The Chemistry of Diphenyl N-Cyanocarbonimidate

by

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Dedicated with love to
my parents
The Road goes ever on and on
Down from the door where it began.
Now far ahead the Road has gone,
   And I must follow, if I can,
   Pursuing it with weary feet,
   Until it joins some larger way,
Where many paths and errands meet.
   And whither then? I cannot say.

Frodo Baggins in 'The Lord of the Rings'

All knowledge is of itself of some value.
There is nothing so minute or inconsiderable,
   that I would not rather know it than not.

Dr Johnson in Boswell's 'Life of Johnson'
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Abstract

The synthesis of a variety of heterocyclic compounds by the sequential addition of two nucleophiles to a one carbon equivalent is described. Treatment of this one carbon equivalent, diphenyl N-cyanocarbonimidate 53, with the first nucleophile leads to N-cyano-O-phenylisourea intermediates. These compounds were shown to be a mixture of isomers by variable temperature $^1$H n.m.r. spectroscopy and the origin of the stereoisomerism is discussed. The N-cyano-O-phenylisoureas were then treated with a second nucleophile which displaced phenol, giving an intermediate which spontaneously cyclised to produce a heterocyclic ring.

In this way 6-substituted and 5,6-disubstituted-dihydro-4(3H)-pyrimidinones were synthesised together with 5,6-dihydro-4(3H)-pyrimidinones and imidazolidin-5-ones substituted with carbocyclic sugar analogues at N-3. An attempt to synthesise pyrimidine isonucleosides failed due to the steric hindrance present in the sugar.

Several of the imidazolidin-5-ones were rearranged to dihydro-4(3H)-pyrimidinone-6-carboxylic acids by a ring expansion reaction.

Investigations into the hydrolysis of the cyanoimine portion of several molecules using trifluoroacetic acid are reported.

The synthesis of several triazoles, using the bifunctional nucleophile hydrazine and its analogues, is reported. A temperature dependent competition between synthesis of the triazole and the corresponding imidazole, via different cyclisation modes, is described, and a mechanism for the reaction is discussed.
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Introduction

For most of the common heterocyclic ring systems there are a wide range of synthetic routes available. These syntheses can be broadly divided into two groups, those involving transformations on preformed heterocycles and those involving cyclisation of acyclic precursors. The latter group can be further sub-divided into cyclisation reactions in which two ring bonds are formed in the ring closure process and cyclisation reactions in which a single bond is formed. This theses is partly concerned with the latter type, in particular the sequential addition to one carbon compounds. One carbon compounds in which the carbon atom is sp2 hybridised and is bonded to two potential leaving groups have long been known. The synthesis and reaction of some of the more common examples is now described.

1.1 Phosgene, thiophosgene and related compounds

Phosgene 1 and thiophosgene 2 were probably the first one carbon compounds to be used in the preparation of heterocycles and their use is now commonplace. Phosgene 1 reacts with primary amines to give N-substituted carbamyl chlorides, N-substituted isocyanates or N, N'-disubstituted ureas depending on the amine used. The carbamyl chlorides are highly unstable with respect to loss of hydrogen chloride and give the corresponding isocyanates. Phosgene reacts with bifunctional nucleophiles such as catechol 3 and 1,2-ethanediol 4 to form phenylene carbonate 5 and 1,3-dithiolan-2-one 6, respectively. Its main use, therefore, is to introduce an oxo substituent between two heteroatoms. Thiophosgene 2 shows analogous reactions to phosgene 1, thus the aminobenzenesulphonamide 7 condenses with 2 to give the benzothiadiazene 8.
Derivatives of phosgene 1 and thiophosgene 2 can also be condensed with bifunctional nucleophiles in a similar fashion. Ethyl chloroformate 9 and 1-imino-2-methyl-1,3-diphenyl-3-phenyliminopropane 10 in pyridine at 0 °C give 5-methyl-1,4,6-triphenyl-2(1H)-pyrimidinone 11.\(^5\) Diethyl carbonate 12 and 2-(m-chlorophenyl)-2-ethylmalondiamide 13 react to give the barbituric acid 14.\(^6\) Similarly 12 condenses with the 1,3-diamine 15 to give the isoquinoline derivative 16.\(^7\)

1.2 The isocyanide dihalides

The oldest method for the preparation of alkyl and aryl isocyanide dihalides is the chlorination of isothiocyanates.\(^8\) Chlorination of phenylisothiocyanate 17 at low temperature in chloroform led to the elimination of sulphur dichloride and the formation of phenylisocyanide
dichloride 18. Nuclear chlorination products are also obtained in this reaction, but this problem can be avoided by using carbon tetrachloride as the solvent. The reaction has a multistep mechanism; the primary chlorinated adduct 19 is formed in a strongly exothermic reaction; further chlorination of this intermediate leads to the elimination of sulphur dichloride and the formation of 18 with no appreciable evolution of heat.

![Reaction scheme]

The chlorination of isothiocyanates is not generally applicable for the synthesis of isocyanide dichlorides, thus a wide range of complementary reactions have been developed including the addition of halogen to isocyanides,9,10 the chlorination of monosubstituted formanilides in the presence of sulphuryl chloride/thionyl chloride,11 and the chlorination of isocyanates with phosphorus pentachloride.12 These and other special methods have been reviewed by Kühle et al.13a

Isocyanide difluorides can generally only be obtained from the corresponding isocyanide dichlorides, for example phenyl isocyanide dichloride 18 reacts with an excess of sodium fluoride at 160 °C to give phenyl isocyanide difluoride 20.14

![Reaction scheme]

The preparation of acyl isocyanide dihalides is similar to the preparation of alkyl and aryl isocyanide dihalides and is encompassed in the review by Kühle et al.13a In addition, isocyanide dichlorides with a variety of other substituents on the imine nitrogen are also available, one example being the sulphonate group.13a

The cyclisation of isocyanide dichlorides requires a variety of reaction conditions depending on the starting materials, and different conditions can lead to different cyclisation products. Thus the reaction of phenyl isocyanide dichloride 18 with mercaptoethanol 21 in the presence of triethylamine yields 2-phenylimido-1,3-oxathiolane 22, while in the presence of pyridine 2-chloro-2-phenylimido-1,3-oxathiolane 23 is obtained.15 The 5-membered heterocycles produced from isocyanide dichlorides have been extensively studied, and the reaction appears to accept almost any combination of heteronucleophiles, for instance N-aminoethanamide 24 reacts with phenyl isocyanide dichloride 18 to give the 1,3,4-oxadiazine 25.13b
More complex heterocycles have been prepared from isocyanide dichlorides in isolated cases. Anthranilic acid 26a (X=OH) and anthranilamide 26b (X=NH₂) react with the isocyanide dihalides 27 and 28 to yield the benzoxazine 29 and the quinazoline 30 respectively.¹³ᵇ
Isocyanide dihalides give 6-membered heterocycles on reaction with 1,3-diamines, 1,3-dithiols or 3-amino-1-propanols. Pentachlorophenyl isocyanide dichloride 31 reacts with 1,4-diaminobutane 32 (n=4) and 1,6-diaminohexane 32 (n=6) to give 7-membered heterocycles 33 (n=4) and 9-membered heterocycles 33 (n=6) respectively.\(^{13b}\)

\[
\begin{align*}
\text{Cl}_2\text{C}_6\text{H}_4\text{N}=\text{C} \quad \text{H}_2\text{N}(\text{CH}_2)_n\text{NH}_2 \quad \rightarrow \\
\text{Cl}_2\text{C}_6\text{H}_4\text{N}=\text{C}(\text{CH}_2)_n
\end{align*}
\]

Dichlorodiazomethane does not exist in the free state but it can be stabilised within the coordination sphere of tungsten to give the dichlorodiazomethane complex 34, which can be condensed with N,N'-dimethyl-1,3-diaminopropane 35 to give the hexahydropyrimidine complex 36.\(^{16}\) This was proposed to have the structure shown on the basis of the \(^1\)H n.m.r. spectrum which showed that the N-methyl signals were equivalent down to -100 °C.

In a similar way to phosgene, the isocyanides have the disadvantage that they are extremely toxic. Their vapours are extremely irritating to the eyes and prolonged exposure to phenyl isocyanide dichloride 18 is reported to cause corneal ulceration and temporary loss of vision, which led to its limited use as a 'blinding gas' during the First World War. There is again the disadvantage of not being able to control the reaction and isolate the product of the first nucleophilic addition-elimination, since this is still highly reactive.

**1.3 Dimethyl cyanodithiocarbonimidate and related compounds**

Dimethyl cyanodithiocarbonimidate 38 has found widespread use in the synthesis of heterocyclic compounds in recent years. It is prepared in two steps by first condensing carbon disulphide with cyanamide in the presence of potassium hydroxide, and then treating the intermediate cyanodithiocarbonimidate dianion with methyl iodide.\(^{17}\) Treatment of 38 with mono functional nucleophiles results in the displacement of methanethiol to give N-substituted-N'-
cyano-S-methylisothioureas, which are stable solids. Primary aliphatic amines react with 38 at room temperature. Benzylamine, for example, reacts with 38 to give N-benzyl-N'-cyano-S-methylisothiourea 39. Primary aromatic amines require boiling in ethanol to effect the reaction and the attachment of electron withdrawing groups to the phenyl ring often results in a failure of the nucleophile to react. t-Butylamine and secondary amines also fail to react with 38.

\[
\begin{align*}
H_2N-\ce{C=NN} & \xrightarrow{\text{CS}_2, \text{KOH}} \xrightarrow{\text{EtOH}} \text{MeI} \xrightarrow{\text{Acetone}} \text{MeS} \xrightarrow{\text{SMe}} \\
37 & \xrightarrow{\text{PhCH}_2\text{NH}_2} \text{NCN} \xrightarrow{\text{H}_2\text{NNH}_2} \text{H}_2\text{N} \xrightarrow{\text{C=NN}} \text{MeS} \xrightarrow{\text{SMe}} \\
38 & \xrightarrow{\text{39}} \text{38} \xrightarrow{\text{40}} \text{41}
\end{align*}
\]

Treatment of 38 with bifunctional nucleophiles such as hydrazine, leads to displacement of one molecule of methanethiol to give the isothiourea 40, which cyclises spontaneously by attack of the NH₂ group at the nitrile carbon, rather than the imine carbon, to give the thermodynamically more favoured 5-membered ring.

Bifunctional nucleophiles, such as o-phenylenediamine 42, react with 38 by sequential displacement of the two molecules of methanethiol to afford the 2-cyanoaminobenzimidazole 43. The reaction fails completely when electron withdrawing groups are attached to the aromatic ring.
Treatment of 38 with the sterically hindered phenylenediamine 44 yielded none of the desired benzimidazole 46 \(^\text{20}\) using the conditions described by Wittenbrook.\(^\text{17}\) When the reaction was carried out in the presence of 1,8-diazabicyclo-[5,4,0]-undec-7-ene (DBU) at 80 °C only the acyclic isothiourea 45 was obtained. A variety of conditions were tried in an attempt to cyclise 45, but success was only achieved using mercuric acetate in methanol, which resulted in an essentially quantitative conversion.

There are isolated cases of one carbon compounds related to 38 being used for heterocyclic syntheses. The carbamate 47 can either undergo 1,3- or 3,3- cyclisations with bifunctional nucleophiles depending on the nature of the nucleophile. Thus hydrazine gives the 1,3-cyclisation product 48 while 1,3-diaminopropane 32 (n=2) gives the pyrimidine derivative 49.\(^\text{21}\)
Dimethyl N-tosylidithiocarbonimidate 50 reacts with aliphatic diamines in refluxing aqueous ethanol to give cyclic tosyl guanidines in high yields.22 Thus 50 reacts with (S)-(+) -2,4-diaminobutanoic acid 51 to give the optically active, cyclic guanidine 52, which was detosylated by treatment with anhydrous hydrogen fluoride.

1.4 Diphenyl cyanocarbonimidate and related compounds

The potential of diphenyl cyanocarbonimidate 53 as a synthon for heterocyclic compounds has been known for several years,23 but until recently little use was made of it in this field. It can be prepared on a large scale in high yield. Treatment of diphenyl carbonate 54 with phosphorus pentachloride, with continuous removal of the phosphorus oxychloride formed, gives 1,1-dichloro-1,1-diphenoxymethane 55. Condensation of 55 with cyanamide affords 53. This reagent has a number of advantages over dimethyl cyanodithiocarbonimidate 38. The first advantage is that bifunctional nucleophiles attack the imine carbon under extremely mild conditions allowing the isolation of O-phenylisoureas. Slightly more vigorous conditions then lead to the displacement of a second molecule of phenol to give heterocyclic compounds.
o-Phenylenediamine 42 condenses with 53 at room temperature in propan-2-ol to give the O-phenylisourea 56, which cyclises to the benzimidazole 43 on refluxing in propan-2-ol. Alternatively, the benzimidazole 43 can be obtained directly by refluxing the two reagents together. Another major advantage of the phenoxy reagent is that the production of foul smelling mercaptans is avoided.

It has been suggested that the ease with which transformations take place is largely due to the stability of the phenoxide ion as a leaving group and its weak nucleophilicity. Even poor nucleophiles such as p-chlorophenylenediamine condense with 53 almost quantitatively on simply stirring in propan-2-ol at room temperature. In addition, the O-phenylisoureas are much more easily attacked by a second nucleophile than the S-methylisothioureas. The O-
phenylisoureas are attacked by hydrazine, in a similar way to the isothioureas. Thus reaction of 53 with aniline gives N-cyano-N'-phenyl-O-phenylisourea 57, which cyclises to give the triazole 58 on treatment with hydrazine.

Further advances in the use of diphenyl cyanocarbonimide 53 in heterocyclic synthesis have recently been made. Thus treatment of 53 with 2-aminobenzyl alcohol 59 gave the 2-N-cyanoimino-4H-1,3-benzoxazine 60. Compound 60 could be further modified by treatment with an amine in boiling propan-2-ol, for example 60 with benzylamine gave 2-benzylamino-1,3-benzoxazine 61 via loss of H₂NCN.

Treatment of 53 with a β-amino ester has been used as a method of synthesising dihydropyrimidines. Thus use of β-alanine methyl ester 62 gave the dihydropyrimidine 64 via the O-phenylisourea 63, which could be further modified to the pyrimidine 65 by a bromination-dehydrobromination sequence.
Recently a new one carbon synthon, diphenyl N-sulphamoylcarbonimidate 66 has been reported\textsuperscript{26} as a versatile building block for the construction of heterocycles. Diphenyl N-sulphamoylcarbonimidate 66 is prepared from dichlorodiphenoxymethane 55 by condensation with sulphamide 67 in acetonitrile at 0 °C.

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{Ph} & \quad \text{O} \quad \text{Ph} \quad + \quad \text{H}_2\text{NSO}_2\text{NH}_2 \\
55 & \quad 67 \quad \xrightarrow{\text{MeCN} \atop 0-20\,^\circ\text{C} \atop 48\,\text{h}} \quad \text{Ph} \quad \text{O} \quad \text{N} \quad \text{SO}_2\text{NH}_2 \\
\text{Ph} & \quad \text{O} \quad \text{Ph}
\end{align*}
\]

As with the previous reagent, nucleophilic displacement of phenol is easily achieved, for example reaction of o-phenylenediamine 42 with 66 gives the bicyclic benzimidazole 68.

Furthermore, N-sulphamoylcarbonimidate 66 has been shown to undergo nucleophilic phenoxy group displacement with C-nucleophiles. With malononitrile 69 in the presence of potassium carbonate, for example, the primary condensation product 70 may either be isolated or cyclized by subsequent addition of 6N hydrochloric acid solution to give the 2H-1,2,6-thiadiazine 1,1-dioxide 71.

1,1-Dichloro-1,1-diphenoxymethane 55 has also been shown to have potential as a reagent for heterocyclic synthesis. Treatment of 55 with o-phenylenediamine 42 yields 2-phenoxybenzimidazole 72.\textsuperscript{27}

\[
\begin{align*}
\text{NH}_2 & \quad \text{NH}_2 \\
\text{NH}_2 & \quad \text{NH}_2 \quad \xrightarrow{\text{Propan-2-ol} \atop \Delta} \quad \text{Ph} \quad \text{O} \quad \text{N} \quad \text{O} \quad \text{Ph} \\
42 & \quad 55 \quad 72
\end{align*}
\]
1.5 Aims of the present work

The use of diphenyl cyanocarbonimidate 53 in the synthesis of various heterocyclic systems is investigated and described. Chapters 2 and 3 describe the synthesis of 6-substituted and 5,6-disubstituted dihydropyrimidinones. Chapter 4 describes the synthesis of carbocyclic dihydropyrimidinones and imidazolones. Chapter 5 describes reactions at the N-cyanoimine functional group, whilst Chapter 6 describes the preparation of 1,2,4-triazoles. Chapter 7 details investigations into the stereoisomerism of some of the compounds synthesised. The experimental sections are grouped together in Chapter 8.
Synthesis of 6-Substituted and 5,6-Disubstituted -
dihydro-4(3H)-Pyrimidinones

2.1 Introduction

Pyrimidines are an essential component of life and they are distributed throughout the spectrum of living organisms. The requirement for pyrimidines can be fulfilled by two synthetic pathways: a de novo route and a salvage pathway. Uridine-5'-monophosphate (UMP) is a common product of both of these pathways. The de novo pathway is generally considered to consist of six enzymes: carbamyl phosphate synthetase II (CPS II); L-aspartate transcarbamylase (ATCase); L-dihydrorotase (DHOase); L-dihydroorotate dehydrogenase (DHO deHase); orotate phosphoribosyl transferase (OPRTase); and orotidine-5'-monophosphate decarboxylase (OMP deCase). A brief overview of the biosynthetic pathway is given here. For a more detailed account the reader is directed to the reviews of Shambaugh and Jones. The main components of the pyrimidine ring are derived from L-aspartic acid and L-glutamine, while the ribosyl and phosphoryl moieties are transferred from phosphoribosyl pyrophosphate (Scheme 2.1).

