.88 (CH Ph), 135.61, 138.06, 159.21, 159.70, 170.03, 171.67 (q-C).

2-Acetamido-4-benzyloxy-6-(2-hydroxyethyl-*N*-methyl)aminopyrimidine (271)

2-Acetamido-6-chloro-4-benzyloxypyrimidine (**264**) (480 mg, 1.73 mmol), Et_3N (0.75 ml, 5.4 mmol), and *N*-methylethanolamine (225 μL, 3 mmol) were refluxed together in methoxyethanol (20 ml) for 24 h. The mixture was concentrated, diluted with H_2O (50 ml), and extracted with EtOAc. The organic extract was concentrated and cooled to give the product (**271**) as a white solid (250 mg, 46 %).

δ_H (300 MHz d_6-DMSO) 2.26 (3H, s, NHCO$\underline{CH_3}$), 3.01 (3H, s, N$\underline{CH_3}$), 3.4 (2H, s, CH_2), 3.55 (2H, s, CH_2), 5.24 (2H, s, $\underline{CH_2}$Ph), 5.64 (1H, s, 5-H), 7.37 (5H, m, Ph), 7.49 (2H, m, Ph), 9.80 (1H, s, NH). δ_C (100 MHz d_6-DMSO). 25.1 (CH_3), 36.4 (CH_3), 51.4 (CH_2), 58.8 (CH_2), 66.8 (CH_2), 79.7 (5-CH), 127.8, 128.1, 128.3, (CH, Ph), 137, 156.1, 162.3, 164.0, 169.8 (q-C)

2-Acetamido-4-chloro-6-ethoxycarbonylmethoxypyrimidine (272)

2-Acetamido-6-chloro-4(3*H*)-pyrimidinone (**264**) (6 g, 32 mmol) and anhydrous Na_2CO_3 (8.48 g, 80 mmol) were heated together in DMF (100 ml) for 15 min at 120^0C. Ethylbromo acetate (3.5 ml, 31.5 mmol) was added and the reaction was heated for a further 15 min. The carbonate was filtered and the excess DMF removed (rot vap). The residue was mixed with H_2O (200 ml) and extracted with ethyl acetate. The extract was dried ($MgSO_4$), concentrated, diluted with hexane and cooled to give a white solid product (3.55 g, 41 %) m.p. 117-118^{0}C (EtOAc/Hex). (Found: C, 43.82, H, 4.37, N, 15.24, Cl, 12.98, $C_{10}H_{12}N_3O_4Cl$ requires C, 43.87, H, 4.39; N, 15.36, Cl, 12.98 %). δ_H (400 MHz $CDCL_3$) 1.29 (3H, s, CH_3, J = 7-7.5), 2.49 (3H, s, CH_3), 4.90 (2H, s, CH_2), 4.25 (2H, q, CH_2, J = 7), 6.58 (1H, s, 5-H), 7.93 (1H, s, NH). δ_C (100 MHz $CDCl_3$) 13.63 (CH_3), 24.66 (CH_3), 61.16 (CH_2), 62.80 (CH_2), 101.52 (5-CH), 155.76, 161.21, 167.06, 169.5, 170.35 (q-C)

ν_{max} (nujol/cm^{-1}) 3341, 1729, 1574, 1503, 1243, 1200, 1124, 819, 730.

4-chloro-2-(ethoxycarbonylmethyl-*N*-acetly)amino-6-ethoxycarbonylmethoxy-pyrimidine (273)

The procedure for the synthesis of 2-acetamido-4-chloro-6-ethoxycarbonyl-methoxypyrimidine (**272**) was followed. After (**272**) had been filtered the hexane rich filtrate was concentrated and purified by flash chromatography (EtOAc-Hex-Et_3N, 1:9:3). This gave an additional 200 mg of (**272**) as well as the above product (**273**) (290 mg, 2.5 %) m.p. 69-74^{0}C (Hex). (Found: C, 46.82; H, 5.01; N, 11.49; Cl, 9.78; $C_{14}h_{18}N_3O_6Cl$ requires C, 46.73; H, 5.0; N, 11.68; Cl, 9.87 %).

δ_C (400 MHz, $CDCl_3$) 1.28 (6H, m, 2 x CH_3, J = 7.5), 2.62 (3H, s, CH_3), 4.21 (4H, m, 2 x CH_2, J = 7.0), 4.74 (2H, s, CH_2), 4.84 (2H, s, CH_2), 6.60 (1H, s, 5-H). δ_C (100 MHz, $CDCl_3$) + DEPT 13.61, (CH_3), 13.65, (CH_3), 26.06, (CH_3), 46.21, (CH_2), 60.72, (CH_2), 61.18, (CH_2), 62.76, (CH_2), 101.72, (5-CH), 158.17, 160.60, 166.98, 168.46, 168.90, 171.71 (q-C)

2-Amino-4-chloro-6-hydrazinocarbonylmethoxypyrimidine (276)

2-Acetamido-4-chloro-6-ethoxycarbonylmethoxypyrimidine (**277**) (200 mg, 0.73 mmol) and hydrazine hydrate (2 ml) were stirred together in ethanol (6 ml) at room temperature overnight. The white solid product was filtered to give (**276**) (100 mg, 63 %). m.p. > 204^{0}C (EtOH). (Found: C, 33.08; H, 3.68; N, 31.71; Cl, 15.79; $C_6H_8N_5O_2Cl$ requires C, 33.10; H, 3.68; N, 32.18, Cl, 16.32 %).

δ_H (400 MHz d_6-DMSO) 4.28 (2H, br s, NH$\underline{NH_2}$), 4.71 (2H, s, CH_2), 6.15 (1H, s, 5-H), 7.0 (2H, br s, NH_2), 9.23 (1H, br s, NH). δ_C (100 MHz d_6-DMSO) + DEPT 63.34 (CH_2), 94.8 (5-CH), 159.9, 162.6, 166.1, 169.8 (q-C).

ν_{max} (nujol/cm^{-1}) 3362, 3306, 3190, 1673, 1553, 1021.