So far as is known, this 'genealogy' of the pyrimidine ring is universal and serves to underscore the intimate relationship of the dicarboxylic amino acids and their amides with nucleic acid biosynthesis. The salvage pathway, by contrast, utilizes preformed nucleosides or bases in the biosynthesis of pyrimidine nucleotides. Two additional enzymes, namely thymidylate synthetase (TS) and cytidylate synthetase (CTP synthetase), catalyze modification of the pyrimidine ring to yield the two other major pyrimidine nucleotides, cytidine-5'-triphosphate and thymidine-5'-monophosphate (TMP).

The intracellular localisation of the six catalytic activities of the de novo pathway appear to be optimized to ensure efficient flux and to permit changing of the output in response to physiological needs. CPS II, ATCase and DHOase exist as a large cytosolic multienzyme complex (pyr 1-3). The proximity of consecutive catalysts serves to channel products from one active site to another without undue dilution by diffusion into the cytoplasmic milieu. The fourth enzyme of the pathway, DHO deHase, is particulate and is sequestered on the outer face of the inner mitochondrial membrane. Thus this enzyme is ideally sited to exert regulatory control over the velocity of pyrimidine ring assembly because both its substrate and product must diffuse across the mitochondrial membrane. Another cytosolic multienzyme complex, (pyr 5,6), composed of OPRTase and OMP deCase, effects the last two steps of pyrimidine biosynthesis, producing UMP as the final product for use as such or for further transformation into cytidine and thymidine nucleotides.

The pyrimidine biosynthetic pathway is subject to complex regulation by its products and substrates; as a result, physiological or drug induced alterations in the levels of these
Scheme 2.1

\[
\text{H}_2\text{N}\text{\textbackslash{}CH}_2\text{\textbackslash{}CH(\textbackslash{}NH}_2\text{\textbackslash{}CO}_2\text{H} + 2\text{ATP} + \text{H}_2\text{O} + \text{CO}_2
\]

\text{L-Glutamine}

\text{Carbamyl Phosphate Synthetase II}

\[
\text{H}_2\text{N}\text{O-PO(OH)}_2
\]

\text{Carbamyl Phosphate}

\text{L-Aspartic acid transcarbamylase}

\[
\text{H}_2\text{N}\text{\textbackslash{}CO}_2\text{H}
\]

\text{L-Aspartic acid}

\[
\text{HO}\text{\textbackslash{}O}\text{\textbackslash{}N}\text{\textbackslash{}CO}_2\text{H}
\]

\text{N-Carbamyl-L-Aspartic Acid}

\text{L-Dihydroorotase + H}_2\text{O}

\[
\text{H}_2\text{N}\text{\textbackslash{}CO}_2\text{H}
\]

\text{L-Dihydroorotic Acid}

\text{L-Dihydroorotate Dehydrogenase}

\[
\text{HN}\text{\textbackslash{}CO}_2\text{H}
\]

\text{Orotic Acid}
Orotic Acid

Orotate Phosphoribosyl Transferase

Orotidine 5'-monophosphate

Orotidine-5'-monophosphate Decarboxylase

Uridine 5'-monophosphate

Several steps

Cytidine 5'-triphosphate

Thymidine 5'-monophosphate
regulators can provoke important changes in the de novo output of UMP. A more detailed account of this control process can be found elsewhere. Inasmuch as the specific activities of five of the six enzymes of the central pathway are similar and low, only that of ATCase being disproportionately high, the system is an attractive one in terms of pharmacological intervention.

This having been said, there are currently no good inhibitors of any step in the pyrimidine biosynthetic pathway. Perhaps the best inhibitor to date is PALA (N-(phosphonoacetyl)-L-aspartic acid) 73, which was synthesised as a stable "transition state analogue" of the reaction catalysed by ATCase and, as such, combines the structural features of the two natural substrates, carbamyl phosphate and L-aspartic acid.

PALA is reported to have a high inhibitory potency in vitro but the in vivo activity has been disappointing. It is expected, however, that PALA will be used in combination chemotherapeutic strategies.

To date there are no good inhibitors of DHOase. Christopherson and Jones have presented a very systematic evaluation of the inhibitory effects of 5-substituted analogues of orotate against mammalian DHOase in vitro. However, only two moderately potent substrate analogues have been identified as chemotherapeutic: 5-fluoro orotate and 5-aminooxotrate, which were active against several transplantable murine leukaemias. Hence, L-dihydroorotase is an enzyme awaiting 'attack'.

L-dihydroorotate dehydrogenase is subject to product inhibition hence orotic acid and some of its analogues, particularly dihydro-5-azaorotic acid, are effective inhibitors. Additionally, naphthoquinones, for example lapachol 74, have been identified as potent inhibitors of DHO deHase. They are believed to act as analogues of the cofactor, ubiquinone, and serve as electron acceptors that alter electron flow.
A number of orotate analogues have been described as inhibitors of OPRTase; many are also substrates for the enzyme and can form fraudulent nucleotides which, in turn, are potent inhibitors of OMP deCase. By contrast, potent inhibitors of OPRTase are scarce. 5-Fluoroorotate is a good inhibitor of OPRTase prepared from mouse Ehrlich ascites cells: 50 μM 5-fluoroorotate inhibited activity by 75%.34,35

Synthetic pyrimidine and purine analogues which, after monophosphorylation, are extremely potent OMP deCase inhibitors (see below) are in general inhibitors of OPRTase, for example allopurinol 75, oxipurinol 76 and 6-azauridine 77.

Two potent antimetabolites, 6-azauridine 77 and pyrazofurin 78, are available for the inhibition of OMP deCase which is involved in the last step in the assembly of the pyrimidine ring. Both agents are phosphorylated in vivo to 5'-monophosphate derivatives through the actions of uridine, cytidine and adenosine kinases, respectively, and it is these anabolites that strongly impede the decarboxylation of orotidin-5'-monophosphate.
At this point in the development of inhibitors of enzymes of the pyrimidine biosynthetic pathway, however, the present generation of drugs are, for the most part, without significant therapeutic value in humans, particularly in the management of neoplasia. The parent inhibitors are non-specific with the notable exception of PALA, and in no instances have they been demonstrated completely to block precursor flow through the pathway.

Use of the chemistry of diphenyl cyanocarbonimidate allows the construction of pyrimidines, and particularly dihydropyrimidines which are difficult to construct by conventional methods.

A brief survey of the common methods for the synthesis of pyrimidines and dihydropyrimidines follows.

2.1.1 **Synthesis of Pyrimidines**

The pyrimidine ring has been synthesized by a wide variety of methods. Syntheses starting from acyclic precursors are most common, but pyrimidines may also be obtained by ring expansion, isomerization or degradation.

The 'principal' synthesis, as the name implies, is the most useful and widely used method. It involves the combination of an N-C-N fragment and a C-C-C fragment. Other useful syntheses involve the combination of a C-C-C-N fragment with a C-N fragment and an N-C-C-C-N fragment with a C fragment (Scheme 2.2). The ring has been constructed from other fragments, but these syntheses are generally of limited use.

**Scheme 2.2**
2.1.2 The Principal Synthesis

The N-C-N fragment used in this approach is commonly urea 80, thiourea 81 or guanidine 82 and the C-C-C fragment is typically a 1,3-diketone, diester or dinitrile. The choice of reagents depends on the substituents required in the product. For instance, the treatment of malic acid 83 with concentrated sulphuric acid resulted in the formation of formyl acetic acid 84, which was condensed with guanidine 82 to give 2-amino-4(3H)-pyrimidinone 85 (isocytosine).\(^ {36} \)

\[
\text{HO}_2\text{C} - \text{CO}_2\text{H} \quad \text{cH}_2\text{SO}_4 \quad \text{OH} - \text{CO}_2\text{H}
\]

\[
\text{NH}_2 \quad \text{NH}_2 \quad \text{O} \quad \text{NH} \quad \text{O}
\]

Heating propiolic acid 86 with urea 80 in the presence of polyphosphoric acid gives 2,4-(1H,3H)-pyrimidinedione 87 (uracil).\(^ {37} \) The condensation of 1-cyano-2,2-diethoxyethane 88 with urea 80 in the presence of sodium butoxide gave 4-amino-2(1H)-pyrimidinone 89 (cytosine).\(^ {38} \)

\[
\text{H} - \text{C} = \text{CO}_2\text{H} \quad + \quad \text{H}_2\text{N} - \text{C} = \text{C} = \text{NH}_2 \quad \text{PPA} \quad \Delta \quad \text{O} \quad \text{NH} \quad \text{O}
\]

\[
\text{EtO} - \text{C} = \text{CN} \quad + \quad \text{H}_2\text{N} - \text{C} = \text{C} = \text{NH}_2 \quad \text{NaOBU} \quad \text{BuOH, } \Delta \quad \text{NH}_2 \quad \text{O} \quad \text{NH}
\]
In these examples the N-C-N fragment is symmetrical and there is no ambiguity in the structure of the product. When unsymmetrical N-C-N fragments are condensed with unsymmetrical C-C-C fragments the structure of the product is ambiguous and care must be taken to obtain absolute proof of the structure. This is exemplified by the condensation of N-methyl thiourea 90 with Z-1-cyano-2-ethoxyethene 91, which gives 4-amino-1-methyl-2(1H)-pyrimidinethione 92 instead of the expected 4-amino-3-methyl-2(1H)-pyrimidinethione 93.39

\[ \text{HN} \quad \text{NH}_2 \quad \text{SN} \quad \text{CN} \quad \text{NaOEt} \quad \text{Me} \"

\[ 90 \quad 91 \quad 92 \quad 93 \]

\[ \text{S} \quad \text{N} \quad \text{NH}_2 \quad \text{Me} \]

2.1.3 Other Primary Syntheses

The synthesis of a pyrimidine ring from a C-C-C-N fragment and a C-N fragment is exemplified by the reaction between ethyl 2-aminocrotonate 94 and methylisocyanate 95.40 The substituted urea 96 is first formed, which then cyclises to 3,6-dimethyl-2,4-(1H,3H)-pyrimidinedione 97.

\[ \text{Me} \quad \text{CO}_2 \text{Et} \quad \text{NH}_2 \quad \text{Me} \quad \text{N} = \text{C} = \text{O} \quad \text{EtO}_2 \text{C} \quad \text{N} \quad \text{Me} \quad \text{Me} \]

\[ 94 \quad 95 \quad 96 \quad 97 \]

The condensation of an N-C-C-C-N fragment with a C fragment is exemplified by the Remfry-Hull synthesis,41 in which malondiamide 98 reacts with ethyl formate 99 to give 6-hydroxy-4(3H)-pyrimidinone 100.
2.1.4 Dihydropyrimidines

In theory there are five possible isomers of dihydropyrimidine, but the situation is complicated by the mobile nature of the hydrogen atoms bound to nitrogen. Thus 1,4- and 1,6-dihydropyrimidine are in tautomeric equilibrium with each other.

Dihydropyrimidines may be prepared by the addition of hydrogen to the pyrimidine nucleus but, in many cases, the pyrimidine nucleus is inert to attack by a variety of reducing agents. The dihydropyrimidines are often unstable under the reaction conditions, with only decomposition products resulting. They can also be prepared by the addition of reagents other than hydrogen, for example alkyl lithuim, to the pyrimidine nucleus.

The most common method of synthesis is from acyclic precursors, as for the pyrimidines, but with starting materials modified appropriately. Having said this, the number of publications regarding pyrimidines far outweighs those regarding dihydropyrimidines. The paucity of publications in this field is attributed to the fact that many dihydropyrimidines are unstable and are difficult to separate and purify. This problem has been noted particularly for 1,4- and 1,6-dihydropyrimidines, but has also been reported for 5,6-dihydropyrimidines.
2.1.5 Synthesis of 5,6-Dihydropyrimidines

The catalytic hydrogenation of 4(3H)-pyrimidinones has been used to prepare the corresponding dihydropyrimidines, but this method is of limited use since it is difficult to control the degree of hydrogenation and the formation of side products is often a problem. Complex metal hydrides have been used with some success. For example the 5,6-double bond of the N,N'-disubstituted uracils 106 (R1=Me, CH2Ph, CH2OCH2Ph, R2=H) and the methyl orotates 106 (R1=Me etc, R2=CO2Me) is specifically reduced by lithium tri-s-butyl borohydride, 'L-selectride', to give the corresponding derivatives 108. Substituents such as F or C=CSiMe3 in the 5-position, which might not survive alternative hydrogenation methods like catalytic reduction, remained unaffected. An additional advantage is that the intermediate anion 107 can be trapped by an alkylating agent, for example ethyl or benzyl bromide with the formation of the 5-substituted uracil 108 (R2=H, R3=Et or CH2Ph).

Since pyrimidine is an electron deficient nucleus, it is susceptible to attack by a variety of nucleophiles and this has been exploited in the preparation of a number of dihydropyrimidines using carbanions as nucleophiles. Treatment of 2,4-dimethoxypyrimidine 109 with organolithium reagents, followed by selective hydrolysis of the resultant dihydropyrimidines 110 leads to 5,6-dihydro-2-methoxy-4(3H)-pyrimidinones 111.

3-Alkyl-5,6-dihydro-4(3H)-pyrimidinones 115 have been prepared by transformidoylation of 1-(N-alkyliminoformyl)-imidazoles 112 with amino acids 113, followed by
cyclisation of the intermediate N-(N'-alkyliminoformyl)-amino acid 114 with acetic anhydride in pyridine.54

\[
\begin{align*}
\text{N\text{=}N} & \quad \text{H} \\
\text{R} & \quad \text{CO}_2\text{H} \\
\text{benzene} & \quad \text{R'} \quad \text{NH}_2 \quad \text{R'} \quad \text{NH} \\
\end{align*}
\]

112 113 114

Dihydropyrimidine derivatives have been obtained by cyclisation under acetic acid conditions of α,β-unsaturated carboxylic acids with urea.55 The yields are usually low, however, due to the instability of the products48 and the formation of bi-products. This synthesis has recently been modified,49 an α,β-unsaturated ester 116 being condensed with an N-alkyl guanidine 117 (R6=H) in t-butanol or propan-2-ol to give 2-amino-5,6-dihydro-4(1H)-pyrimidinone 118. The 2-amino-5,6-dihydro-4(1H)-pyrimidinone 120 is formed in an interesting ring expansion reaction when diphenylcyclopropenone 119 is treated with the alkylguanidine 117 (R4, R5=H, R3, R6=Ph)56 but this reaction is somewhat limited in its applicability.
The synthesis described in this work involves a skeletal assembly which appears to be novel, and is potentially of general applicability. It involves the condensation of a C-C-C-N fragment sequentially with a C fragment and an N fragment. This route differs slightly from the conventional synthesis in that a dihydropyrimidine results from the sequential condensations as opposed to the usual pyrimidine. However, the dihydropyrimidines can easily be converted to pyrimidines, and the synthesis offers scope for directly synthesising pyrimidines by introducing unsaturation into the C-C-C-N fragment.

Chapters 2 and 3 describe the synthesis of 6- and 5,6-disubstituted dihydropyrimidines by this method and Chapter 4 describes the synthesis of pyrimidine and imidazolidine analogues substituted at N-3 by a carbocyclic sugar analogue. That the N-cyanoguanidine moiety has been proposed to be an isostere for urea suggests that these pyrimidines will act as analogues that are accepted by various enzymes of the pyrimidine biosynthetic pathway, leading to inhibition by product/substrate feedback pathways, in particular for the enzymes L-dihydroorotate dehydrogenase and orotate phosphoribosyl transferase.
2.2 Results and Discussion

Synthesis of the simplest dihydropyrimidine in the series from β-alanine methyl ester has already been described.\textsuperscript{24,59} Thus reaction of β-alanine methyl ester 62 with diphenyl cyanocarbonimidate 53 gives the intermediate O-phenylisourea 63, which upon treatment with benzylamine gave the cyclised product 64, presumably via the acyclic adduct 121.

\[ \text{NCN} \quad \text{PhO} \quad \text{OPh} + \quad \text{H}_2\text{N} \quad \text{CO}_2\text{Me} \quad \rightarrow \quad \text{NCN} \quad \text{PhO} \quad \text{NH} \quad \text{CO}_2\text{Me} \]

\[ 53 \quad 62 \quad 63 \]

Similarly the 2-cyanoethylamine 122 could be coupled to 53 to give the intermediate 123 which when reacted with benzylamine gave N-cyanoguanidine 124. Cyclization was then achieved by the use of sodium methoxide in methanol, to give the dihydropyrimidine 125.

\[ \text{NCN} \quad \text{PhCH} \quad \text{2NH}_2 \quad \rightarrow \quad \text{PhCH}_2\text{N} \quad \text{NH} \quad \text{CN} \quad \text{NaOMe} \quad \text{PhCH}_2\text{N} \quad \text{NH} \quad \text{NCN} \]

\[ 53 \quad 122 \quad 123 \quad 124 \quad 125 \]

When the synthesis is applied to dimethyl aspartate however, a problem occurs, in that two modes of cyclisation are possible.\textsuperscript{24} The structure of the product was assigned by comparison of the I.R. stretching frequencies of the ring carbonyl, this being diagnostic of ring size.\textsuperscript{60} Hence the intermediate O-phenylisourea 127 reacts with benzylamine to give the imidazolidin-5-one 128 and not the dihydropyrimidinone 129.
In an attempt to alter this preference for ring closure to a 5-membered ring system, we have investigated the effect of changing the nature of the ester, presuming that a more hindered alcohol would be less likely to act as a leaving group in the cyclisation step.

(S)-α-tert-Butyl-β-methyl aspartate 130, prepared from (S)-α-tert-butyl aspartate and diazomethane, was treated with diphenyl cyanocarbonimidate 53 in propan-2-ol to give the isourea 131 in 84% yield. HPLC, using (R)-N-3,5-dinitrobenzoyl phenylglycine chiral stationary phase (CSP) as a chiral support, showed that the compound had ca 100% ee and it had an optical rotation \([\alpha]_D = -7.39\)°. It was found, however, that upon storing racemization occurred, and a 3:1 mixture of stereoisomers was noted by HPLC. A corresponding reduction in the value of the optical rotation was also noted with time. Treatment of 131 in propan-2-ol with benzylamine gave a ca 1:1 mixture (ca 68% yield) of the dihydroimidazole 128 and the dihydropyrimidine 132.
As was predicted, substitution of tert-butyl for methyl at the \( \alpha \)-ester group has decreased cyclisation through this centre and allowed cyclisation at the \( \beta \)-ester to become competitive.

Structural assignments were made on the basis of I.R. absorptions in comparison to known compounds\(^{60} \) and to the imidazole 135, prepared in 40\% yield from the O-phenylisourea 134, which was itself prepared from \( \alpha \)-methyl-\( \beta \)-tert-butyl aspartate 133.

\[
\text{NCN} \quad \text{PhO} \quad \longrightarrow \quad \text{NCN} \quad \text{PhO}
\]

\[
\text{CO}_2\text{Bu} \quad \text{H}_2\text{N} \quad \text{CO}_2\text{Me} \quad \text{PhO} \quad \text{H}_2\text{N} \quad \text{CO}_2\text{Bu}
\]

\[
53 \quad 133 \quad 134
\]

The imidazole 128 showed I.R. absorptions at 2190 cm\(^{-1} \) (CN) and 1759 cm\(^{-1} \) (C=O) compared to 2194 cm\(^{-1} \) (CN) and 1778 cm\(^{-1} \) (C=O) for the imidazole 135. In both cases the values were within the range found for imidazoles.\(^{60} \) The pyrimidine 132 had absorptions at 2183 cm\(^{-1} \) (CN) and 1700 cm\(^{-1} \) (C=O) which were in fairly close agreement with previous findings.\(^{60} \) However, it seems that for the substituted pyrimidines the range of frequencies over which the ring carbonyl stretch occurs should be extended from 1710-1716 cm\(^{-1} \) to 1700-1720 cm\(^{-1} \) (see later).

Measurement of the optical activity of the 5-membered ring 128 showed that, as expected, racemization had occurred at position C-5 of the ring. This is to be expected since keto-enol tautomerization is a well known phenomenon in the related hydantoin system.\(^{66,67} \)

\[
\text{OH} \quad \text{N} \quad \text{NH} \quad \text{R} \quad \text{OH} \quad \text{N} \quad \text{NH} \quad \text{R} \quad \text{OH} \quad \text{N} \quad \text{NH} \quad \text{R}
\]

HPLC measurements using the chiral support indicated, however, that racemization was not complete since two peaks in the ratio 2.5:1 were resolved. Proof that the racemization
was occurring slowly, over a period of several days in solution, came from an examination of the $^1$H n.m.r. spectrum of the amide 136 in d$_4$-methanol. Initially the spectrum showed the C-5 proton at δ 4.4 ppm but after a period of 7 days in d$_4$-methanol this signal had disappeared due to the keto-enol tautomerism process, deuterium being more readily available to add back to the enol than hydrogen.

The (S)-dihydropyrimidine 132 was found to be optically active with [α]$_D$=-92.8 °. The retention of optical activity is to be expected in the 6-membered derivatives since the chiral centre is now one carbon removed from the ring carbonyl and the exocyclic form of the double bond in the 6-membered ring is less likely. HPLC using the chiral support showed the S enantiomer was eluted after the R enantiomer from the column, and the enantiomeric excess was found to be 80%, which gave a calculated [α]$_D$=-114 ° for the pure enantiomer.

Repetition of the synthesis with (R)-α-tert-butyl-β-methyl aspartate gave the enantiomer of 132. This was found to have [α]$_D$=+108.4 ° and an enantiomeric excess of 96%, giving a calculated [α]$_D$=+113 °. The close agreement of the two calculated [α]$_D$ values seems to suggest that the chiral HPLC column separations observed are real and that the peaks observed are those due to the enantiomers present in the sample. It should be noted, however, that the optical purity of the dihydropyrimidine 132 varied quite widely from reaction to reaction. This suggests that racemization is occurring either during the reaction, or in the O-phenylisourea 131, or both, hence old samples of this isourea should be avoided. Racemization during the reaction could be attributed to a keto-enol tautomerism involving the exocyclic ester group.
The regioselectivity of the cyclisation could be improved by substituting benzyl for the methyl group in 130. Thus the α-tert-butyl-β-benzyl aspartate 137 was prepared from β-benzyl aspartate by the method of Roeske. Coupling with diphenyl cyanocarbonimidate 53 followed by reaction with benzylamine and cyclisation gave the dihydropyrimidine 132 and the imidazolidinone 139 in the ratio 3.75:1.

\[
\begin{align*}
\text{NCN} & \quad \text{PhO' 'OPh} \\
\text{PhO} & \quad \text{CO}_2\text{CH}_2\text{Ph} \\
\text{H}_2\text{N} & \quad \text{CO}_2\text{tBu} \\
\text{PhO} & \quad \text{NCN} \\
\text{CO}_2\text{CH}_2\text{Ph} & \quad \text{NCN}
\end{align*}
\]

\[
\begin{align*}
53 & \quad 137 & \quad 138 \\
\text{NCN} & \quad \text{PhCH}_2\text{NH}_2 \\
\text{PhCH}_2\text{N} & \quad \text{CO}_2\text{CH}_2\text{Ph} \\
\text{NCN} & \quad \text{CO}_2\text{tBu}
\end{align*}
\]

It was found, however, that the products could not be separated by conventional chromatography, hence the product ratios are based on signals in the \(^1\)H n.m.r. spectrum of the combined purified products.

An examination of the solvent dependence of this reaction showed that whilst the product ratio was in favour of the 6-membered ring 132 in propan-2-ol, carrying out an identical reaction in THF gave very little reaction in a similar time period. The reaction was faster in acetonitrile as solvent at lower temperatures (room temperature compared to 50 °C), but the product ratio was now found to be only 1.18:1 in favour of 132. Presumably the difference in rates of reaction reflect the different solvating abilities of the three solvents towards the different transition states of the reaction, the use of acetonitrile leading to the two transition states being nearly equal in energy, whilst propan-2-ol as solvent leads to a lowering of the energy of the transition state leading to the 6-membered ring.

Attempts to synthesis α-tert-butyl-β-allyl aspartate from the Z-protected aspartate were unsuccessful owing to the difficulty of removal of the protecting group in the presence of the allyl ester.
Following on from this work the synthesis of 5,6-disubstituted dihydropyrimidines was investigated. The required β-substituted amino acids were prepared by the method of Baldwin et al.\textsuperscript{70} (Scheme 2.3).

Thus (S)-aspartic acid 140 was converted to its β-methyl ester 141 by the method of Coleman,\textsuperscript{71} the amine function protected with benzyl chloroformate and potassium carbonate, and 142 converted to the required diester 143 by treatment with isobutene and sulphuric acid.\textsuperscript{61,68,72} The protected amino acid 143 was alkylated to a mixture of 144a and 144b by treatment with lithium hexamethyldisilazide at -78 °C followed by benzyl bromide. Whilst a claim of a diastereomeric excess of 5:1 has been made for this reaction,\textsuperscript{70} in our hands the best diastereomeric ratio obtained for 144a:144b was estimated by \textsuperscript{1}H n.m.r. spectroscopy to be 3:1. The diastereomers were separated by column chromatography and the benzylxycarbonyl group removed by hydrogenation over palladium to give 145a and 145b as separate compounds. Reaction of each with diphenyl cyanocarbonimidate 53 in propan-2-ol at 40 °C gave the O-phenylisoureas 146a and 146b. HPLC on the chiral support indicated that 146a was greater than 98% enantiomerically pure whilst 146b appeared to be approximately 85% enantiomerically pure. This would seem to indicate that, as had been noted previously for 134, a small amount of racemization at the α centre was occurring with time.

It was noted, by comparison with the reaction of the unseparated diastereomers 145, that diphenyl cyanocarbonimidate 53 reacted approximately twice as fast with the major diastereomer, so that for the diastereomeric mixture the diastereomeric ratio in the O-phenylisourea 146 was 6:1 and not the 3:1 seen in 144.

Reaction of O-phenylisourea 146a with benzylamine gave a 4:1 mixture of 148a and 147. HPLC on the chiral support of 148a showed that it was a 5.2:1 mixture of diastereoisomers and this was confirmed by \textsuperscript{1}H n.m.r. spectroscopy. As expected, the imidazole 147 was a 1:1 racemic mixture of diastereoisomers due to racemization at C-5 of the ring. This was again confirmed by HPLC. No evidence for racemization at the benzyl substituted carbon was seen, however, since separation of enantiomers was not observed on the chiral support.

Repetition of the latter reaction with O-phenylisourea 146b led to the pyrimidinone 148b as the only isolated product. This is probably merely a reflection of the smaller amount of 146b used. \textsuperscript{1}H n.m.r. spectroscopy showed this compound to be diastereomerically pure, only a single set of peaks being seen, and HPLC on the chiral support showed that 148b was enantiomerically pure, only a single peak being seen.

Attempts to grow crystals of 148 failed, hence an X-ray structure could not be obtained. The \textsuperscript{1}H n.m.r. coupling constants do not allow an assignment of relative stereochemistry of the C-5 and C-6 centres, so neither absolute or relative stereochemistry can be defined. Hence the structures shown for compounds 145a and 145b and all compounds derived from these amino acids are arbitrary and are used for illustrative purposes only.
That racemization in 148a had occurred at C-6 and not at C-5 (a keto-enol tautomerism mechanism similar to the imidazoles could be imagined at this position) was shown by HPLC, using the chiral support. If racemization had occurred at C-5 than the product should have been 148b. That the retention time of the minor isomer present in 148a was different from that of 148b (18 min compared to 12 min) showed this was not the case.
Repetition of the latter reaction on a large scale using a diastereomeric mixture of 146 lead to the isolation to the guanidine 149. That this product does not spontaneously cyclize and can be isolated seems to reflect the increased steric hindrance present in the aspartate portion of the molecule.

Interestingly, the HPLC of the diastereomeric mixture of pyrimidines 148 resulting from this reaction showed that most of the product resulted from the major diasteromer 146a and only 2% came from the minor diastereomer, suggesting again that the minor diastereomer 146b reacts with benzylamine much more slowly. This was also borne out by the longer reaction time needed for complete reaction with the minor diastereoisomer 146b. A clue to the point at which racemization occurs was also obtained from this reaction, which was carried out at 70 °C as opposed to 40 °C for the separated diastereoisomers. HPLC on the chiral support revealed that approximately 30% of the major isomer 148a had racemized at C-6, indicating that lower reaction temperatures and longer reaction times are required to give products of high optical purity. Higher temperatures must lead to more keto-enol tautomerism in the products hence lower product optical purity.

The reaction sequence was repeated for the 3-propyl substituted derivative 151, obtained by catalytic reduction from the corresponding allyl N-protected derivative 150, that was itself prepared by the method of Baldwin70 (Scheme 2.4). Reaction of a 2.8:1 diastereomeric mixture of 151 with diphenyl cyanocarbonimidate 53 gave the isourea 152 as a 3.7:1 mixture of diastereomers as assessed by HPLC. This was found to be in agreement with the 1H n.m.r. spectrum of the mixture 152. Once again apparently reaction of one diastereomer is favoured over reaction of the other. Treatment of 152 with benzylamine gave a mixture of three products from which 153 was separated by chromatography. Imidazolone 154 was separated from the guanidine 155 by fractional crystallisation from the column eluant, and then 155 was completely purified by a second chromatographic separation. The pyrimidine 153 was initially isolated as an oil but, on standing, one crystalline diastereoisomer was deposited. HPLC of the crystalline material on the chiral support showed the presence of one diastereoisomer with about 6% of the other. Interestingly, there appears to be no sign of racemization at C-6 for this compound.

The imidazolidinone 154 was isolated as a mixture of diastereoisomers, as expected, in the ratio 1.67:1. This seemed to suggest that, in this reaction, the minor isomer of 152 is the more reactive, unlike the case for the β-benzyl aspartate. This was borne out by the observation that a large proportion of the pyrimidine 153 seemed to be from the minor diastereoisomer.
HPLC of 154 on the chiral support showed that racemization had occurred at C-5 of the ring since three peaks were observed. The fact that a fourth peak was not seen is probably a reflection of the limits of the chiral column to efficiently separate enantiomers rather than as a result of the fourth enantiomer not being present.

Similarly, the guanidine 155 was found to be a 1.7:1 mixture of diastereoisomers by $^1$H n.m.r. spectroscopy. HPLC on the chiral support seemed to show that some racemization had
occurred at the α centre. The resolution obtained was not, however, sufficiently good to quantify this. That the diastereoisomer ratio was the same as for the imidazolidinone 154 seems to suggest that it is at the formation of the guanidine that the differential reaction rates occur and not at the subsequent cyclisation step.

A comparison of the I.R. stretching frequencies of the ring carbonyl group (Table 2.1) shows that the previous findings still hold over this wider range of compounds. For the 5-membered rings the ring carbonyl stretching frequency is between 1748 and 1778 cm\(^{-1}\) whereas for the 6-membered ring compounds the ring carbonyl stretch is between 1700 and 1730 cm\(^{-1}\). The correlation of ring size with the position of the nitrile stretching frequency is, however, less reliable.

A further method for determining ring size becomes apparent on inspecting the position in the \(^1\text{H} \) n.m.r. spectrum of the CH\(_2\) group of the benzylamine portion of the molecules containing this group (Table 2.1). It is found that for the compounds with an ester side chain the CH\(_2\) group occurs at ca 4.7 ppm for the 5-membered ring compounds and ca 5.0 ppm for the 6-membered ring compounds. This relationship does not seem to hold for the 6-membered ring carboxylic acids, however, when the CH\(_2\) moves upfield to ca 4.68 ppm.