2,4-Diamino-6-(2-hydroxyethyl-*N*-methyl)aminopyrimidine (281)

4-Chloro-2,6-diaminopyrimidine (**277**) (2.0 g, 14 mmol), Et_3N (8 ml, 57.5 mmol) and N-methylethanolamine (2.0 ml) were refluxed together in ethoxyethanol (50 ml) for 11 hr. The solvent was removed to give an oil which was purified by flash chromatography (MeOH 30/DCM 70). This gave recovered starting material (**277**) (1 g) and the product (**281**) as a yellow solid (150 mg. 12 %) m. p. > 260^{0}C.

δ_H (400 MHz, d_6-DMSO) 2.9 (3H, s, CH_3), 3.44 (2H, t, CH_2 J = 5), 3.50 (2H, t, CH_2, J = 5-6), 4.94 (1H, s, 5-H), 5.44 (2H, br s, NH_2), 5.64 (2H, br s, NH_2). δ_c (100 MHz d_6-DMSO) + DEPT 36.13 (CH_3), 50.98 (CH_2), 59.07 (CH_2), 73.20 (5-CH), 162.31, 163.32, 164.57 (q-C).

ν_{max} (nujol/cm^{-1}) 1654, 1590.

4-Chloro-2,6-diacetamidopyrimidine (282)

4-Chloro-2,6-diaminopyrimidine (**277**) (10 g, 69.2 mmol) and acetic anhydride (50 ml) were refluxed for 1 hr. Initially the substrate dissolved and after 30 min the product precipitated. The reaction was cooled and filtered of the cream solid product, which was recrystallised from aqueous MeOH giving (**282**) (9.5 g, 60 %) m.p. 240^{0}C.

δ_H (400 MHz, d_6-DMSO) 2.17 (3H, s, CH_3), 2.20 (3H, s, CH_3), 7.72 (1H, s, 5H), 10.56 (1H, s, NH), 10.90 (1H, s, NH). δ_c (100 MHz d_6-DMSO) + DEPT. 24.20 (CH_3), 24.74 (CH_3), 103.05 (5-H), 156.96, 159.63, 160.40, 169.15, 171.0 (q-C)

4-Chloro-2,6-bis(trifluoroacetamido)pyrimidine (283)

4-Chloro-2,6-diaminopyrimidine (**277**)(3 g, 20.8 mmol) and trifluoroacetic anhydride (50 ml) were refluxed together for 1 hr. The excess anhydride was removed (rot vap) and the residue treated with H_2O (200 ml). After stirring vigorously, the solid product was filtered and dried to give () (4.5 g, 59 %) m.p. 85-89^{0}C.(EtOAc). δ_H (400 MHz, d_6-DMSO) 7.87 (1H, s, 5-H), 12.51 (2H, br s, 2 x NH). δ_C (100Mhz d_6-DMSO) + DEPT 107.85 (5-CH), 113.7, 116.5, 155.66, 159.0, 161.63 (q-C).

ν_{max} (nujol/cm^{-1})3600, 3300, 3150, 1710, 1690, 1610.

2,4-Diacetamido-6-(2-hydroxyethyl)aminopyrimidine (284 A)

4-Chloro-2,6-diacetamidopyrimidine (**282**) (1 g, 4.4 mmol), ethanolamine (3 ml), Et_3N (3 ml) were refluxed together in methoxyethanol (30 ml) for 2 hr. The solvent was partially removed and the solution cooled to give a cream solid precipitate of (**284A**) (560 mg, 50%) m.p.>180^{0}C Dec (EtOH). δ_H (400 MHz, d_6-DMSO) 2.07 (3H, s, CH_3), 2.25 (3H, s, CH_3), 3.32 (2H, br s, CH_2), 3.50 (2H, t, CH_2), 4.65 (1H, br s, NH), 6.92 (1H, s, 5H), 7.35 (1H, br s, OH), 9.5 (1H, s, NH), 9.98 (1H, s, NH). δ_c (100 MHz d_6-DMSO) + DEPT 24.1 (CH_3), 24.85 (CH_3), 43.1 (CH_2), 59.85 (CH_2), 87.16 (5-CH), 156.65, 159.0, 164.51, 169.90, 170.10 (q-C).

ν_{max} (nujol/cm^{-1}) 3260, 3188, 3121, 1660, 1047.

2,4-Diacetamido-6-(2-hydroxyethyl-*N*-methylamino)pyrimidine (284 B)

4-Chloro-2,6-diacetamidopyrimidine (**282**) (1 g, 4.4 mmol), *N*-methylethanol-amine (2.5 ml), and Et_3N (3 ml) were refluxed together in ethoxyethanol (30 ml) for 10 min. The heavy white precipitate, which formed, was filtered and recrystallised

from ethanol to give (**284**) (960 mg, 82 %) m.p. 235-238^{0}C (EtOH). (Found: 49.05, H, 6.23 N, 25.70; $C_{19}H_{14}N_3O_2F_3$ requires C, 49.44; H, 6.37; N, 26.22 %)

δ_H (400 MHz, d_6-DMSO) 2.09 (3H, s, CH_3), 2.25 (3H, s, CH_3), 3.03 (3H, s, CH_3), 3.56 (4H, br s, 2 x CH_2), 4.67 (1H, br s, OH), 7.01 (1H, s, 5H), 9.52 (1H, br s, NH), 10.08 (1H, br s, NH).

ν_{max} (nujol/cm^{-1}) 3364, 3272, 1684, 1663, 1624, 1570, 1522, 1254, 810.

2,6-Diacetamido-4(3*H*)-pyrimidinone (286)

2,6-Diamino-4(3*H*)-pyrimidinone (**285**)(2 g, 15.89 mmol) was mixed with acetic anhydride (20 ml) and refluxed for 15 min. The yellow solid product was filtered, and extracted with boiling methanol. The solid was refiltered and dried to give the title compound (2.05 g, 97 %) m.p, >320^{0}C

2,4-Diacetamido-6-ethoxycarbonylmethoxypyrimidine (287)

2,6-Diacetamido-4(3*H*)-pyrimidinone (**286**) (630 mg, 3 mmol), anhydrous potassium carbonate (1.04 g, 7.5 mmol) and ethylbromoacetate (335 μL, 3 mmol) were stirred together in DMSO (15 ml) at 120^{0}C for 10 minutes. The solvent was removed and the residue diluted with water (50 ml). The crude solid product was recrystallised from ethyl acetate with added charcoal giving white plates of the title product (300 mg, 34%) m.p. 210^{0}C (EtOAc). (Found: C, 48.67; H, 5.50; N, 18.76; $C_{12}H_{16}N_4O_5$ requires C, 48.65; H, 5.40; N, 18.92 %). δ_H (400 MHz, d_6-DMSO) 1.19 (3H, t, $CH_2\underline{CH_3}$, J= 7.0), 2.13 (3H, s, CH_3), 2.29 (3H, s, CH_3), 4.15 (2H, q, $\underline{CH_2}CH_3$, J = 7.0), 4.95 (2H, s, CH_2) 7.17 (1H, s, 5-H), 10.07 (1H, s, NH), 10.55 (1H, s, NH). δ_c (100 MHz d_6-DMSO) + DEPT 13.97 (CH_3), 24.16 (CH_3), 24.85(CH_3), 60.67 (CH_2), 62.38 (CH_2), 88.73 (5-H), 156.23, 159.47, 168.08, 169.76, 169.80, 170.63 (q-C).