2.3 Conclusion

It has been shown that 6-membered rings can be synthesised by differentiating the two esterifying alcohols on the two carboxylic acid groups of aspartic acid, even though there is a preference for the formation of the 5-membered ring. This is reasonable in terms of a kinetic effect, fewer degrees of freedom being lost on forming a 5-membered ring. Cyclisation to the 6-membered dihydropyrimidine occurs enantiospecifically whereas cyclisation to the 5-membered ring occurs with a considerable degree of racemization. A β-substituent favours 6-membered ring formation and enhances the enantiospecificity. Given the ready availability of β-substituted amino acids\(^{69,73-76}\) this synthesis should be applicable to a wide range of substituted dihydropyrimidines.
156 \( R=\text{CH}_2\text{CO}_2\text{Me}, R'=\text{H} \)

157 \( R=\text{PhCH}_2, R'=\text{H} \)

158 \( R=\text{CH}_2\text{CH}_2\text{CO}_2\text{Me}, R'=\text{H} \)

128 \( R=\text{PhCH}_2, R'=\text{CH}_2\text{CO}_2\text{Me} \)

135 \( R=\text{PhCH}_2, R'=\text{CH}_2\text{CO}_2\text{tBu} \)

159 \( R=\text{H, } R'=\text{CH}_2\text{CO}_2\text{Me} \)

160 \( R=\text{H, } R'=\text{CH}_2\text{CONH}_2 \)

166 \( R=R'=\text{CH}_2\text{Ph} \)

161 \( R=\text{CH}_2\text{CH}_2\text{CO}_2\text{Me} \)

164 \( R=R'=\text{PhCH}_2, R'=\text{CO}_2\text{H} \)

165 \( R=\text{PhCH}_2, R'=\text{CO}_2\text{H} \)

162 \( R=R'=\text{H, } R'=\text{CO}_2\text{H} \)

148a \( R=R'=\text{PhCH}_2, R'=\text{CO}_2\text{Bu} \)

148b \( R=R'=\text{PhCH}_2, R'=\text{CO}_2\text{tBu} \)

132 \( R=\text{PhCH}_2, R'=\text{CO}_2\text{tBu}, R''=\text{H} \)

153 \( R=\text{PhCH}_2, R'=\text{CO}_2\text{tBu}, \)

\( R''=\text{CH}_2\text{CH}_2\text{CH}_3 \)

147 \( R=\text{CH}_2\text{Ph} \)

154 \( R=\text{CH}_2\text{CH}_2\text{CH}_3 \)
<table>
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<th>CN Stretch/cm(^{-1})</th>
<th>CO Stretch/cm(^{-1})</th>
<th>CH(_2) resonance/ppm</th>
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</tr>
<tr>
<td>164</td>
<td>2195</td>
<td>1718</td>
<td>4.70</td>
</tr>
<tr>
<td>165</td>
<td>2176</td>
<td>1718</td>
<td>4.67</td>
</tr>
</tbody>
</table>
Rearrangement of 5-Methoxycarbonylmethyl-2-cyanoiminoimidazolones. Synthesis of 6-Carboxydihydropyrimidines

3.1 Introduction

In 1897 Müller\textsuperscript{77} reported the synthesis of a compound through the condensation of oxaloacetic acid diethyl ester 167 and urea 80 to which he assigned a 6-membered ring structure, but much later it was shown that the product of the reaction was a 5-membered ring hydantoin 168.\textsuperscript{78} Treatment of 168 with potassium hydroxide solution resulted in hydrolysis of the ester without ring expansion, to give the carboxylic acid 169. Treatment of 169 with aqueous potassium hydroxide at 100 °C resulted in rearrangement to 4-carboxy-2,6-pyrimidinedione (orotic acid) 170. This assignment was confirmed by examining the reactions of 169 and 170 with bromine. Treatment of 170 with aqueous bromine gave 5,5-dibromo-2,4,6-pyrimidinetrione (5,5-dibromobarbituric acid) 171, whereas 5-(carboxymethylidine)-hydrantoin 169 gave 2-ureido-1,1-dibromoacrylic acid 172 under similar conditions.
Hobbs\textsuperscript{24} initially assigned the structure of the product of the reaction between O-phenylisourea 127 and benzylamine to the 6-membered ring pyrimidinone 129 (Scheme 3.1). The correct structure of the product was subsequently shown, using a variety of spectroscopic techniques, to be that of the 2-cyanoimino-imidazolidin-5-one 128.\textsuperscript{60} Hobbs reacted 128 with bromine in the belief that a pyrimidine 174 would be produced, but it is now known that the product had the 5-membered ring structure 173, produced as a result of the bromination-dehydrobromination sequence together with hydrolysis of the cyanoimino group catalysed by the acetic acid present (see Chapter 7). Treatment of 173 with boiling 2M sodium hydroxide solution, followed by acidification with hydrochloric acid solution resulted in hydrolysis of the ureido group and also rearrangement to the 6-carboxypyrimidine 175, a known compound. The fact that the product was produced under such mild conditions was taken by Hobbs as evidence for the 6-membered nature of 173, since previous rearrangements had required much more vigorous conditions. It is now known that rearrangement had indeed occurred under these mild conditions.

Scheme 3.1
The product of the bromination-dehydrobromination was in fact closely related to the previously reported system 169 (Scheme 3.2). Guareschi and Grimeau had independently synthesised malyureidic acid, but the two authors assigned different structures to this compound. Guareschi assigned a 5-membered ring structure 176, whilst Grimeau assigned a 6-membered ring structure 177. Gabriel repeated the synthesis and treated the product with bromine in acetic acid to give a 'bromine free' product, pyvureidic acid 169, which was assigned a 5-membered ring structure, since when treated with aqueous bromine it yielded 2-ureido-1,1-dibromoacrylic acid 172, the same product that was obtained by treatment of hydrantoin 178 with aqueous bromine. This was taken as evidence for a 5-membered ring structure for pyvureidic acid 169, and since 169 was obtained from malyureidic acid it was concluded that it must also have the 5-membered ring structure 176.

Scheme 3.2

Hobbs also treated 2-cyanoimino-imidazolidin-5-one 128 with 2M sodium hydroxide solution at room temperature for 2 min, and observed the carboxylic acid 163. This was originally taken as evidence for the 6-membered ring structure for 128. Since 128 was subsequently shown to have a 5-membered ring structure a ring expansion reaction must have taken place.
In conjunction with Delisser\textsuperscript{84,85} a number of ring expansion reactions have been performed, and from the results it can be concluded that this is a general method for the rearrangement of 2-cyanoimino-5-carboxymethyl substituted imidazolidin-5-ones to the corresponding 6-carboxydihydropyrimidines under very mild conditions.
3.2 Results and Discussion

A number of simple imidazolidin-5-ones were prepared by the reaction of diphenyl cyanocarbonimidate 53 with S-aspartic acid dimethyl ester 126, followed by subsequent reaction with various amines, nucleophilic addition with concomitant cyclisation occurring to give the desired products (Scheme 3.3).

Scheme 3.3

\[
\begin{align*}
\text{PhO} & \quad \text{NCN} \quad \text{PhO} \\
\text{H}_2\text{N} & \quad \text{CO}_2\text{Me} \\
\text{CO}_2\text{Me} & \quad \text{NCN} \\
\text{H}_2\text{N} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{53} & \quad \text{126} & \quad \text{127}
\end{align*}
\]

\[
\text{RNH}_2 \quad \text{propan-2-ol, } \Delta
\]

\[
\begin{align*}
\text{PhO} & \quad \text{NCN} \quad \text{PhO} \\
\text{H}_2\text{N} & \quad \text{CO}_2\text{Me} \\
\text{CO}_2\text{Me} & \quad \text{NCN} \\
\text{H}_2\text{N} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
178 & \quad \text{R}=\text{CH}_3\text{CH}_2\text{CH}_2, \\
179 & \quad \text{R}=\text{C}_6\text{H}_{11}, \\
180 & \quad \text{R}=\text{CH}_3(\text{CH}_2)_6, \\
181 & \quad \text{R}=\text{C}_5\text{H}_9, \\
128 & \quad \text{R}=\text{PhCH}_2
\end{align*}
\]

In order to prepare the aniline analogue 182, the addition had to be performed in the reverse order, that is the aniline was added first. Since the nitrogen of aniline is also significantly less nucleophilic than that of the other amines used, it was also necessary to generate the anion using sodium hydride in order for addition to occur.

\[
\text{PhO} \quad \text{NCN} \quad \text{PhO}
\]

\[
\text{NH}_2
\]

\[
\text{NaH, THF}
\]

\[
\begin{align*}
\text{PhO} & \quad \text{NCN} \\
\text{H}_2\text{N} & \quad \text{CO}_2\text{Me} \\
\text{CO}_2\text{Me} & \quad \text{NCN} \\
\text{H}_2\text{N} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{53} & \quad \text{126} & \quad \text{182}
\end{align*}
\]
The parent imidazolidin-5-one 159 could also be prepared using aqueous ammonia but it was found that careful monitoring of the reaction was required to prevent further reaction at the ester, leading to the unwanted amide 160.

A further two imidazolidin-5-ones 154 and 147, prepared from β-substituted aspartic acids as described previously, were also used to test the scope of the reaction.

Rearrangements of the imidazolidinones to the corresponding pyrimidinone carboxylic acids were all carried out under similar conditions (Scheme 3.4). Stirring of the imidazolidinone in 2M sodium hydroxide solution for 5-10 min followed by acidification with concentrated hydrochloric acid and cooling to 4 °C precipitated a product that yielded the pure carboxylic acid on recrystallisation from water. In most cases good yields were obtained although for the substituted imidazolidinones 154 and 147 the yields were lower, probably due to the extremely small scale reactions that had to be performed which led to product isolation difficulties.
In all cases the $^1$H n.m.r. spectrum of the product was consistent with the dihydropyrimidine carboxylic acid as shown, except for 162 which had an unusual spectrum. Compound 162 showed two sets of peaks in the ratio 1.8:1 for each proton signal present. Since the product has only one chiral centre this can only be explained as being the result of two zwitterionic species 162/1 and 162/2 existing in equilibrium in solution.

Due to the low solubility of 162 a mixture of D$_2$O and DMSO was required as n.m.r. solvent in this case, as opposed to all other cases where the n.m.r. spectra were obtained in DMSO alone. This may account for the appearance of two products in the $^1$H n.m.r. spectrum since ionisation is more likely in a solvent containing a significant proportion of D$_2$O.

The mechanism proposed for the rearrangement reaction is as shown (Scheme 3.5).
The driving force for this reaction appears to be the reclosure of the linear intermediate to give the 6-membered ring structure. Evidence for this comes from the observation that imidazolidin-5-one 166 is stable in 2M sodium hydroxide solution, as would be expected since the ring closure step is not possible in this case.

Whilst this methodology readily provides high yields of pyrimidinone carboxylic acids it should be noted that since the starting imidazolidin-5-ones are racemic the product pyrimidinones are also racemic. For the preparation of carbocyclic nucleoside analogues (Chapter 4) this seems, however, to be the only viable method for the synthesis of pyrimidinones.

It is conceivable that the amide 160 has a 5- or 6-membered ring structure since the initially formed ester 159 could have been ring opened again by attack of ammonia at the ring carbonyl in a similar manner to the hydroxide mechanism. That the product 160 had a 5-membered ring structure and is not the 6-membered ring structure 183 was confirmed by comparison of the IR frequencies of the ring carbonyl and cyanide groups to those of the imidazolidinone esters already prepared and also to the frequencies for the amide 136, prepared directly from the imidazolidin-5-one 128.
Imidazolidin-5-one 128 could also be ring opened with sodium amide in THF, followed by aqueous workup (Scheme 3.6). In light of the fact that ammonia readily reacts with methyl esters in this series to give the corresponding amides it seems likely that initially an amide is formed and that ring opening occurs under the strongly basic conditions that exist when the reaction is quenched, giving as product the guanidine 190. However it should be noted that quenching the reaction with 2M hydrochloric acid solution also leads to the same product.

Scheme 3.6

The possibility exists that the sodium amide first attacks at the ring carbonyl leading to ring opening. 2-Imidazolidin-5-ones similar to 128 have been ring opened using excess ammonia (Scheme 3.7). Thus α-amino esters 193 (R=H, -(CH₂)₂SCH₃) have been condensed with dimethyl cyanothiocarbonimidate 38, to give the isothioureas 194, by heating the two
compounds in the presence of sodium ethoxide. Prolonged heating of the isothioureas 194 with a series of aliphatic amines resulted in the displacement of methanethiol and the concomitant cyclisation to give the 2-imidazolidin-5-one derivatives 195. Treatment of 194 with an excess of the amine resulted in the formation of the acyclic amides 196, presumably via the initial ring closure followed by ring cleavage with excess amine. In this case, however, forcing conditions were required and the possibility exists that the amide forms first and then substitution via elimination of methanethiol occurs.

**Scheme 3.7**

![Scheme 3.7](image)

In our case if amide attack occurred first to open the ring the possibility exists for ring closure to a 6-membered ring, which is then reopened during workup, or the acyclic intermediate does not reclose but ester hydrolysis occurs to give the acyclic product.

A fourth possibility exists that the initial product is a di-amide produced from a combination of reaction of the ester and also ring opening, and that at the quenching step one of the amides is selectively hydrolysed to the carboxylic acid seen in the product. At present the product cannot be confidently assigned to either of the two possible structures 190 or 192.

### 3.3 Conclusion

It can be seen that the rearrangement reaction of imidazolidin-5-ones offers a simple and convenient route to pyrimidinone 6-carboxylic acids and, for pyrimidinones with more hindered substituents at N-1, this seems to be a better method of synthesis than attempts to construct them directly, but with the corollary that the products will be racemic.
Synthesis of Carbocyclic Isonucleosides

4.1 Introduction

Nucleoside analogues display a wide range of biological activities and have attracted particular attention as anti-tumour and anti-viral agents. Consequently, extensive modifications have been made to both the heterocyclic base and the sugar moiety. Replacement of the furanose ring oxygen by carbon is of particular interest since the resulting carbocyclic nucleosides possess greater metabolic stability to the phosphorylase enzymes which cleave the glycosidic linkage of normal nucleosides.

Although certain carbocyclic nucleosides occur in nature they were first described in 1966 with Sheally and Clayton's synthesis of the racemic carbocyclic analogue (±) 197 of adenosine. Two years later the (-) enantiomer, named aristeromycin, was isolated as a metabolite of Streptomyces citricolo. Synthetic interest was renewed in 1981 with the isolation of the structurally more diverse neoplanocin family of carbocyclic nucleosides and, in particular, the cyclopentenyl derivative neoplanocin A 198.

The first enantiospecific synthesis was provided by Ohno et al with a chemicoenzymatic approach to (-) aristeromycin 197 and (-) neoplanocin 198. This synthesis again utilised the stepwise construction of the heterocyclic base onto a cyclopentylamine which was a feature of Shealy and Clayton's approach. This method has been extensively employed in providing a wide range of racemic carbocyclic nucleoside analogues.

In the last five years nucleoside analogues have been investigated with renewed urgency in the search for agents effective against the Human Immunodeficiency Virus (HIV), the causative agent in the AIDS epidemic. More effective treatment has also been sought for other viral infections, in particular Herpes Simplex virus (HSV types 1 and 2), Varicella Zoster virus (VZV), Cytomegalovirus (CMV) and Epstein Barr virus (EBV), which can prove lethal to AIDS patients and other immunocompromised individuals. This has resulted in an explosion in synthetic activity in the field of carbocyclic nucleosides and the discovery of several derivatives with potent anti-viral
activity. Thus, carbocyclic BVDU 200 is being developed for the treatment of HSV1 and VZV infections\textsuperscript{96} while carbocyclic 2'-ara-fluoro-guanosine 201 is exceptionally effective against HSV1 and HSV2.\textsuperscript{97,98}

\[
\begin{align*}
\text{HO} & \quad \text{HO} & \quad \text{NH}_2 \\
\text{HO} & \quad \text{OH} & \quad \text{HO} \\
\text{199} & & \\
\text{HO} & \quad \text{HO} & \quad \text{O} & \quad \text{X} & \quad \text{HO} & \quad \text{NH} & \quad \text{HO} \\
\text{200} & & \\
\text{HO} & \quad \text{X} & \quad \text{N} & \quad \text{N} & \quad \text{NH} & \quad \text{NH} & \quad \text{201} \quad X=\text{CH}_2 \\
\text{HO} & \quad \text{O} & \quad \text{202} \quad X=\text{O} \\
\end{align*}
\]

Compound 201 established carbocyclic nucleosides as more than simply metabolically stable versions of the active furanose nucleosides since its furanose parent 202 is only weakly active against herpes.