ν_{max} (nujol/cm^{-1}) 3273, 3183, 1757, 1716, 1673, 1623, 1590, 1533.

7-Acetamido-1-acetyl-2,3-dihydro-5(1H)-imidazo-[*1,2*-A]-pyrimidinone (288)

2,6-Diacetamido-4(3*H*)-pyrimidinone (**286**) (500 mg, 2.4 mmol) and anhydrous K_2CO_3 (990 mg, 7.14 mmol) were heated together in DMF (30 ml) at 120^{0}C for 10 min. 1-Bromo-2-chloroethane (0.2 ml, 2.3 mmol) was added and the reaction continued for 1 h. After removal of the excess carbonate the DMF was evaporated to give an oil. H_2O (100 ml) was added and the solution extracted with EtOAc. After drying ($MgSO_4$) the organic extract was concentrated, diluted with hexane and chilled. The precipitated solid was filtered and dried to give (**188**) (50 mg, 8 %) m.p. (EtOH). δ_H (400 MHz, d_6-DMSO) 2.10 (3H, s, CH_3), 2.6 (3H, s, CH_3), 3.91 (4H, s, 2 x CH_2, J = 2.5), 6.64 (1H, s, 5-H), 10.13 (1H, br s, NH). δ_C (100 MHz, d_6-DMSO) + DEPT 24.21 (CH_3), 24.58 (CH_3), 38.95 (CH_2), 41.90 (CH_2), 90.55 (5-CH), 151.15, 155.88, 161.2, 169.05, 169.94, (q-C)

ν_{max} (nujol/cm^{-1}) 3456, 3268, 1696, 1669.

2-Acetamido-9-acetyl-6,7,8,9-tetrahydro-pyrimido[*1,2*-A]-pyrimidin-4-one (289)

2,6-Diacetamido-4(3*H*)-pyrimidinone (**286**) (1 g, 4.76 mmol) and anhydrous K_2CO_3 (1.52 g, 14.3 mmol) were heated together in DMSO (150 ml) for 15 min. 1-Bromo-3-chloropropane (0.46 ml, 4.6 mmol) was added and the reaction continued for 2 h. The excess carbonate was filtered, and the DMSO removed (rot vap). The resulting oil was dissolved in saturated NaCl solution and extracted with EtOAc. The organic extract was dried ($MgSO_4$), concentrated to approximately 5 ml of solution and cooled, to give the product as a white solid (550 mg, 37 %). m.p. >230^{0}C (EtOH). (Found: C, 52.22; H, 5.62; N, 21.93; $C_{11}H_{14}N_4O_3$ requires C, 52.8; H, 5.60; N, 22.44 %). δ_H (400 MHz, d_6-DMSO 1.99 (2H, m, $NCH_2\underline{CH_2}CH_2$, J = 6.0), 2.10 (3H, s, CH_3), 2.51 (3H, s, CH_3), 3.68 (2H, t, CH_2, J = 6.5), 3.84 (2H, t, CH_2, J = 6.0), 6.74 (1H, s, 5-H), 10.09 (1H, s, NH), 10.55(1H, s, NH). δ_C (100 MHz, d_6-DMSO) + DEPT 21.43 (CH_2), 24.16 CH_3), 26.20 (CH_3), 39.5 (CH_2), 42.0 (CH_2), 91.46 (5-CH), 150.41, 155.90, 161.96, 170.0, 171.66 (q-C)

ν_{max} (nujol/cm^{-1}) 3291, 1712, 1671, 1304, 1170, 1020

4-Acetamido-6,7,8,9-tetrahydro-pyrimido-[1,2-A]-pyrimidin-2-one (290)

(**289**) (150 mg, 0.52 mmol) was dissolved in hot EtOH (10 ml) and to this was added hydrazine hydrate (2 ml) and the mixture stirred at room temp. After 5 min a solid began to precipitate. The reaction was stirred overnight, cooled, filtered and dried to give the product as a white solid (80 mg, 63 %) map.>300^{0}C (EtOH). (Found: C, 51.71; H, 5.76; N, 26.57; $C_9H_{12}N_4O_2$ requires C, 51.2; H, 5.70; N, 26.92 %)

δ_H (400 MHz, d_6-DMSO) 1.89 (2H, m, CH_2, J = 6.0), 2.02 (3H, s, CH_3), 3.25 (2H, br s, NH_2), 3.30 (2H, t, CH_2, J = 6.5), 3.75 (2H, t, CH_2, J = 6.0), 6.30 (1H, s, 5-H), 9.70 (1H, br s, NH). δ_C (100 MHz, d_6-DMSO) + DEPT 19.94 (CH_2), 24.56, (CH_3) 38.88, (CH_2), 39.0, (CH_2), 86.0, (5-CH), 152.61, 155.93, 162.60, 169.70 (q-C).

ν_{max} (nujol/cm^{-1})3353, 3318, 1691, 1661, 1541, 1260.

The reaction of 2,4-diacetamido-6-ethoxycarbonylmethoxypyrimidine (287) with NH_2NH_2

2,4-Diacetamido-6-ethoxycarbonylmethoxypyrimidine (**287**) (2.1 g, 7.7 mmol) was dissolved in refluxing ethanol (300 ml). Hydrazine hydrate (16 ml) was added to the refluxing solution. After approximately 5 min a solid precipitated from the reaction mixture. The reaction was cooled and the solid filtered and recrystallised from MeOH to give **product 1** (60 mg, 3 %) map. 256-258^{0}C (MeOH). The filtrate was concentrated until signs of precipitation occurred and upon cooling a second compound, **product 2,** was obtained (830 mg, 45 %) map. 164-172^{0}C (EtOH). The remaining filtrate was concentrated, yielding a third compound, **product 3**, (440 mg, 29 %) m.p. 188-200^{0}C gradual Dec (EtOH).

Product 1

2,4-Diacetamido-6-hydrazinocarbonylmethoxypyrimidine (292)

(Found: C, 41.88; H; 5.11; N; 27.66; $C_{10}H_{14}N_6O_4$ requires C, 42.55; H, 4.96; N; 29.78; %). δ_H (400 MHz, d_6-DMSO 2.12 (3H, s, CH_3), 2.25 (3H, s, CH_3), 3.32 (2H, br s, NH<u>NH_2</u>), 4.75 (2H, s, CH_2), 7.20 (1H, s, 5-H), 9.30 (1H, s, NH), 10.08 (1H, s, NH), 10.50 (1H, s, NH). δ_c (100 MHz d_6-DMSO) + DEPT 24.16 (CH_3), 24.93

(CH_3), 63.71 (CH_2), 89.266 (5-CH), 156.21, 159.24, 162,16, 166.20, 170.02, 170.53 (q-C). ν_{max} (nujol/cm^{-1}) 3298, 1702, 1680, 1534

Product 2

2-Amino-4-acetamido-6-hydrazinocarbonylmethoxypyrimidine (293)

(Found: C, 39.81; H, 5.23; N, 33.37; $C_8H_{12}N_6O_3$ requires C, 40.0; H, 5.0; N, 35.0 %). δ_H (400 MHz, d_6-DMSO 2.05 (3H, s, CH_3), 3.60 (2H, br s NH$\underline{NH_2}$), 4.67 (2H, s, CH_2), 6.32 (2H, s, NH_2), 6.77 (1H, s, 5-H), 9.35 (1h, br s, NH), 10.0 (1H, br s, NH). δ_c (100 MHz d_6-DMSO) + DEPT 24.10 (CH_3), 62.97 (CH_2), 84.0 (5-CH), 159.37, 162.17, 166.57, 170.07, 170.14 (q-C).

ν_{max} (nujol/cm^{-1}) 3437, 3320, 3206, 1686, 1550.

Product 3

2,4-Diamino-6-hydrazinocarbonylmethoxypyrimidine (294)

(Found: C, 36.33; H, 5.14; N, 40.72; $C_8H_{12}N_6O_3$ requires C, 36.36; H, 5.05; N, 42.42; %). δ_H (400 MHz, d_6-DMSO) 3.90 (2H, br s, NH_2), 4.58 (2H, s, CH_2), 5.14 (1H, s, 5-H), 5.88 (2H, s, NH_2), 6.07 (2H, s, NH_2), 9.10 (1H, br s, NH).

δ_c (100 MHz d_6-DMSO) + DEPT 62.50 (CH_2), 76.71 (5-CH), 162.68, 166.02, 167.08, 169.11 (q-C).

ν_{max} (nujol/cm^{-1}) 3470, 3340, 3393, 3285, 3160, 1686, 1636.

2,4-Diamino-6-butoxycarbonylmethoxypyrimidine (296)

2,4-Diacetamido-6-ethoxycarbonymethoxypyrimidine (**287**) (500 mg, 1.69 mmol) was mixed with NaOH solution (30 ml of 0.5 M soln) and refluxed for 2 h. The cooled clear solution was acidified with conc. HCl to pH 4. The white solid precipitate was filtered and dried over P_2O_5 to give 300 mg of a highly insoluble product. This crude material was refluxed in butanol (10 ml) containing conc. H_2SO_4 (30 drops) for 45 min. The clear solution was concentrated to an oil, diluted with saturated $NaHCO_3$ solution and extracted with EtOAc. The organic phase was concentrated, diluted with hexane and cooled to give a white solid product.

δ_H (400 MHz, d_6-DMSO) 0.86 (3H, t, CH_3), 1.29 (2H, quintet, $OCH_2\underline{CH_2}CH_2CH_3$), 1.52 (2H, m, $OCH_2CH_2\underline{CH_2}CH_3$), 4.10 (2H, t, $O\underline{CH_2}CH_2CH_2CH_3$), 4.84 (2H, s, CH_2), 5.30 (1H, s, 5-CH), 7.1 (2H, s, NH_2), 7.31 (2H, s, NH_2). δ_c (100 MHz d_6-DMSO) + DEPT 13.6 (CH_3), 18.6 (CH_2), 30.0 (CH_2), 62.0 (CH_2), 64.2 (CH_2), 76.3 (5-CH), 157.82, 161.04, 168.3, 169.4 (q-C).

2,4-Diacetamido-6-*N*^{2}-acetylhydrazinocarbonylmethoxypyrimidine (297)

2,4-Diacetamido-6-hydrazinomethoxy-2-phenylpyrimidine (**292**) (100 mg, 0.35 mmol) and acetic anhydride (3 ml) were heated together at 90^{0}C for 20 min. There was simultaneous removal of starting material and formation of product, which was filtered and recrystallised from aqueous ethanol to give (**297**) (100 mg., 88 %) m.p. >280^{0}C (EtOH/H_2O) (Found: C, 44.44; H, 5.10; N, 25.78; $C_{12}H_{10}N_6O_5$ requires C, 44.44; H, 4.94; N, 25.93 %). δ_H (400 MHz, d_6-DMSO) 1.86 (3H, s, CH_3), 2.12 (2H, s, CH_3), 2.27 (3H, s, CH_3), 4.84 (2H, s, CH_2), 7.21 (1H, s, 5-H), 9.78 (1H, s, NH), 10.02, (2H, s, 2 x NH), 10.52 (1H, s, NH). δ_c (100 MHz d_6-DMSO) + DEPT 20.46 (CH_3), 24.96 (CH_3), 63.41 (CH_2), 89.10 (5-H), 156.05, 159.21, 166.20, 168.3, 169.9, 170.5, 170.6 (q-C).

ν_{max} (nujol/cm^{-1}) 3282, 3195, 1720, 1681, 1589.