The unsaturated derivative carbovir 203 has also attracted much attention\textsuperscript{99} with activity against HIV comparable to that of AZT. Carbocyclic derivatives now include cyclohexyl and cyclobutyl derivatives with the latter showing promising anti-viral properties. For example, carbocyclic oxetanocin G 204 displays broad spectrum anti-viral activity against HIV and herpes viruses.\textsuperscript{100,101}

\[
\begin{align*}
\text{HO} & \quad \text{N} & \quad \text{203} \\
\text{HO} & \quad \text{N} & \quad \text{204} \\
\end{align*}
\]

The pharmacological importance of these newer analogues has focussed attention on more efficient and flexible syntheses. There are two approaches that can be used, linear or the convergent. The realisation that the biological activity normally resides in one enantiomer,\textsuperscript{97,102-104} and the increasing demand for the new drug substance to be enantiomerically pure has made the development of routes to chiral carbocyclic nucleosides of paramount importance. Both the approaches used will be described briefly with examples, followed by a description of our proposed approach to the synthesis of carbocyclic isonucleosides and nucleosides. For more examples of currently used synthetic methods see Borthwick and Biggadik.\textsuperscript{105}
4.1.1 Linear Approaches

Linear approaches to chiral carbocyclic nucleosides rely on the construction of the heterocyclic base onto a suitable chiral cyclopentylamine. The chemistry involved in the construction of the pyrimidine and purine moieties is as follows.

a) Pyrimidines

Synthesis of uridine and thymidine derivatives employs methodology developed originally by Shaw and Warrener. Thus reaction of the carbocyclic amine 205 with an acryloyl isocyanate 206 provides the intermediate acryloyl urea 207 which is then cyclised with concentrated ammonia or with acid catalysis, to afford the uridine 208 and thymidine 209 analogues.

\[
\text{RNH}_2 + (\text{Et})\text{MeO-C\text{CH}_2\text{C-NCO}} \xrightarrow{X} \text{R} \text{NMe}_2 \text{C-H} \text{N-O}
\]

\[
\begin{align*}
205 & \quad 206 \quad 207 \\
\text{NH}_2 & \quad \text{Y} & \quad \text{X} \\
213 & \quad 210 & \quad 208 \\
\text{Y}=\text{Cl} & \quad \text{X}=\text{H} \\
211 & \quad \text{Y}=\text{MeS} & \\
212 & \quad \text{Y}=1,2,4\text{-triazol-1-yl} & \quad \text{X}=\text{Me}
\end{align*}
\]

Cytidine derivatives 213 are derived from the corresponding uridines 208 by ammonolysis of either the 4-chloro 210, 4-methylthio 211, or 4-(1,2,4-triazol-1-yl) 212 intermediates.

b) Purines

Construction of the purine derivatives is based on the Traube synthesis. Adenosine derivatives are prepared from the cyclopentylamine 205 in three stages. Thus,
reaction with the dichloropyrimidine 214 affords the diamino derivative 215 which is then cyclised with triethylorthoformate to give the 6-chloropurine 216. Aminolysis of the chloro function then provides adenosine analogues 217.

Synthesis of the guanidine base requires two extra steps to introduce the 5-amino moiety. Reaction of 205 with the pyrimidine 218 affords the diamine 219 and the 5-amino group is then introduced by a diazotization/reduction sequence. The resulting triamine 220 is then
cyclised and the chloro function hydrolysed to provide guanosine analogues 221.

Griengl et al.\textsuperscript{107,108} have gained access to either enantiomer of 2'-deoxy carbocyclic nucleosides via enzymatic resolution of an \textit{endo} norbornenyl ester (±) 223. After 11 steps they arrived at the carboxylic acid 226. Curtius degradation and trapping of the resulting isocyanate with gaseous ammonia afforded the urea 227 which was converted in two stages into (+) carbocyclic 2'-deoxy-uridine 228 (overall yield 3.5% for 14 steps from (±) 223). Further elaboration of the pyrimidine base afforded (+) carbocyclic IDU 229 and (+) carbocyclic BVDU 200.

![Diagram of chemical synthesis](https://example.com/diagram.png)

Reagents: b) DPPA, NH\textsubscript{3}; c) 3-ethoxyacryloyl chloride; d) aq NH\textsubscript{3}; e) R=I, I\textsubscript{2}, HNO\textsubscript{3}; f) R=(E)CH:CHBr, methyl acrylate, Pd(OAc)\textsubscript{2}, PPh\textsubscript{3}, NEt\textsubscript{3}; KOH; NBS, KHCO\textsubscript{3}

### 4.1.2 Convergent Approaches

Convergent syntheses of carbocyclic nucleosides bring together the functionalised carbocyclic ring and the intact heterocyclic base. The convergent approaches that have been developed have employed three distinct strategies. These involve coupling the heterocyclic base with the carbocycle moiety by:
a) Nucleophilic displacement of an activated hydroxyl group.

\[
\text{RO–SO}_2\text{OR} \rightarrow \text{HO} - \text{B}
\]

b) Nucleophilic opening of an epoxide

\[
\text{RO–OR} \rightarrow \text{HO} - \text{B}
\]

c) Michael addition to an α,β unsaturated nitro compound

\[
\text{RO–NO}_2 \rightarrow \text{HO} - \text{B}
\]

An example of the convergent approach is the opening of the epoxide 230 with uracil to give the alcohol 231.109

\[
\text{BnO–} \rightarrow \text{BnO–} \rightarrow \text{N–OH}
\]

In comparison to the number of reports on the synthesis of nucleosides and carbocyclic nucleosides very little work has been done in the field of isonucleosides. Isouridine 232 was not screened for anti-tumour activity by the NIH until 1983 despite its characterisation and synthesis over 30 years before.110,111 The most complete biological investigation of isouridine was conducted by Holy and his collaborators who studied the behavior of the nucleotide derivative as well as its 2', 3'-cyclic phosphate, with respect to a range of nucleolytic enzymes.112-114 In addition, the same group found that, in a reaction catalyzed by ribonuclease, 232 behaved as a good acceptor with adenosine 2',3'-cyclic phosphate to form the
The most recent report on the synthesis of isouridine\textsuperscript{189,190} used a convergent approach similar to that of the carbocyclic nucleosides. Thus the dihydropyrimidinone 234 was readily converted to the cyclic nucleoside 235, which was oxidised to the chlorine containing intermediate 236 via an unknown mechanism. Exchange of the chlorine by hydroxide, together with spontaneous rearrangement led to the desired product, isouridine 232.

\[
\begin{align*}
\text{BzO} & \quad \text{OAc} \\
\text{BzO} & \quad \text{OBz} \\
\text{BzO} & \quad \text{OBz}
\end{align*}
\]

\[
\begin{align*}
\text{SnCl}_4 & \quad \text{Me}_3\text{SiO} \\
\text{ClCH}_2\text{CH}_2\text{Cl}
\end{align*}
\]

\[
\begin{align*}
\text{BzO} & \quad \text{O} \\
\text{BzO} & \quad \text{OBz}
\end{align*}
\]

several steps

\[
\begin{align*}
\text{Cl} & \quad \text{N} & \quad \text{O} \\
\text{O} & \quad \text{O}
\end{align*}
\]

\[
\begin{align*}
\text{Chloranil} & \quad \text{pTsOH} \\
\text{HO} & \quad \text{OH}
\end{align*}
\]

Biological testing of isouridine 232 against P388 cell culture showed, however, no inhibition of cell growth at concentrations as high as $5 \times 10^{-4}$ M. In addition at $1 \times 10^{-4}$ M, $1 \times 10^{-3}$ M and $1 \times 10^{-2}$ M concentrations it failed to inhibit uridine kinase extracted from the P388 cells. The
lack of activity is not surprising when one considers that the pyrimidine ring is now in an orientation that is unlikely to be recognized by most enzymes that utilize pyrimidine nucleosides.

A recent report on the synthesis of carbocyclic nucleosides\textsuperscript{116} led us to believe that the chemistry of diphenyl cyanocarbonimidate 53 might be applicable to the synthesis of carbocyclic nucleosides. Amide 237 was treated with methyl isocyanate to give the urea 238. Reductive cleavage of its dihydro derivative 239 gave 240 which, after protection, was reacted with 2,2-dimethyl-1,3-dioxin-4-one to give the carbocyclic nucleosides 241 and 242.

\[
\text{NHMe} \quad \text{NHMe}
\]

\[
\text{O} \quad \text{N} \quad \text{O} \quad \text{N} \quad \text{O} \quad \text{N} \quad \text{O}
\]

\[
\text{L} \quad \text{N} \quad \text{L} \quad \text{N} \quad \text{L} \quad \text{N}
\]

\[
\text{L} \quad \text{N} \quad \text{L} \quad \text{N} \quad \text{L} \quad \text{N}
\]

It was envisaged that a sequence in which cyclopentylamine derivatives were treated with diphenyl cyanocarbonimidate 53 followed by reaction with an aspartic acid derivative would give carbocyclic isonucleosides with a variety of functionality on the base. In this way it was hoped that biological activity might be seen even though the products are closer in structure to isouridine than to uridine.
Subsequent reverse order addition was also envisaged that would lead to carbocyclic nucleosides, joined at N-1 of the heterocyclic base.
4.2 Results and Discussion

Initial model studies were carried out using cyclopentylamine 243 as the 'sugar mimic'. It was found that substantially different behaviour occurred with this amine to the comparable reaction in which benzylamine was used. Thus O-phenylisourea 63 reacted with cyclopentylamine 243, but only to give the guanidine 244, further cyclisation which occurred with benzylamine not being observed.

\[
\begin{align*}
\text{PhO} & \quad \text{NCN} \\
\text{H} & \quad \text{H} \\
\text{N} & \quad \text{N} \\
\text{C} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

Similarly, the more substituted O-phenylisourea 146 also gave only the linear product 245, the yield, however, being considerably worse.

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{N} \\
\text{C} & \quad \text{O} \\
\text{Me} & \quad \text{Bu} \\
\end{align*}
\]

Imidazolidin-5-ones did readily form however, albeit with reduced yields, when compared to the corresponding benzylamine reactions (Scheme 4.1). This once again demonstrates that formation of a 5-membered ring is the favoured ring closure reaction in this system. Reaction of cyclopentylamine with a variety of α-amino acid esters led to the imidazolidin-5-ones shown.

Perhaps the most significant result is that reaction of cyclopentylamine with the O-phenylisourea 138 derived from α-tBu-β-Bzl-Asp 137 led only to the imidazolidinone 248 together with the guanidine 249. In this system therefore cyclisation onto a t-butyl ester is favoured over any cyclisation to any group that would lead to the pyrimidinone system.

These results seem to indicate that a fine line exists between benzylamine and the cyclopentylamine derivatives, with formation of a 6-membered ring being possible for the former but not the latter. The reduced yields and absence of pyrimidinone products can be attributed to the greater steric hindrance that is present in the cyclopentyl structure at the amine nitrogen as compared to benzylamine. This is a recurring theme in the chemistry of diphenyl...
cyanocarbonimidate 53 where any substitution that leads to increased steric crowding at the amine centre results in rapidly decreasing product yields. This increased steric hindrance at the amine centre must lead to the transition state for the 6-membered ring product being more disfavoured than it is in the case of benzylamine. Hence it seems that any amine will present problems at the initial substitution or subsequent cyclisation step if it is more complex at the nitrogen than a primary amine.

**Scheme 4.1**
The imidazolidin-5-one 181 derived from dimethyl aspartic acid could, however, be rearranged to the pyrimidine carboxylic acid 187 by making use of the rearrangement reaction as previously stated (Chapter 3). The spectral changes in going from 181 to 187 were completely consistent with the changes in structure.

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{NH} \\
\text{O} & \quad \text{C} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad ^\text{a} \\
\text{C} & \quad \text{NCN} \\
\end{align*}
\]

187

1) NaOH
2) H⁺

With these model results in hand attention was turned to the synthesis of 1,4-disubstituted carbocyclic pyrimidinones. The cyclopentylamines required for this chemistry were constructed using literature methods\textsuperscript{117,118} (Scheme 4.2).

\textbf{Scheme 4.2}

![Scheme 4.2 diagram](image-url)
All four racemic carbocyclic amines 250-253 were effectively coupled to diphenyl cyanocarbonimidate 53, either by direct coupling or by modification of a preformed O-phenyisourea (Scheme 4.3).

Scheme 4.3

Interestingly, amine 250 reacted to give only the cis isomer 254 and not the corresponding trans isomer 258.
That only one isomer was formed was confirmed by n.O.e. measurements. These clearly showed that on irradiating one of the C-5 protons an enhancement occurred only at the NH proton and the other C-5 proton, whilst irradiating at the second C-5 proton led to an enhancement at both the C-1 and C-4 protons. These results are those that would be expected for 254 and not 258.

This result seems to contradict the literature\textsuperscript{117} where it has been reported that the cyclopentylamine 250 readily undergoes base catalysed epimerization on stirring the amine hydrochloride with triethylamine in THF. The site of inversion was clearly shown by incubation of 250 with sodium deuteroxide in CD\textsubscript{3}OD to be C-4, as would be expected since this is the most acidic proton, being $\alpha$ to both an ester and olefin.

Since this result seemed to contradict our own observations, the epimerization was reinvestigated by monitoring the reaction using $^1$H n.m.r. spectroscopy. Thus the free amine of 250 was generated using triethylamine in THF and the salt subsequently regenerated with HCl gas. The $^1$H n.m.r. spectrum of the regenerated salt clearly indicated the presence of the second isomer, a new set of peaks being seen.

The reason for only one isomer being seen on reaction with diphenyl cyanocarbonimidate 53 is unclear. Since epimerization is apparently occurring during the reaction it must be concluded that either only the \textit{cis} isomer can react or, as seems more likely, the \textit{cis} isomer is the more stable of the two possible products and any \textit{trans} isomer that is produced is converted to the more thermodynamically stable \textit{cis} isomer by epimerization subsequent to its formation.

Attempts to react O-phenylisourea 254 with a number of amine nucleophiles under a variety of conditions (Et\textsubscript{3}N, NaH, or BuLi) to give pyrimidinones directly proved to be unsuccessful. No reaction was obtained with $\beta$-alanine-methyl ester, $\alpha$-tBu-$\beta$-Me Aspartate, or even benzylamine.
O-Phenylisoureas 256 and 257 did, however, react with β-alanine-methyl ester 62 when the anion of the amine was generated using sodium hydride. In the case of 256 dioxan was used as the solvent and a small amount of the cyclised product 259 was obtained. For 257 THF was used as the solvent and the guanidine 260 was obtained. However, yields were low at less than 10% in both cases.

Once again, however, imidazolidin-5-ones could be formed (Scheme 4.4) but even in these cases yields were greatly reduced (10-15%) in comparison to those observed where the carbocycle was not substituted at C-4. Phenylalanine benzyl ester was generally used since the resulting imidazolidinones still contained a chromophore, making isolation of the products easier. The products were mixtures of diastereoisomers as seen by $^{13}$C n.m.r.
As a result of the low yields it proved to be impossible to obtain enough of the carbocyclic imidazolidin-5-one methyl ester 264 to perform the ring rearrangement reaction. Given that this reaction was successful in all other cases it would be predicted that, given sufficient of the imidazolidinone, it would be successful in this case.
From these results it is seen that further increasing the steric bulk of the cyclopentylamine by the introduction of a second group at C-4 led to a substantial decrease in product yield, such that either no product is formed or the yield of product is synthetically unacceptable.

Attention was then turned to the use of ribitylamine as the amine source. It was hoped that the oxygen now present in the ring would lead to a conformation sufficiently different for reaction with a second nucleophile to be possible. However it was found that whilst the protected ribitylamine would readily react with diphenyl cyanocarbonimidate 53 to give the intermediate O-phenylisourea 266, further reaction with a second amine such as benzylamine or \( \beta \)-alanine methyl ester did not occur. In the light of the previous results with cyclopentylamine derivatives it seemed unlikely that this even more hindered amine source would give better results, hence this was not pursued further.
Attempts to perform the reverse addition were also investigated. Reductive amination\textsuperscript{195} of cyclopentanone with dimethyl aspartate 126 occurred smoothly to give the cyclopentylamine derivative 267 but again this was found not to react with diphenyl cyanocarbonimidate 53 even when sodium amide was used to generate the amine anion. This is again attributed to the steric hindrance present in the amine.

\textbf{4.3 Conclusion}

Once again it can be seen from the model studies that the formation of imidazolidin-5-ones is favoured over formation of pyrimidinones. It seems that the steric hindrance present in these cyclic amines is sufficiently large to prevent the efficient addition of the second amine group and that where addition does occur the subsequent cyclisation is now inhibited.
Reactions of the N-cyanoimine Functional Group

5.1 Design of Enzyme Inhibitors of Carboxypeptidase A

During attempts to prepare a potential inhibitor 268 of the enzyme Carboxypeptidase A, an unusual cyclisation reaction was observed. Further investigation of similar systems led to a mechanism that explains the observation.

![Chemical structure](image)

Carboxypeptidase A is a zinc-containing proteolytic enzyme which removes the C-terminal amino acid from a peptide chain if the C-terminal carboxylate is free. In order that a substrate may be susceptible to lysis by carboxypeptidase A, certain requirements and preferences are exerted by the enzyme.120 Firstly, the peptide bond which is to undergo hydrolysis must be adjacent to a terminal free carboxyl group, as for 269. Secondly, the rate of hydrolysis is usually enhanced if the terminal residue has an aromatic or branched aliphatic side chain. Thirdly, dipeptides having a free amino group are hydrolysed slowly, but if this group is blocked by N-acylation, the hydrolysis is rapid. Fourthly, the carboxyl-terminal residue must be in the L-configuration. Fifthly, substitution of a methyl group for the H atom of the NH group of the peptide bond to be split either prohibits or greatly reduces hydrolysis.