2-Acetamido-5-acetyl-6-hydroxy-4(3*H*)-pyrimidinone (305)

6-Amino-4(3*H*),6(1*H*)-pyrimidindione (**243**) (5 g, 0.04 mol) and acetic anhydride were refluxed together for 45 min. The reaction mixture was cooled and filtered. The solid product was extracted with boiling MeOH. The cooled methanolic extract yielded a yellow powder, which was recrystallised, from MeOH/charcoal to give the product as a pure white solid. (2.1 g, 25 %) m.p.240^{0}C Dec (MeOH)

δ_H (400 MHz, d_6-DMSO) 2.20 (3H, s, CH_3), 2.58 (3H, s, CH_3), 11.8 (2H, br s, 2 x NH), 12.5 (1H, s, OH) δ_C (100 MHz, d_6-DMSO) + DEPT 24.12 (CH_3), 29.3 (CH_3), 98.14, 154.0, 174.6, 201.8 (q-C) note that there are two sets of equivalent carbon atoms.

2,5-Diacetamido-6-hydroxy-4(3*H*)-pyrimidinone (306)

2,5-Diamino-4(3*H*),6(1*H*)-pyrimidindione mono hydrochloride (**304**) (0.5 g, 3.7 mmol) and acetic anhydride (25 ml) were refluxed together until full dissolution of the solid had occurred to give a clear yellow solution. Upon cooling a cream solid precipitate was collected and recrystallised from MeOH/charcoal giving a white solid (400 mg, 50 %) m.p.>270^{0}C Dec. δ_H (400 MHz, d_6-DMSO) 2.18 (3H, s, CH_3), 2,50 (3H, s, CH_3), 12.02 (2H, br s, 2 x NH), 12.6 (2H, br s, NH and OH). δ_C (100 MHz, d_6-DMSO) + DEPT 13.90 (CH_3), 23.80 (CH_3), 116.13, 149.07, 154.20, 158.61, 163.93, 177.8 (q-C)

ν_{max} (nujol/cm^{-1}) 3172, 1670.

5-Acetyl-4,6-di(ethoxycarbonylmethoxy)pyrimidine-2-(ethoxycarbonylmethyl-*N*-acetyl)-aminopyrimidine (307)

The procedure for the preparation of (**308**) was followed. After filtration of (**308**), the filtrate was concentrated and recooled for 1 week in a freezer to give the product as a white solid (50 mg, 2 %) m.p. 124-126^{0}C (EtOAc-Pet ether). (Found: C, 50.78; H, 5.64; N, 8.95; $C_{16}H_{21}N_3O_8$ requires C, 51.17; H, 5.76; N, 8.95 %).

δ_H (400 MHz, $CDCl_3$) 1.26 (9H, t, 3 x CH_3), 2.6 (3H, s, $COCH_3$), 2.7 (3H, s, $COCH_3$), 4.2 (6H, q, 3 x O$\underline{CH_2}CH_3$), 4.67 (2H, s, N(Ac)$\underline{CH_2}CO_2Et$), 4.87, (4H, s, 2 x O$\underline{CH_2}CO_2Et$). δ_C (100 MHz, $CDCl_3$) + DEPT 14.05 (3 x $CH_2\underline{CH_3}$), 26.50 (CO$\underline{CH_3}$), 31.64 (CO$\underline{CH_3}$), 46.5 (N(Ac)$\underline{CH_2}CO_2Et$), 60.08 (3 x $\underline{CH_2}CH_3$), 63.07 (2 x O$\underline{CH_2}CO_2Et$), 101.0, 157, 166.7, 167, 168.3, 171.4, 195.44 (q-C) (one of these peaks represents three equivalent carbons).

2-Acetamido-5-acetyl-4,6-di(ethoxycarbonylmethoxy)pyrimidine (308)

2-Aceamido-5-acetyl-6-hydroxy-4(3*H*)pyrimidinone (**305**) (1 g, 5.9 mmol) and anhydrous Na_2CO_3 (1.88 g, 17.7 mmol) were heated together in DMF (50 ml) at 100^{0}c for 20 min. Ethyl bromoacetate (0.66 ml, 6 mmol) was added and heating continued for 5 min. The excess carbonate was filtered and the DMF removed to furnish an oil. The oil was mixed with H_2O and extracted with EtOAc. The extract was dried

(MgSO4), concentrated, diluted with hexane and cooled. The product was isolated as a yellow solid (200 mg, 8 %) m.p. 128-130^{0}C. (EtOAc-Hex). (Found: C, 49.88; H, 5.46; N, 10.96; $C_{16}H_{21}N_3O_8$ requires C, 50.13; H, 5.48; N, 10.96 %).

δ_H (400 MHz, $CDCl_3$) 1.28 (6H, t, 2 x CH_3), 2.46 (3H, s, CH_3), 2.59 (3H, s, CH_3), 4.23 (4H, q, 2 x CH_2), 4.91 (4H, s, 2 x CH_2), 7.83 (1H, s, NH). δ_C (100 MHz, $CDCl_3$) + DEPT 13.63 (2 x CH_3), 24.62 (CH_3), 31.64 (CH_3), 61.05 (CH_2), 63.07 (CH_2), 101.01 (5-CH), 101.0, 154.54, 167.15, 167.39, 170.40, 195.44 (q-C) (one set of equivalent carbons)

ν_{max} (nujol/cm^{-1}) 1751, 1684, 1577.

2,5-Diacetamido-6-ethoxycarbonylmethoxy-4(3*H*)-pyrimidinone (309)

2,5-Diacetamido-4(3*H*),6(3*H*)-pyrimidindione (**306**) (1.13 g, 5 mmol) and K_2CO_3 (2.07 g, 15 mmol) were heated together in DMF (50 ml) at 120^{0}C for 15 min. Ethyl bromoacetate (0.57 ml, 5.1 mmol) was added and the reaction was continued for 1 h at 120^{0}C. The excess DMF was removed (rot vap) and the residue dissolved in H_2O (100 ml) and extracted with EtOAc. The extract was dried ($MgSO_4$), treated with charcoal and concentrated. The residue was purified by flash chromatography (EtOAc/Hex 6:4) which gave the above product as the slower eluting component (250 mg, 16 %) m.p. 139-140^{0}C (EtOAc/Hex). δ_H (400 MHz, $CDCl_3$) 1.28 (3H, t, CH_3, J = 7.5), 2.53 (3H, s, CH_3), 2.64 (3H, s, CH_3), 4.26 (2H, q, CH_2, J = 7.0), 5.05 (2H, s, CH_2), 8.01 (1H, br s, NH), 12.44 (2H, br s, NH and OH). δ_C (100 MHz, $CDCl_3$) + DEPT 13.64 (CH_3), 14.10 (CH_3), 24.57 (CH_3), 61.13 (CH_2), 63.07 (CH_2), 113.0, 152.0, 159.1, 161.1, 166.9, 167.2, 170.3 (q-C).