![Chemical structure](image)

The detailed mechanism of action of Carboxypeptidase A remains controversial. Binding of the substrate is believed to involve charge pairing of the terminal carboxylate group with the guanidinium of Arg145, setting up the carbonyl oxygen of the terminal peptide bond to become a ligand of the active site zinc.121 This liganding polarizes the carbonyl group, increasing the electrophilicity of the carbonyl carbon and facilitating nucleophile mediated hydrolysis. The phenolic hydroxyl of Tyr248 is in sufficient proximity to the susceptible amide linkage in the substrate to donate a proton to the amine fragment on cleavage, facilitating its expulsion as a leaving group by general acid catalysis.
However the distinction between the so-called ‘anhydride’ mechanism (Scheme 5.1),
where Glu$^{270}$ attacks the carbonyl of the substrate to form an acyl-enzyme intermediate (an
anhydride), and the ‘direct’ mechanism (Scheme 5.2), where Glu$^{270}$ acts as a general base to
activate a water molecule which directly cleaves the substrate, cannot be made.$^{122}$

Scheme 5.1

Various mechanistic claims have been made for particular substrates, but even these
have been disputed.$^{123,124}$ Combined with the observation that this enzyme can catalyse
stereospecific enolisation of a ketonic substrate,$^{125}$ and $\alpha,\beta$-elimination reactions$^{126}$ it is perhaps
a moot point to attempt to formulate a general mechanism for all substrates for this enzyme.

Our potential substrate/inhibitor seemed to satisfy many of the criteria for a good
substrate for carboxypeptidase A. The ‘peptide’ bond to be hydrolysed is adjacent to an L-
aromatic terminal residue with a free carboxylate group. There is no free amino group which is
known to slow down hydrolysis. The fact that the peptide bond oxygen has been replaced by the
N-cyanoimino group leads to uncertainty over whether 268 would behave as an inhibitor or substrate. Whilst this group is known to be an isostere for the carbonyl group\textsuperscript{57,58} it is uncertain whether the enzyme would accept this group and carry out the hydrolysis, thus removing the phenylalanine and leaving behind a group that could act as an inhibitor of the enzyme, or whether the enzyme would accept the substrate 268 but then be unable to carry out the peptide bond hydrolysis, thus inhibiting the enzyme at this earlier stage.

### 5.2 Reactions of the N-cyanoimine group

N-cyanoimines react with hydrazine to give 1,2,4-triazoles 271 (Chapter 6), and also with hydroxylamine to give 1,2,4-oxadiazoles 272 and 273.\textsuperscript{27}
The N-cyanoimine group can also be converted to other groups once the heterocycle has been formed. Recently, the regioselective hydride reduction of 2-(N-cyanoimino)-thiazole derivatives has been reported.\(^{127}\) Hence reductive cleavage of the imino double bond was achieved using lithium aluminium hydride, and reduction of the nitrile group and/or the cleavage of the imino nitrile bond was achieved with diisobutylaluminium hydride.

\[
\text{LiAlH}_4 \rightarrow \text{N} - \text{H}
\]

The 2-formylimino compound 277 was easily converted to the 2-imino derivative 278 by hydrolysis with aqueous sodium hydroxide, and treatment of 278 with acetic anhydride gave the 2-acetyliminothiazolidine 279.

\[
\text{NaOH} \rightarrow \text{N} - \text{H} \rightarrow \text{N} - \text{CO}_2\text{Me}
\]

Treatment of 2-N-cyanoimino-4H-1,3-benzoxazine 60 with benzylamine in boiling propan-2-ol gave the 2-benzylamino-1,3-benzoxazine 61 by nucleophilic addition to the \(\text{C}=\text{N}\) carbon with subsequent ejection of \(\text{H}_2\text{NCN}\).\(^{25}\)
The N-cyanoimine group can also be hydrolysed. During the course of a reaction to introduce a double bond into the dihydropyrimidine 64 using bromine in acetic acid, the N-cyanoimine group was also hydrolysed to the amine 65.\textsuperscript{24}

Similarly treatment of 3-benzyl-2-cyanoimino-4(1H, 3H)-quinazolinone 280 with concentrated hydrochloric acid resulted in hydrolysis of the N-cyanoimino group to give 2-amino-3-benzyl-4(3H)-quinazolinone hydrochloride 281.

Recently it has been reported that gonadotropin-releasing hormone (GnRH) antagonists containing modified N\textsuperscript{o}-cyano-N\textsuperscript{o}'-alkyl or arylguanidino moieties on homoarginine, when stored in lyophilized form as the trifluoroacetate salts decompose into a major hydrophobic impurity.\textsuperscript{128} From infra-red and mass spectrometry data it was concluded that, in the presence of water of hydration, hydrolysis of the nitrile had occurred under the acidic conditions induced by the TFA counter-ion, yielding the corresponding guanylurea derivative. In order to assess the lability of the cyanoguanidino function in acid, the hydrolysis of 282 in 0.1% TFA was monitored by HPLC and was found to be complete within 4 days at room temperature.
We have investigated this reaction under both anhydrous and hydrated conditions and have found that the results can be used to explain the formation of unusual cyclisation products upon attempts to synthesise inhibitors of the enzyme carboxypeptidase A.
5.3 Results and Discussion

It was envisaged that synthesis of the benzyl ester 284 followed by subsequent deprotection would give the required guanidine 285. Hence diphenyl cyanocarbonimidate 53 was coupled with L-phenylalanine benzyl ester 286 to give the O-phenylisourea 246 (Scheme 5.3). Reaction of this with N-methyl benzylamine then gave the guanidine 284. It was found, however, that use of this secondary amine led to a poor yield of the guanidine 284, the best yield obtained being 56%. This is believed to be due to the fact that the more hindered secondary amine cannot readily approach the imine carbon. Deprotection of the benzyl ester 284 by hydrogenation over palladium did not, however, give the desired free carboxylic acid 285, but instead led to a compound whose spectral properties were consistent with those of the imidazole 287. This compound showed broad peaks in the $^1\text{H}$ n.m.r. spectrum at room temperature and heating the sample caused these peaks to coalesce ($T_c=393$ K, $\Delta\nu=169$ Hz, $K'=375$ s$^{-1}$, $\Delta G^\ddagger=18.6$ Kcal/mol). These spectral properties are believed to arise as a result of restricted rotation about the N-methyl benzyl carbon due to it coming into close proximity in some positions with the hydrogen attached to the ring nitrogen.

![Structure of 285](image)

Deprotection of the intermediate O-phenylisourea 246 using identical conditions did not, however, lead to a similar cyclisation reaction. In this case the carboxylic acid 288 was isolated. Subsequent reaction with benzylamine at room temperature led to a compound whose spectral data were consistent with those of the benzylamine salt 289. Reaction of this salt with benzylamine at 100 °C gave another imidazole 290. Interestingly this compound did not show the presence of hindered rotation, which reflects the absence of both the N-Me and N-H groups from this molecule.

A similar product 295 could also be obtained from the corresponding 2-amino butyric acid benzyl ester 292. Thus coupling with diphenyl cyanocarbonimidate 53 gave the O-phenylisourea 293 which was reacted with N-methyl benzylamine to give the guanidine 294. Deprotection of the guanidine 294 by hydrogenation over palladium led to the imidazole 295 which again showed the presence of hindered rotation in its $^1\text{H}$ n.m.r. spectrum ($T_c=293$ K, $\Delta\nu=22.8$ Hz, $K'=50.6$ s$^{-1}$, $\Delta G^\ddagger=14.8$ Kcal/mol).

The imidazole 287 could also be synthesised from the methyl ester 291 either by deprotection using trifluoroacetic acid/water in boiling THF, or chymotrypsin in a phosphate buffer at pH=7.8. Cleavage of methyl esters is usually achieved under basic or neutral conditions.
Scheme 5.3

\[
\begin{align*}
53 & \quad \text{PhCN} \quad \text{PhCN} \\
& \quad \text{PhO} \quad \text{PhO} \\
\text{H}_2\text{N} \quad \text{CO}_2\text{H}_2\text{Ph} & \quad \text{PhCN} \quad \text{PhCN} \\
& \quad \text{PhO} \quad \text{PhO} \\
286 & \quad 246 \\
\text{PhCH}_2\text{NHMe} & \quad \text{H}_2, \text{Pd/C} \\
& \quad \text{PhCN} \quad \text{PhCN} \\
& \quad \text{PhO} \quad \text{PhO} \\
284 & \quad 288 \\
\text{PhCN} \quad \text{PhCN} & \quad \text{PhCN} \quad \text{PhCN} \\
& \quad \text{PhO} \quad \text{PhO} \\
287 & \quad 289 \\
\text{PhCN} \quad \text{PhCN} & \quad \text{PhCN} \quad \text{PhCN} \\
& \quad \text{PhO} \quad \text{PhO} \\
291 & \quad 290 \\
\text{PhCH}_2\text{NHMe} & \quad \text{PhCH}_2\text{NH}_2, \Delta \\
\alpha\text{-Chymotrypsin} \quad \text{or} \quad \text{TFA/H}_2\text{O} &
\end{align*}
\]
conditions,\textsuperscript{129} however anhydrous TFA has been used to cleave methyl esters,\textsuperscript{130} though under the more vigorous conditions of heating the ester in a sealed tube to 105 °C for 20 h. That chymotrypsin cleaves the methyl ester is to be expected, since there are many reports of the use of chymotrypsin to cleave esters,\textsuperscript{131} and also because 291 resembles a dipeptide with a phenylalanine as its terminal residue; phenylalanyl peptide bonds are among those that are primarily attacked by chymotrypsin. In this case, however, evidence was found for the intermediacy of the free carboxylic acid 285. Monitoring the reaction by TLC showed a more polar product spot below that of the imidazole 287. Attempts to isolate this product however, by either extraction or flash chromatography failed. In both cases the acid was apparently converted to the imidazole during the work-up procedure.

\[
\begin{align*}
\text{NCN} & \quad \text{PhO} \quad \text{OPh} \\
\text{H}_2\text{N} & \quad \text{CO}_2\text{CH}_2\text{Ph} \\
\text{PhCH}_2\text{NHMe} & \quad \text{Ph} \\
\text{Me} & \quad \text{H} \\
\end{align*}
\]

It would seem, therefore, that once the ester protecting group has been removed an unstable intermediate acid 285 is formed which readily reacts further to give the imidazole 287. A clue as to the possible mechanism of formation of these cyclisation products came from an investigation of the reaction of simple cyanoimines with TFA under anhydrous and hydrous conditions.

Under anhydrous conditions reaction of the O-phenylisourea 296 with 6-equivalents of TFA in boiling THF led to two products, the trifluoroacetyl compound 297 and the trifluoroacetoxy compound 298, 297 being the major product.
The guanidine 299, however, under identical conditions yielded only the trifluoroacetyl product 300.

\[
\text{Ph} - \text{NCN} - \text{Ph} \xrightarrow{\text{TFA}} \text{Ph} - \text{NCOCF}_3
\]

A similar set of products were observed when glacial acetic acid was used in place of TFA. However reaction times were considerably longer and, in the case of the O-phenylisourea 296, some hydrolysis of the phenoxy group was seen, probably as a consequence of the longer reaction times allowing moisture to get into the system.

\[
\text{PhO} - \text{NCN} - \text{Ph} \xrightarrow{\text{CH}_3\text{CO}_2\text{H}} \text{PhO} - \text{HN} - \text{Ph} + \text{HO} - \text{HN} - \text{Ph}
\]

The presence of rotamers in the $^1H$ and $^{13}C$ n.m.r. spectra of 302 together with an absorption in the IR spectrum consistent with an imine stretch suggest that 302 has the structure shown and not the corresponding tautomeric urea structure 303.

Addition of an equivalent amount of water to the TFA present in the reaction mixture led to a change in the course of the reaction. Hydrolysis products similar to those obtained
previously\textsuperscript{128} were seen. Thus several imidazoles were converted to their corresponding urea derivatives (Scheme 5.4).

**Scheme 5.4**

\[
\begin{align*}
\text{NCN} & \quad \text{R} \quad \text{NH}_2 \\
\text{O} & \quad \text{R'} \\
\end{align*}
\]

166 \hspace{1cm} R=R'=\text{CH}_2\text{Ph} \hspace{1cm} 306 \\
128 \hspace{1cm} \text{R=CH}_2\text{Ph, R'=CH}_2\text{CO}_2\text{Me} \hspace{1cm} 307 \\
181 \hspace{1cm} \text{R=cC}_5\text{H}_9, \text{R'=CH}_2\text{Ph} \hspace{1cm} 308 \\
305 \hspace{1cm} \text{R=NH}_2, \text{R'=Et} \hspace{1cm} 310
\]

Urea 307 could also be rearranged to give the dihydropyrimidine 309 using the rearrangement reaction described previously (Chapter 3).

\[
\begin{align*}
\text{PhCH}_2\text{N} & \quad \text{NH} \\
\text{O} & \quad \text{CO}_2\text{Me} \\
\end{align*}
\]

1) NaOH \\
2) H\textsuperscript{+}

The guanidine 299 could also be converted to its urea derivative 311, but in the case of the O-phenylisourea 296 it was found that under reflux conditions hydrolysis of the phenoxy group occurred. Hence the O-phenylisourea 296 was stirred with TFA alone in THF at room temperature for 13 days to give the urea 312. Presumably during the reaction water is slowly absorbed into the reaction mixture from the atmosphere, thus allowing the hydrolysis of the N-cyanoimine to occur, but insufficient water is present for hydrolysis of the phenoxy group.
That the NH proton is not necessary for the anhydrous reaction to proceed is evident from the fact that the O-phenylisourea 313 can be converted to its corresponding trifluoroacetyl derivative 314 by reaction with TFA in boiling THF.

A common mechanism can be postulated to explain all of these results (Scheme 5.4). Initial attack of the acid upon the nitrile carbon gives an intermediate 316 which under anhydrous conditions collapses to the product due to intramolecular electron transfer from the imine bond, but under aqueous conditions is attacked by the more nucleophilic water present, with resulting collapse to the urea 320.

Presumably 298 which does not fit into this reaction scheme must result from the nucleophilic displacement of the cyanide group from 296 to give the trifluoroacetoxy product.

Formation of the imidazole during attempts to prepare carboxypeptidase A inhibitors can also be explained by this mechanism (Scheme 5.5).
In the presence of an excess of amine the intermediate urea 324 formed can react further by an amine exchange mechanism thus explaining the formation of 290.

Attempts to extend this synthesis to dihydropyrimidines were unsuccessful. O-phenylisourea 63 was readily coupled with N-methylbenzylamine to give the guanidine 326, but on deprotection of the ester using sodium hydroxide in methanol the carboxylic acid 327 was obtained and no cyclic product was observed. The corresponding benzyl ester could not be prepared since in this case the N-methylbenzylamine reacted with the ester group of 328 in preference to the phenoxyimine to give the amide 329. This is again a reflection of the fact that O-phenylisoureas are not very reactive toward secondary amines, and in this case the relatively reactive and unhindered ester is much more readily attacked.
5.4 Conclusion

It can be seen that the N-cyanoimine compound can readily be converted either to the trifluoroacetyl or the urea analogue. A different class of imidazoles can also be formed in a related reaction, the only restriction apparently being the coupling of the O-phenylisourea to a secondary amine, this step giving the lowest yield in the sequence. This synthesis does not, however, appear to be applicable to dihydropyrimidines, probably because the putative transition state would be an 8-membered ring in this case, once again illustrating that the 5-membered ring is the favoured product.
Synthesis of 1,2,4-Triazoles

6.1 Introduction

The heteroaromatic triazole ring system is composed of five atoms, two carbons and three nitrogens which can be arranged in two combinations to give either 1,2,3-triazole or 1,2,4-triazole. Although two NH (330 and 331) and one CH₂ (332) tautomeric forms are possible for 1,2,4-triazoles, this structure is best represented as a positively charged hydrogen associated with a resonance stabilised triazole anion.¹³²

In Chemical Abstracts 3-substituted and 3,5-disubstituted 1,2,4-triazoles are usually indexed as s-triazoles.

Bladin reported the preparation of derivatives of s-triazole 330 in 1885¹³³ and soon thereafter Pellizzari obtained the parent ring system from the reaction of formylhydrazine with formamide.¹³⁴

These reactions gave low yields of s-triazoles. Subsequent methods led to improved yields, culminating in a 95% yield using the method of Grundmann and Rätz.¹³⁵ This method involved the treatment of s-triazine with hydrazine hydrochloride.
6.1.1 3(or 5)-Amino(unsubstituted)-s-Triazoles

Many related methods for the preparation of amino-1,2,4-triazoles have been reported in the literature, a few of which are illustrated.