ν_{max} (nujol/cm^{-1}) 3314, 1745, 1691, 1622

5-Acetyl-6-di(ethoxycarbonylmethoxy)pyrimidine-2-(ethoxycarbonylmethyl-*N*-acetyl)amino-4(3*H*)-pyrimidinone (310)

The procedure for the preparation of (**309**) was followed and the product (**310**) was obtained as the faster eluting component (100 mg, 6 %) m.p.48-50^{0}C (EtOAc-Hex). δ_H (400 MHz, d_6-DMSO) 1.19 (6H, m, 2 x CH_3, J = 4.5), 2.50 (4H, s, 2 x CH_2,), 2.63

(3H, s, CH_3), 4.14 (4H, m, 2 x CH_2, J = 7.0), 4.70 (2H, s, CH_2), 5.15 (2H, s, NH_2). δ_C (100 MHz, d_6-DMSO) + DEPT 14.32 (CH_3), 14.63 (CH_3), 25.98 (CH_3), 47.34 (CH_3), 61.0, (CH_3), 61.3, (CH_3), 63.92 (CH_3), 114.2, 154.55, 158.7, 162.76, 167.13, 167.92, 168.95, 171.70 (q-C)

1,3-Dimethyl-4-ethylenediaminouracil (331)

4-Chloro-1,3-dimethyluracil (5 g, 0.029 mol), and ethylenediamine (5.8 ml) were stirred overnight at room temperature in THF (150 ml). Removal of the solvent furnished an oil, which was recrystallised several times from ethanol, eventually yielding the product as white crystals, which were washed thoroughly with ethanol and diethyl ether, to give (**331**) (2.6 g, 45 %) m.p. 238^{0}C (EtOH).

δ_H (400 MHz CD_3OD) 3.2 (2H, t, CH_2), 3.28 (3H, s, CH_3), 3.44 (3H, s, CH_3), 3.5 (2H, t, CH_2), 4.9 (1H, s, 5-H). δ_C (400 MHz CD_3OD) + DEPT 28.5 (CH_3), 29.7 (CH_3), 40.5 (CH_2), 46.2 (CH_2), 74.8 (5-CH), 153.2, 155.8, 165.5 (q-C).

ν_{max} (nujol/cm^{-1}) 3155, 1766, 1655, 1190.

1,3-Dimethyl-4-ethoxycarbonylmethyl-*N*-methyl-aminouracil (333)

4-Chloro-1,3-dimethyluracil (**328**)(5 g, 28.6 mmol) was dissolved in a hot dioxane/H_2O mixture (100/25 ml) with the aid of vigorous stirring and a little heat. Sarcosine ethyl ether hydrochloride (13.2 g, 85.8 mmol) was then added and the solution heated for 15 minutes at 100°C. To the hot solution was added triethylamine (18 ml. 0.129 mmol) and the reaction mixture refluxed for 12 h. The dioxane was removed under reduced pressure and the aqueous mixture diluted with a saturated sodium chloride solution and extracted with chloroform and ethyl acetate. The combined extracts were dried ($MgSO_4$), concentrated and then treated with charcoal. The filtrate was concentrated, redissolved in ethyl acetate, and diluted with hexane to give a yellow powder (3.6 g, 49 %) m.p. 99-100°C (EtOAc/Hex). (Found: C, 51.75; H, 6.66; N, 16.40; $C_{11}H_{17}N_3O_4$ requires: C, 51.76; H, 6.67; N, 1 6.47 %). δ_H (300MHz, d_6-DMSO): 1.23 (3H, t, $CH_2\underline{CH_3}$, J = 7.0), 2.77 (3H, s, CH_3), 3.14 (3H, s, NCH_3), 3.28 (3H, s, NCH_3), 3.94 (2H, s, CH_2), 4.17 (2H, q, $C\underline{H_2}CH_3$, J = 7.0), 5.16

(1H, s, 5-H). δ_C (75.5MHz, d_6-DMSO) + DEPT: 13.98 ($\underline{CH_3}CH_2$), 27.15 (CH_3), 33.11 (CH_3), 39.50 (CH_3), 54.03 (CH_2), 60.68 ($\underline{CH_2}CH_3$), 86.36 (CH), 152.38, 158.93, 161.87, 169.0 (q-C).

ν_{max} (nujol/cm^{-1}) 1741, 1701, 1647, 1191, 1100, 1025.

1,3-Dimethyl-4-ethoxycarbonylmethylaminouracil (334)

4-Cholro-1,3-dimethyluracil (**328**)(1.47 g, 8.4 mmol) was dissolved in a solution of dioxane/H_2O (30/7ml). Glycine ethyl ester hydrochloride was then added (4.1 g, 29.4 mmol) and the mixture heated. To this was added triethylamine (6 ml, 43.5 mmol) and the reaction refluxed for 8hr. After evaporation of the dioxane saturated sodium chloride solution was added and the mixture extracted with ethyl acetate and chloroform. The pooled extracts were dried ($MgSO_4$), concentrated and treated with charcoal. This solution was evaporated to an oil, dissolved in ethyl acetate and precipitated with hexane to give white crystals (740 mg, 37 %). m.p.178-180^{0}C. (EtOAc/Hex). (Found: C, 51.12; H, 6.47; N, 17.48; $C_{10}H_{13}N_3O_4$ requires: C, 49.79; H, 6.22; N, 17.43 %). δ_H (300MHz, d_6-DMSO): 1.23 (3H, t, $CH_2\underline{CH_3}$, J = 7.0), 3.12 (3H, s, NCH_3), 3.35 (3H, s, NCH_3), 3.96 (2H, d, CH_2), 4.17 (2H, q, $\underline{CH_2}CH_3$, J = 7.0), 4.57 (1H, s, 5-H), 7.23 (1H, t, NH). δ_C (75.5MHz, d_6-DMSO): 14.04 ($CH_2\underline{CH_3}$), 27.09 (CH_3), 29.33 (CH_3), 43.76 (CH_2), 60.79 ($O\underline{CH_2}CH_3$), 74.17 (5-CH), 151.34, 153.46, 161.46, 169.23 (q-C).

ν_{max} (nujol/cm^{-1}) 3316, 1740, 1696, 1636, 1581, 1211.

1,3-Dimethyl-4-*N*-hydroxycarbamoylmethyl-*N*-methylaminouracil (335)

1,3-Dimethyl-4-ethoxycarbonylmethy-(*N*-methyl)aminouracil (**333**) (1 g, 3.92 mmol) was dissolved in ethanol (60 ml) and cooled in an ice bath with stirring. A solution of free hydroxylamine in ethanol (21mmol) was prepared by neutralising a solution of the hydrochloride salt with sodium ethoxide and filtering the sodium chloride. The solution of free hydroxylamine was then added to the solution of the ester and the mixture stirred for 15 minutes at ice bath temperature. A solution of sodium ethoxide (16.6 mmol) in ethanol (30ml) was added and the reaction mixture

stirred for 20 minutes. The reaction was acidified to pH5 with HCl (5M) and the precipitate sodium chloride was filtered. The filtrate was evaporated until a solid precipitated and further precipitation was induced by addition of ethyl acetate. Filtration gave (**335**)(650mg, 68%) as a white solid. m.p. 175-178°C (EtOH 95/H_2O 5). (Found: C, 44.60; H, 5.99; N, 22.68; $C_9H_{14}N_4O_4$ requires: C, 44.63; H, 5.78; N, 23.14 %). δ_H (300 MHz, d_6-DMSO): 2.72 (3H, s, CH_3), 3.14 (3H, s, NCH_3), 3.32 (3H, s, NCH_3), 3.61 (2H, s, CH_2), 5.15 (1H, s, 5-H), 9.01 (1H, s, OH), 10.74 (1H, s, NH). δ_C (75.5MHz, d_6-DMSO) + DEPT 27.18 (CH_3), 33.16 (CH_3), 39.50 (CH_3), 53.61 (CH_2), 86.21 (5-CH), 152.49, 159.26, 161.93, 164.39 (q-C).

ν_{max} (nujol/cm^{-1}) 3161, 1684, 1632, 1168, 999.

1,3-Dimethyl-4-hydrazinocarbonylmethyl(*N*-methyl)aminouracil (336)

1,3-Dimethyl-4-ethoxycarbonylmethy-(*N*-methyl)aminouracil (**333**) (1 g, 3.92 mmol) was dissolved in hot ethanol (50 ml). Hydrazine hydrate (8 ml), was added and the reaction mixture stirred overnight and cooled, to produce a white solid product which was recrystallised from EtOH, (700 mg, 79 %). δ_H (300 MHz, d_6-DMSO 2.78 (3H, s, CH_3), 3.11(3H, s, CH_3), 3.35 (3H, s, CH_3), 3.82 (2H, br s, NH_2), 4.10 (2H, s, CH_2), 5.04 (1H, s, 5-H), 10.40 (1H, s, NH). δ_C (75.5 MHz, d_6-DMSO) + DEPT 25,1 (CH_3), 27.2 (CH_3), 33.5 (CH_3), 54.1 (CH_2), 85.4 (5-CH), 152.25, 159.6, 162.0, 169.3 (q-C).

1,3-Dimethyl-4-*N*-methoxycarbamoylmethyl-(*N*-methyl)aminouracil (344)

1,3-Dimethyl-4-*N*-hydroxycarbamoylmethyl-(*N*-methyl)aminouracil (**335**) (500 mg, 2.07 mmol) was dissolved in ethanol/H_2O (10/12 ml), and to this was added anhydrous sodium carbonate (660 mg, 6.23 mmol) and dimethylsulphate (0.2 ml, 2.09 mmol) and the mixture stirred for 16 h. The precipitate sodium sulphate was filtered and the filtrate evaporated to a yellow solid. The solid was then extracted with boiling methanol and the insoluble material filtered. The filtrate was concentrated and cooled giving a white solid, which was filtered and washed with ethyl acetate and hexane (400 mg, 75 %). (MeOH). δ_H (300 MHz, d_6-DMSO) 2.71 (3H, s, CH_3), 3.12 (3H, s, NCH_3), 3.24 (3H, s, CH_3), 3.30 (3H, s, NCH_3), 3.46 (2H, s, CH_2), 4.15 (1H br

s, NH), 5.10 (1H, s, 5-H).. δ_C (75.5MHz, d_6-DMSO) + DEPT 27.11, 34.0, 38.54, 59.5 (CH_3), 56.0 (CH_2), 84.76 (5-CH), 152.8, 160.10, 162.05, 162.50 (q-C).

2,4-Dimethoxy-6-ethoxycarbonylmethyl(*N*-methyl)aminopyrimidine (349)

Method A

6-Chloro-2,4-dimethoxypyrimidine (**348**)(5 g, 28.63 mmol) and sarcosine ethyl ester hydrochloride (26.4 g, 0.172 mol) were heated together in methoxyethanol (80 ml) until dissolution was complete. Triethyamine (42 ml, 0.3 mol) was added and the reaction was refluxed for 4 h. The cooled reaction mixture was filtered of $Et_3N.HCl$ and the filtrate concentrated to a red/brown residue. Water (100ml) was added and the solution extracted with $CHCL_3$ (500 ml). The combined organic extracts were dried ($MgSO_4$), treated with charcoal and concentrated to an oil which was purified by flash chromatography, EtOAc 40/pet ether 60, giving (**349**) as white needles (3.6 g, 49 %) m.p 55-60^{0}C (EtOAc-Hex). (Found: C, 51.99; H, 6.71; N, 16.46; $C_{11}H_{17}N_3O_4$ requires C, 51.76; H, 6.66; N, 16.47 %). δ_H (400 MHz d_6 DMSO) 1.25 (3H, t, $CH_2\underline{CH_3}$ J = 7.0), 3.05 (3H, s, CH_3), 3.87 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.17 (2H, q, $\underline{CH_2}CH_3$, J = 7.0), 4.30 (2H, s, CH_2), 5.47 (1H, s, 5-H). δ_C (100 MHz d_6 DMSO) + DEPT 14.12 (CH_3), 36.98 (CH_3), 51.32 (CH_2), 53.43 (OCH_3), 54.03 (OCH_3), 60.86 (CH_3), 79.09 (CH), 164.06, 164.62, 169.65, 171.92 (q-C) ν_{max} (nujol/cm^{-1}) 1744, 1603, 1565.