The preparation of 3-aminotriazole 335 via N-(formylamino)-guanidine 334 was accomplished by heating a mixture of an aminoguanidine 333 salt (HCl, HNO₃) and formic acid in toluene and separating the water generated in the reaction.¹³⁶

Extensive work has been reported on the condensation of aliphatic carboxylic acids and lactones with N-aminoguanidine 333, of which one example is the conversion of 336 to the C-nucleoside 337.¹³⁷,¹³⁸
In the reaction of hydrazides with 2-methyl-2-thiopseudourea 338 under mild conditions, the intermediate N-(acylamino) guanidines 340 are usually not isolated, but undergo cyclisation to triazoles, as demonstrated by the reaction of (benzamido)-acetylhydrazide 339 with 338 to give 3-amino-5-(benzamidomethyl)-triazole 341.139

\[
\begin{array}{c}
\text{NH} & \text{H}_2\text{N} \text{SMe} \\
\text{PhCONH} & \text{H}_2\text{NNCOH}_2\text{C} \\
\end{array} \xrightarrow{\Delta} \begin{array}{c}
\text{NH} \\
\text{H}_2\text{N} \\
\text{N-N} \\
\text{COCH}_2\text{NHCOPh} \\
\end{array}
\]

338 339 340

341

Good yields of 3-amino-5-alkyltriazoles resulted from the condensation of imino ethers with N-aminoguanidine in refluxing pyridine. For example, ethyl propionimidate hydrochloride 342 and N-aminoguanidine 333 gave 3-amino-5-ethyltriazole 343.140

\[
\begin{array}{c}
\text{NH} & \text{H}_2\text{N} \text{NH}_2 \\
\text{EtO} & \text{Et} \\
\end{array} \xrightarrow{86\%} \xrightarrow{\Delta, \text{pyr, 2h}} \begin{array}{c}
\text{NH} \\
\text{H}_2\text{N} \\
\text{N-N} \\
\text{Et} \\
\end{array}
\]

333 342 343

The 3-amino-5-aryltriazoles are prepared via similar types of intermediates. For example treatment of the aroylhydrazine 344 with cyanamide in refluxing acetic acid gave 3-amino-5-phenyltriazole 345.141

\[
\begin{array}{c}
\text{H}_2\text{N} \text{CN} \\
\text{H}_2\text{NNHCOPh} \\
\end{array} \xrightarrow{\Delta, \text{AcOH}} \begin{array}{c}
\text{H}_2\text{N} \\
\text{N-N} \\
\text{Ph} \\
\end{array}
\]

344 345
6.1.2 3(or 5)-Amino-1H-1,2,4-Triazoles

The cyclisation of N-aminoguanidine derivatives to give 1-substituted aminotriazoles has been directed toward the preparation of both 1-alkyl- and 1-aryl-3-amino- or 5-amino-1H-1,2,4-triazoles. Treatment of N-anilino-N'-phenylguanidine 346 with formic acid gave 3-anilino-1-phenyltriazole 347 in good yield.\(^{142}\)

\[
\text{PhNH}_2\text{NNHPh} + \text{HCO}_2\text{H} \rightarrow \text{PhHN} \quad \text{N} \quad \text{N} \quad \text{Ph}
\]

346 \hspace{1cm} 347

In the cyclisation of N-amino-N-methylguanidine 348 with formic acid, a good yield of 5-amino-1-methyltriazole 350 was obtained.\(^{143}\)

\[
\text{NH}_2\text{NH} \quad \text{NMeNH}_2 \hspace{1cm} \text{HCO}_2\text{H} \rightarrow \text{NH} \quad \text{NMeNHCHO} \rightarrow \text{H}_2\text{N} \quad \text{N} \quad \text{NH}_2 \quad \text{Me}
\]

348 \hspace{1cm} 349 \hspace{1cm} 350

Another method for the preparation of 1-(substituted)-5-aminotriazoles involves the cyclisation of N-(acylamino) guanidines in a basic medium, for example the conversion of 351 to 352.\(^{144}\)

\[
\text{H}_2\text{N} \quad \text{N} \quad \text{MeHH} \hspace{1cm} \text{CO} \hspace{1cm} \text{NH} \quad \text{MeH} \quad \text{5M NaOH} \quad 53\% \rightarrow \text{H}_2\text{N} \quad \text{N} \quad \text{N} \quad \text{MeH}
\]

351 \hspace{1cm} 352

The N-(acylamino) guanidines (for example 354) can also be generated in situ and converted directly to triazoles, as demonstrated by the condensation of the hydrazide 353 with cyanamide to give 355.\(^{145}\)

\[
\text{PhNH} \quad \text{N} \quad \text{HCO} \quad \text{Ph} \hspace{1cm} \text{H}_2\text{NCN} \rightarrow \text{H}_2\text{N} \quad \text{N} \quad \text{MePh}
\]

353 \hspace{1cm} 354 \hspace{1cm} 355
In the thermal cyclisation of the amidrazone derivative 356, it was found that water rather than aniline was eliminated to give a good yield of 357.\textsuperscript{145}

\[
\begin{array}{c}
\text{NCONHPh} \\
\text{Me} \\
\text{NMeNH}_2
\end{array} 
\xrightarrow{250^\circ\text{C}} 
\begin{array}{c}
\text{Me} \\
\text{N} \\
\text{N} \\
\text{NHPh} \\
\text{Me}
\end{array}
\]

356 \quad 357

The N-cyanoamidrazones are implicated in several conversions to give aminotriazoles in good yields under mild conditions. For example, the reaction of phenylhydrazine with ethoxymethylene cyanamide 358 gave 360, presumably via the formation of 359.\textsuperscript{146} However, treatment of 358 with methylhydrazine produced a mixture of the 1-methyl-5-amino and 1-methyl-3-aminotriazoles (350 and 361), respectively in which 350 was the major product.\textsuperscript{147}

\[
\begin{array}{c}
\text{NC} \cdot \text{N} \cdot \text{CHOEt} \\
\text{H}_2\text{NNHPh}
\end{array} 
\xrightarrow{\text{MeNHNH}_2} 
\begin{array}{c}
\text{NC} \cdot \text{N} \cdot \text{PhNHHN}
\end{array}
\]

358 \quad 359

6.1.3 3,5-Diamino-1,2,4-Triazoles

The preparation of a variety of 1-aryl-3,5-diaminotriazoles (1-arylguanazoles) was accomplished in good yield by the treatment of the hydrochlorides of aryl hydrazines with the dicyanamide 362 in boiling water, as shown for the preparation of 1-phenyltriazole 363.\textsuperscript{148-150}
Variations on this method include the interaction of the alkaline salts of dicyanamide 364 with hydrazine and its alkyl and aryl derivatives to give 3,5-diamino-s-triazole (guanazole) 365 and the 1-substituted derivative 366.\textsuperscript{151,152}

\[ \text{NaN(CN)}_2 + \text{H}_2\text{NNH}_2 \rightarrow \text{H}_2\text{N}^=\text{N}^\text{N}^=\text{N}^\text{N}^=\text{N}^\text{NH} \]

\[ \text{MeNHNNH}_2 \]

\[ \text{H}_2\text{N}^=\text{N}^\text{N}^=\text{N}^\text{N}^=\text{N}^\text{NH}_2 \]

\[ \text{Me} \]

A number of 3,5-diaminotriazoles have been prepared from carbodiimides. Treatment of N,N'-dicyclohexylcarbodiimide 367 with hydrazine in hot DMF gave a 75% yield of 368.\textsuperscript{153}

\[ (\text{cC}_6\text{H}_{11}\text{N})_2\text{C} + \text{H}_2\text{NNH}_2 \rightarrow \text{RHN}^=\text{N}^\text{N}^=\text{N}^\text{N}^=\text{N}^\text{NHR} \]

\[ \text{R}=\text{cC}_6\text{H}_{11} \]

6.1.4 O-substituted Oxy-1,2,4-Triazoles

Alcoholysis of a variety of 5-alkyl and aryl-2-amino-1,3,4-oxadiazoles (eg 369, 370) in the presence of potassium hydroxide gave good yields of alkoxytriazoles (373, 374), presumably formed via the corresponding imino ether intermediates (371, 372).\textsuperscript{154,155}
Aryl ethers of 1,2,4-triazoles have been prepared by the 1,3-dipolar addition of nitrilimines to aryl cyanates. For example, refluxing a benzene solution of \( \text{375} \) in the presence of triethylamine generated the nitrilimine \( \text{376} \), which reacted with phenyl cyanate to give \( \text{377} \) in 48% yield.

Nucleophilic displacement of the halogen of halotriazoles also gives O-1,2,4-triazoles. For example, treatment of \( \text{378} \) with methoxide or phenoxide gave \( \text{379} \) and \( \text{380} \) respectively.
Recently a new method for the synthesis of dihydro-1,2,4-triazolo[1,5-a]pyrimidines has been reported. This involves heating acetophenones with 5-amino-1H-1,2,4-triazole 335 in the presence of a catalytic amount of zinc chloride, giving rise to a mixture of condensation products, 5,7-diaryl-4,5-dihydro-5-methyl-1,2,4-triazolo[1,5-a] pyrimidines 381 and 5,7-diaryl-4,7-dihydro-7-methyl-1,2,4-triazolo[1,5-a] pyrimidines 382, which were easily separated by column chromatography or fractional crystallisation.

\[
\text{RCOCH}_3 + \text{ZnCl}_2, 160-190 \degree C \rightarrow \begin{array}{c}
\text{335} \\
\text{381} \\
\text{382}
\end{array}
\]

Several 1,2,4-triazoles have been found to have interesting therapeutic actions, amongst which is included 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (virazole) 383. It has been suggested that 1,2,4-triazole nucleoside analogues resemble the natural nucleosides in various biochemical systems, on the basis that the five membered ring in showdomycin 384 results in an antibiotic that specifically inhibits uridine monophosphate kinase and uridine phosphorylase. Virazole has been found to be inhibitory to both RNA and DNA viruses in vitro and in vivo.

\[
\begin{array}{c}
\text{383} \\
\text{384}
\end{array}
\]

Synthesis of virazole 383 was achieved by treatment of an acyl-blocked ribofuranosyl bromide with the tetramethylsilyl derivative of methyl 1,2,4-triazole-3-carboxylate, followed by treatment of the purified product with methanolic NH\textsubscript{3}.
A number of potential antidepressant agents with a general 2,4-dihydro-3H-1,2,4-triazole-3-thione structure 388 have been prepared\textsuperscript{162} using the methodology of Sandström and Wennerbeck.\textsuperscript{163} The reaction of aroyl chlorides 385 and thiosemicarbazides 386 in either chloroform or pyridine gave 1-aryltiosemicarbazides 387 which, without purification, were cyclised in refluxing aqueous sodium bicarbonate to yield the desired 2,4-dihydro-3H-1,2,4-triazole-3-thiones 388.
Webb and Labaw\textsuperscript{23,27} have reported that diphenyl cyanocarbonimidate 53 and derivatives of this compound can be treated with hydrazine nucleophiles to give triazoles, for example 57 is smoothly converted to triazole 58 with hydrazine in methanol at room temperature\textsuperscript{23}.

\begin{center}
\begin{tikzpicture}
  \node (a) {\textbf{57}};
  \draw[->] (a) -- node[midway,above]{$\text{H}_2\text{NNH}_2$} (b);
  \node (b) {\textbf{58}};
\end{tikzpicture}
\end{center}

Compound 389, a potent antagonist of the H\textsubscript{2}-receptor of histamine has been synthesised using the same reaction sequence.

\begin{center}
\begin{tikzpicture}
  \node (a) {\textbf{53}};
  \draw[->] (a) -- node[midway,above]{$\text{H}_2\text{NNH}_2$} (b);
  \node (b) {\textbf{389}};
\end{tikzpicture}
\end{center}

Using this reaction of diphenyl cyanocarbonimidate 53 we set out to develop the methodology to allow synthesis of bicyclic triazoles, and also to conduct an investigation into the regioselectivity of attack when using substituted hydrazines.
6.2 Results and Discussion

It was initially envisaged that reaction of diphenyl cyanocarbonimidate 53 with hydrazine, followed by nucleophilic displacement of the remaining phenoxy group with an amine, would give the desired products. However, whilst it was found that 53 readily reacted with hydrazine to give the triazole 390 in 59.5% yield, further reaction with a second amine did not occur.\(^{164}\)

\[
\begin{align*}
\text{PhO} & \quad \text{NCN} & + & \quad \text{RNHNNH}_2 \\
\text{Propan-2-ol} & & & \Delta \\
\text{53} & & & \rightarrow \\
\text{PhO} & \quad N & \quad \text{N} & \quad N & \quad \text{NH}_2 \\
\end{align*}
\]

Similar treatment of 53 with methylhydrazine and phenylhydrazine gave 391 and 392, respectively, both in 63% yield. It would be expected that the orientation of the substituents in 391 and 392 would be that with the substituent at position 1 of the ring system, and not position 2, since attack on the phenoxy group is expected to occur via the substituted nitrogen which is the more nucleophilic. That this was the case was shown from n.O.e. experiments on the \(^1\)H n.m.r spectrum of 391.\(^{165}\) Irradiation at the position of the methyl signal led to an enhancement of the O-phenyl ortho proton resonance, whereas irradiation of the NH\(_2\) signal showed no enhancement of the methyl signal.

The alternative method of synthesis was then investigated. It was envisaged that the reaction of 53 with \(\omega\)-aminoesters 393 would give the monosubstituted compounds 394 which, on treatment with hydrazine should give the N-cyanoguanidine that could, in principle, cyclise twice (Scheme 6.1).

The ester 395, obtained from the reaction of 53 with methyl glycine, was treated with hydrazine in propan-2-ol at reflux when the triazole 396 was obtained in 97% yield. The
reaction had proceeded as expected, in that the triazole ring formed, but the second cyclisation has not occurred.

**Scheme 6.1**

\[
\begin{align*}
53 & \quad + \quad H_2N(CH_2)\_nCO_2Me \\
\xrightarrow{H_2NNH_2} & \quad \xrightarrow{NHC} \quad (\_)_n
\end{align*}
\]

Similarly, treatment of 63 and 398 with hydrazine also gave only the monocyclic products 397 and 399 respectively. Compound 399 was not expected to cyclise further as this requires the formation of a 7-membered ring,\(^{166}\) but the failure to form the 5- and 6-membered rings in 396 and 397 suggests that the nitrogen in the triazole ring is less nucleophilic than the amines previously used.

\[
\begin{align*}
395 & \quad n=1, R=H \\
63 & \quad n=2, R=H \\
398 & \quad n=3, R=Me
\end{align*}
\]

\[
\begin{align*}
396 & \quad n=1, R=H \\
397 & \quad n=2, R=H \\
399 & \quad n=3, R=Me
\end{align*}
\]
Turning to the reaction of the derivative 246 prepared from 53 and the benzyl ester of phenylalanine 286, indicated, however that this was not the sole influence on the reaction. Treatment of 246 with hydrazine in propan-2-ol at reflux gave the bicyclic product 400 in 67% yield. The spectral properties of 400 clearly showed the loss of both the phenoxy and benzyl groups from the precursor 246.

\[
\begin{align*}
\text{246} & \quad R'^{'}=R''=\text{CH}_2\text{Ph} \\
\text{127} & \quad R'^{'}=\text{CH}_2\text{CO}_2\text{Me}, R''=\text{Me} \\
\end{align*}
\]

Similarly, 127, obtained from 53 and dimethyl aspartate 126, on treatment with hydrazine in propan-2-ol at 60 °C gave 401 in 43% yield. In this case, if the reaction was carried out at reflux, some ester exchange occurred and a mixture of the methyl and 2-propyl esters was formed.

Presumably with both 400 and 401 the conformation required for ring closure is less disfavoured than in the case of 396 and 397 because of the substituent R'. However the question as to which ring forms first is not clear, and it might be considered that these double cyclisations are observed because the rate of closure to the imidazole is increased so that this ring is formed first and the triazole second, whereas in the previous system the triazole ring is formed first and this precludes the formation of the imidazole ring. Subsequent experiments suggested, however, that the process is more complex than this.

Treatment of 402, prepared from 53 and L-alanine methyl ester, with hydrazine in propan-2-ol at reflux gave the triazole 404 (71%), apparently reproducing the behaviour of the non-substituted derivative 395. Treatment of 403, prepared from 53 and methyl 2-aminobutanoate, gave a 9:1 mixture of 405 and 407, from which 405 could be isolated in 70% yield. When the reactions were carried out at 0 °C, however, the imidazoles 408 and 305 were obtained in 77% and 85% yields respectively. Attempts to react 246 with hydrazine at room temperature lead only to the bicyclic triazole product 400, and the dimethyl ester 127 did not react with hydrazine at this temperature, only starting material being isolated from the reaction mixture. In a further experiment, after 305 had been formed at 0 °C the reaction mixture was heated to reflux and monitored by TLC. The imidazole slowly decreased in concentration with time and the triazole concentration increased, so that after a period of 5 h only the triazole 405 could be isolated from the reaction mixture.

These reactions are clearly delicately balanced and therefore the benzyl ester 293 was prepared, since it was expected that the leaving propensity of the benzyl group would
encourage the formation of 407. Treatment of 293 with hydrazine in boiling propan-2-ol gave a 1:1.2 mixture of 406 and 407, which was transformed into a 1:9 mixture, from which 407 could be isolated in 72% yield, when the reaction was carried out at 25 °C.
Finally, further insight into the reaction came from examination of the transformations of the imidazolone 305. Treatment of 305 with hydrazine and methanol in propan-2-ol at 80 °C gave the bicyclic tetraazaoctane 407, whereas a similar treatment without hydrazine gave the urea 310. Each of these reactions, and that in which the reaction mixture containing 305 is converted to 405, differs in the components dissolved in the propan-2-ol and it is this difference that presumably results in the different transformations that occur. The reaction mixture from 403 contains a mole equivalent of phenol and 0.2 mole equivalents of hydrazine and is presumably acidic, whereas the direct reaction of 305 contains a mole equivalent of hydrazine and is basic while the reaction mixture leading to 310 is approximately neutral. Finally attempts to convert the tetraazaoctane 407 to the monocyclic triazole 405 by heating to reflux in propan-2-ol containing a mole excess of methanol failed to have any effect. The simplest coherent reaction scheme would be that in which the primary reaction is to form the imidazolone which can then ring close to the bicyclic tetraazaoctane. The formation of the monocyclic triazole arises via ring opening of the imidazolone and reclosure to the thermodynamically more stable triazole ring system.