(349) Method B

Bis(trifluoroacetoxy)iodobenzene 327 mg, 0.76 mmol) was dissolved in $CHCl_3$ under an N_2 atmosphere and heated for 5 min. 2,4-Dimethoxy-6-*N*-methoxy-carbamoylmethyl(*N*-methyl)aminopyrimidine (**352**) (150 mg, 0.58 mmol) was added by syringe and the reaction mixture refluxed for 15 min, and stirred at room temperature overnight. The reaction mixture was poured into saturated $NaHCO_3$ solution and extracted with CH_2CH_2. The organic phase was treated with charcoal, concentrated to an oil and dissolved in EtOAc and diluted with hexane. The resulting hexane rich solution was refrigerated for 2 weeks, eventually yielding the product as a pale yellow solid (34 mg, 23 %). The product was identical in every respect to the

specimen prepared in Method A including additional analytical results (Found: C, 51.65; H, 6.62; N, 16.40 %)

2,4-Dimethoxy-6-ethoxycarbonylmethyl(*N*-benzyl)amino pyrimidine (350)

6-Chloro-2,4-dimethoxypyrimidine (**348**) (2.5 g, 14.3 mmol), Et_3N (5 ml, 36 mmol), and *N*-benzyl glycine ethyl ester (17 ml, 90 mmol), were heated together in methoxy ethanol (50 ml) at 120^0C for 2 days. After cooling the solvent was removed to give a brown oil. This was purified by flash chromatography (EtOAc 20/Hex 80), to give the product (**350**) as white plates (1 g, 22 %). (Found: C, 61.54; H, 6.37; N, 12.55; $C_{17}H_{21}N_3O_4$ requires C, 61.63; H, 6.34; N, 12.69 %).

δ_H (400 MHz $CDCl_3$) 1.26 (3H, t, CH_3, J = 2.5), 3.88 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 4.18 (2H, q, $\underline{CH_2}CH_3$, J = 7), 4.21 (2H, br s, CH_2), 4.71 (2H, br s, CH_2), 5.5 (1H, s, 5H), 7.26 (5H, m, Ph). δ_C (100 MHz $CDCl_3$) + DEPT 13.71 (CH_3), 49.22 (CH_2), 52.30 (CH_2), 53.0 (CH_3), 53.7 (CH_3), 61.0 (CH_2), 79.1 (5-CH), 126.6, 127.0, 128.3 (CH-Ph), 136.4, 164.2, 164.6, 169.6, 172.0 (q-C).

ν_{max} (nujol/cm^{-1}) 1735, 1597, 1560, 1203.

2,4-Dimethoxy-4-(*N*-hydroxycarbamoylmethyl(*N*-methyl)amino)pyrimidine (351)

2,4-Dimethoxy-4-ethoxycarbonylmethyl(*N*-methyl)aminopyrimidine (**349**) (1.2 g, 4 mmol) was dissolved in ethanol (50 ml) and cooled in an ice bath. To this was added a solution of hydroxylamine (21.4 mmol) (prepared by neutralising the HCl salt with sodium ethoxide) in ethanol (100 ml), followed 10 min later by a solution of sodium ethoxide (17 mmol) in ethanol (50 ml). The solution was stirred at ice bath temperature for 55 min. The reaction was acidified with 5M HCl to pH 5 and cooled. The precipitated NaCl was filtered and the filtrate concentrated, diluted with ethyl acetate and cooled to give the product as a white solid (980 mg, 86 %). m.p.134-136^{0}C. (EtOH). (Found: C, 44.60; H, 5.84; N, 22.95; $C_9H_{14}N_4O_4$ requires C, 44.63; H, 5.78; N, 23.14 %). δ_H (400 MHz d_6 DMSO) 3.01 (3H, s, N-CH_3), 3.79 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.05 (2H,s, CH_2), 5.56 (1H, s, 5-H), 8.79 (1H, br s, OH),

10.51 (1H, br s, NH). δ_C (100 MHz d_6 DMSO) + DEPT 36.90 (CH_3), 49.97 (CH_2), 53.23 (OCH_3), 53.67 (OCH_3), 78.64 (5-H), 164.10, 165.0, 165.73, 171.60 (q-C)

ν_{max} (nujol/cm^{-1}) 3181, 2718, 1692, 1670, 1607.

2,4-Dimethoxy-6-*N*-methoxycarbamoylmethyl(*N*-methyl)aminopyrimidine (352)

2,4-Dimethoxy-4-*N*-hydroxycarbamoylmethyl(*N*-methyl)aminopyrimidine (**351**) (100 mg, 0.413 mmol) was dissolved in a 50/50 mixture of ethanol/water (10 ml). To this was added anhydrous $NaCO_3$ (110 mg, 1.03 mmol) and the mixture was stirred at room temperature for 0.5 h. Dimethylsulfate (0.45 mmol, 45 μL) was added and the solution stirred for 27.5 h. The reaction was filtered of inorganic solids and the filtrate concentrated to remove ethanol. The aqueous layer was further diluted with water (20 ml) and extracted with $CHCl_3$. The organic phase was dried ($MgSO_4$) and concentrated to an oil. Addition of EtOAc and cooling gave white crystals of product (35 mg, 28 %) m.p. 146-147^{0}C (EtOH). (Found: C, 46.91; H, 6.24; N, 21.72; $C_{10}H_{16}N_4O_4$ requires C, 46.87; H, 6.25; N, 21.87 %). δ_H (400 MHz $CDCl_3$) 3.06 (3H, s, NCH_3), 3.75 (3H, s, $NHOCH_3$), 3.90 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 4.16 (2H,s, CH_2), 5.49 (1H, s, 5-H), 9.26 (1H, br s, NH). δ_C (100 MHz $CDCl_3$) + DEPT 36.75 (NCH_3), 53.20(OCH_3), 53.83(OCH_3), 51.70(CH_2), 64.41(CH_3), 79.40 (5-H), 164.23, 164.40, 165.5, 172.0 (q-C)

ν_{max} (nujol/cm^{-1}) 3168, 1654, 1598.

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