Treatment of 246 with methylhydrazine gave two products, neither of them bicyclic. One compound was the expected triazole 411 while the other was identified as the isomer 409, in which the unsubstituted nitrogen of the methylhydrazine had acted as the initial nucleophile. The structures of 409 and 411 were determined by n.O.e. experiments. Irradiation of the Me group protons in 411 caused enhancement of the NH, CH2 and aromatic protons whereas irradiation of the Me group in 409 gave only enhancement of the NH2 protons. These observations were supported by other n.O.e. experiments in which the NH resonance signals were irradiated. Treatment of 403 with methylhydrazine gave only 410.

![Chemical structures](image)

The formation 391, 392, 410, and 411 indicates that the substituted nitrogen of the hydrazine is the most nucleophilic and the failure to observe the products of ester hydrazine cyclisation can be attributed to this mode of reaction requiring the formation of a quaternary nitrogen. Presenting a more sterically hindered centre to the substituted hydrazine may lead to the formation of more of the product from the initial reaction of the unsubstituted nitrogen. The N-methyl substituted derivative 398, however, on treatment with methylhydrazine gives a ca 50:50 mixture of 412 and 413, the former arising from initial nucleophilic addition of the N-methyl group.
and the latter from the N-H group, a similar ratio to that found for the reaction of 246 with methylhydrazine. The triazoles 412 and 413 were again distinguished by n.O.e. experiments. Irradiation of the exocyclic N-Me group causing enhancement of the ring N-Me signal in 412 and irradiation of the ring N-Me group showing enhancement of the exocyclic N-Me and the acyclic methylene signals, whereas irradiation of the exocyclic N-Me in 413 gave only enhancement of the acyclic methylene signals and irradiation of the ring N-Me gave enhancement only of the NH₂ signals.

\[
\text{PhO} \begin{array}{c}
\text{H₂N} \\
\text{NCN} \\
\text{N} \\
\text{Me} \\
\end{array} \begin{array}{c}
\text{CO₂Me} \\
\text{Me} \\
\text{Me} \\
\text{C} \\
\end{array} \rightarrow \begin{array}{c}
\text{H₂N} \\
\text{N} \\
\text{N} \\
\text{Me} \\
\end{array} \begin{array}{c}
\text{N} \\
\text{Me} \\
\text{Me} \\
\text{C} \\
\end{array} \begin{array}{c}
\text{CO₂Me} \\
\text{Me} \\
\text{Me} \\
\text{C} \\
\end{array} \\
\text{N} \\
\text{Me} \\
\text{Me} \\
\text{C} \\
\end{array}
\]

\[398 \rightarrow 412\]

\[
\begin{array}{c}
\text{H₂N} \\
\text{Me} \\
\text{N} \\
\text{N} \\
\end{array} \begin{array}{c}
\text{N} \\
\text{Me} \\
\text{Me} \\
\text{C} \\
\end{array} \begin{array}{c}
\text{CO₂Me} \\
\text{Me} \\
\text{Me} \\
\text{C} \\
\end{array} \\
\text{N} \\
\text{Me} \\
\text{Me} \\
\text{C} \\
\end{array}
\]

\[413\]

6.3 Conclusion

The reaction of hydrazines with pseudoureas of the type 394 is clearly influenced by both the nature of 394 and that of the specific hydrazine involved. Careful control of the reaction conditions and the leaving group propensities on the substrate can, however, give the desired bicyclic tetraazaoctanes in most cases in which there will be a substituent on C-7 of the tetraazabicyclooctane. However, it appears that once again in this system the formation of bicyclic molecules containing 6-membered rings is precluded. In all of the examples investigated the triazole appears to be the thermodynamically preferred product while, at least in some cases, the imidazole is kinetically preferred.
Stereoisomerism of N-cyano-O-phenylisoureas

7.1 Introduction

A variety of N-cyano-O-phenylisoureas show, in their $^1$H n.m.r. and $^{13}$C n.m.r. spectra, the presence of two isomers at ambient temperature. Gradual heating of the samples causes the peaks to broaden, coalesce, and eventually become sharp at elevated temperatures. This process is reversible, the original isomeric mixture being obtained on cooling to ambient temperature.

N.m.r. spectroscopy provides the means to study intramolecular processes with activation energies of 5 to 25 Kcal/mol. In the rotation about a bond there are certain energetically favoured positions of the substituents. For example, the dependence of the energy on the angle of rotation about a double bond is shown. \(^{167}\) To convert the isomer A into the isomer B it is necessary to supply the free energy of activation $\Delta G^{+}_{AB}$. The energy $\Delta G^{+}_{BA}$ that must be supplied for the reverse isomerisation differs by $\Delta G^0$ from $\Delta G^{+}_{AB}$.

The magnitude of the free enthalpy of activation determines the rate of thermal isomerisation. The rate constant $k'$ is related to $\Delta G^{+}$ in accordance with the Eyring equation. \(^{168}\)

$$k' = K(K_BT/h) \exp[-\Delta G^{+}/RT]$$

$K_B=$Boltzman's constant, $h=$Planck's constant

$R=$gas constant, $T=$absolute temperature

$K=$transmission coefficient
Isomerisation of this nature can be followed particularly readily by $^1$H n.m.r. spectroscopy when $\Delta G^\circ$ is small so that the concentration of isomers are comparable.

The shape of the signal in the transition region can be used to determine the rate constants. One simple method is to make use of the line separation $\Delta v$ found for the spectrum at low temperature and the coalescence temperature, $T_C$, this being the temperature at which the two signals just coalesce. The rate constant $k'$ of the chemical exchange at the coalescence temperature $T_C$ is given by:

$$k' = \pi \Delta v / \sqrt{2} \quad 7.2$$

This equation is valid for the two states having equal populations and lifetimes.$^{169,170}$ The signal width must be small in comparison with the signal separation.

Combination of equations 7.1 and 7.2 allows approximate free energies of activation for the isomerisation at the temperature of coalescence to be determined, when the transmission coefficient is assumed to be unity.

$$\Delta G^\ddagger = RT_C[\ln(T_C) - \ln(k') + 23.760] \quad 7.3$$

There are in principle three possible mechanisms for the isomerisation observed in $N$-cyano-$O$-phenylisoureas and related imines.

1) **Syn-anti isomerisation** in which the nitrile substituent describes a circle about the axis of the $C=N$ double bond. This mechanism proceeds via a dipolar intermediate and is favoured by polarisation of the $C=N$ double bond. The $sp^2$-hybridization of the nitrogen atom, and hence the bond angle ($C-N-CN$) is retained.

2) **Syn-anti isomerisation via inversion of the imine nitrogen** through a linear $C-N-CN$ transition state in the isourea plane (lateral shift mechanism). The bond angle ($C-N-CN$) increases to 180° in the transition state. The $C=N$ double bond is, to a first approximation, unaffected.
There has been considerable discussion as to which of these mechanisms operates in imine isomers of this sort. The inversion mechanism is favoured for the N-phenylimine 414, as a result of its remarkably lower barrier to rotation (21 Kcal/mol), since there is no known reason for such a low torsional barrier in a relatively unactivated double bond. However, the N-phenyl group would be expected to stabilise a diagonal transition state.

Furthermore, there is a similar effect of the substituent Z on the syn-anti isomerisation in imines (X₂C=NZ) and on the inversion of the sp³ hybridised nitrogen of aziridines. Electronegative substituents on nitrogen are expected to decrease the rate of inversion because of the tendency of such substituents to increase the s character of the unshared electron pair on nitrogen. In the planar transition state this electron pair must be in a p orbital. Conjugative or overlap effects, especially of the p-p type, should increase the rate of inversion because such effects are greater in the planar than in the non-planar system. Thus the isomerisation rate increases rapidly as the substituent Z is varied in the order:

\[ \text{RO} \equiv \text{R₂N} \text{<halogen<alkyl<aryl<acyl}} \]

The substituents X on the imino carbon atom also increase the inversion rate, the order being:
However, care must be taken in taking this analogy with nitrogen inversion too far. The barrier to rotation in N-(1,2,3-trimethyl-2-butenylidene) benzenesulphonamide 415 is considerably lower than that in N-isopropylideneaniline 414 ($\Delta G^\dagger=16.4$ Kcal/mol compared to 20.3 Kcal/mol).

\[
\text{SO}_2\text{Ph}
\]

\[
\text{N}^+\]

\[
\text{Me} \quad \text{Me}
\]

\[
\text{Me} \quad \text{Me}
\]

415

This can be attributed to the benzenesulphonyl group being considerably more effective than phenyl in lowering the barrier to rotation by delocalisation of electrons on nitrogen. However, in the corresponding N-substituted aziridines, the free energies of activation, which must correspond to barriers to inversion of pyramidal nitrogen, exhibit a different order in their relative magnitudes. Thus the coalescence temperature of N-phenylaziridine ($T_c=-40 \degree C$) is actually somewhat lower than that for N-benzene-sulphonylaziridine ($T_c=-30 \degree C$). Clearly different factors are more important in the two systems.

The inversion mechanism is favoured in the guanidines 416,175,176 because of steric effects. As the series R=H, CH$_3$, CH$_2$CH$_3$, CH(CH$_3$)$_2$ is ascended, the isomerisation barrier decreases, while for the guanidinium salts 417 substantial increases in the barrier occur. The introduction of ortho-substituents causes the phenyl ring to be twisted out of the plane of the C=N double bond to stabilise the transition state for inversion but not rotation. Rotation would be hindered by the substituents R, as can be seen for the guanidinium salts 417 in which the lone pair of electrons is fixed and inversion is consequently impossible, hence the rapidly increasing barrier.
Additionally, good hydrogen bonding solvents, for example methanol, raise the barrier by approximately 1 Kcal/mol compared to that in non-hydrogen bonding solvents, for example chloroform, which is consistent with operation of the inversion mechanism but not with the rotation mechanism.

The small influence of the polarity of the solvent on the rate of isomerisation of tetramethyl-phenylguanidine 418 also points to inversion.\textsuperscript{175,177} A polar solvent should facilitate isomerisation by rotation as has been found for example for ketene aminals.\textsuperscript{178}

\[
\text{PhN} = \text{Me}^*\text{NMe} \quad 418
\]

In N-arylimines of the type 419 the influence of \textit{para} substituents of the aryl residue on the free enthalpy of activation of the syn-anti isomerisation follows the Hammett relation.\textsuperscript{171,177,179,180} Irrespective of the substituent \(\text{Ar}\) the reaction constant is \(\rho=1.7\).\textsuperscript{171} On the other hand a substituent \(X\) in benzylideneamines 420 has a much smaller influence \((\rho=0.4)\).\textsuperscript{181} The difference in the effects of variations at the N or the C atom has been taken as evidence of inversion,\textsuperscript{171} with a linear transition state involving a contribution from a resonance structure of type 421.

\[
\text{419}
\]

\[
\text{420}
\]

\[
\text{421}
\]

The rotation mechanism has been favoured by Marullo and Wagener\textsuperscript{182,183} on the grounds that the attachment of lone pair bearing substituents to the imino carbon atom dramatically lowers the barrier. Thus they accept that the low activation energy for the isomerisation of imines relative to olefins and the effects of substituents on the rate, particularly the insensitivity of the isomerisation rate to substituents on the aryl group bonded to the imino.
carbon in compounds such as $\text{Ar}_1\text{Ar}_2\text{C}=\text{NCH}_3$, can be interpreted in terms of a mechanism which proceeds via a linear transition state in which the $\pi$ bond remains intact and the non-bonded electron pair on nitrogen rehybridises to a $p$ orbital. They contend, however, that the very low activation energy and large isomerisation rate found for iminocarbonates is more easily explained in terms of a mechanism proceeding through a polar transition state in which unpairing of the electrons of the $\pi$ bond has occurred. Since oxygen is more electronegative than carbon they argue that substitution of methoxy for alkyl or aryl groups attached to the imino carbon might be expected to decrease the extent of polarization of the carbon-nitrogen bond. Resonance effects would operate in an opposite fashion, but can be neglected since they do not make an important contribution to the ground state. The over-all effect would be stabilization of the ground state. However, resonance effects become important in excited states and, in this case, would be expected to stabilise the transition state by delocalisation of the positive charge being generated on the imino carbon. The expected net effect should be a decrease in the required activation energy.

Furthermore, in the series of imines 422 ($\text{R=CH}_3$, $\text{OCH}_3$, $\text{SCH}_3$) and 423, they report\textsuperscript{183} that the isomerization rates parallel the relative conjugative ability of the groups bonded to the imino carbon ($\text{X=N>S>O>C}$) rather than their relative electronegativities ($\text{O>N>S>C}$). This, it is argued, is also evidence for the rotation mechanism.

However, in a similar study\textsuperscript{184} on the isomerisation rate of iminocarbonates relative to imines, the rates were interpreted in terms of the greater electron withdrawing ability of oxygen relative to carbon, this being consistent with the lateral shift mechanism.

Also, in a study on N-cyanoimines of type 424 ($\text{R=OCH}_3$, $\text{SCH}_3$, $\text{NDCH}_3$), the ability of these groups to stabilise a linear transition state 425 was suggested to be consistent with the lateral shift mechanism.\textsuperscript{185} It should be noted that these results also fit with the theory of conjugative ability of the heteroatom, following the scale previously proposed.\textsuperscript{183}
Marullo and Wagner\textsuperscript{183} do acknowledge that if the lateral shift mechanism is modified to include $\Pi$ bond participation, then both the rotational and lateral shift mechanisms are consistent with the data, and electronic effects cannot be used to make a choice between the two pathways. The transition states for the two pathways however differ in geometry. From theoretical calculations on the isomerisation barriers of compounds having sp$^2$ nitrogen of the type NH=(C=)$n$NH,\textsuperscript{186} it was found that the lateral shift pathway requires less energy than the rotational pathway for $n=0$ or $n=2$, but for $n=1$ or $n=3$ the rotational pathway is slightly favoured.

A detailed study of the isomerisation of compounds of type 426\textsuperscript{172} has revealed that there is a slow process due to restricted rotation about the C-N single bond, and that the syn-anti isomerisation is much more rapid.

With increasing electronegativity of the Z group in 426a there is an increasing contribution from the polar form 426b, resulting in greater double bond character in the C-N single bond. This is supported by the fact that the order of increasing activation enthalpy for Z is:

\[ \text{COC}_6\text{H}_5 < \text{COCH}_3 < \text{CN} < \text{NO}_2 \]

For Z=COCH$_3$ one would expect the methyl signal to be split as a result of the double bond character of the C-N bond, which was not the case. This was explained on the ground that the carbonyl group and the C=N double bond adopts a cisoid configuration to minimise steric effects. A strong piece of evidence supporting hindered rotation about the single bond is that in the N-acetylguanidine 427 no splitting was observed above -100 °C.
Hindered rotation, however, does not readily explain why N-cyano-N',N''-dimethylguanidine 428 has a higher barrier than N-cyano-N',N',N'',N''-tetramethylguanidine 429.

These authors then go on to state that a mixed mechanism, as discussed by Raban, is also a possibility, but as yet there is no experimental evidence to support it. This mixed mechanism is based on the fact that the only differences between the two transition states for the rotation and inversion mechanisms is the C-N-CN bond angle, and associated differences in the hybridization of the nitrogen and its formal charge. The angle is ca 109° in the rotation model and 180° in the inversion model. However the angle need not be restricted to one of these two values, but might well adopt values between the two extremes. Thus, a continuum of mechanisms with intermediate bond angles is possible. Substituents such as methoxy, methanethio, and dimethylamino which can stabilize a positive charge would effect a diminution of the bond angle while substituents which lower barriers to nitrogen inversion would result in transition states with larger bond angles.
7.2 Results and Discussion

The following tables (Tables 1, 3, 4) show the results of $^1$H n.m.r. spectroscopy experiments to determine the barrier to rotation in N-cyanoimines and related compounds. The $\Delta G^\ddagger$ values were calculated using the assumptions implicit in equations 7.2 and 7.3.

Table 1

<table>
<thead>
<tr>
<th>$T_c$ (°K)</th>
<th>$\Delta V$ (Hz)</th>
<th>$K^{-1}$ (s$^{-1}$)</th>
<th>$\Delta G^\ddagger$ (kcal/mol)</th>
<th>Solvent</th>
<th>Isomer ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>296</td>
<td>308</td>
<td>34.50</td>
<td>76.6</td>
<td>15.4</td>
<td>CDCl$_3$</td>
</tr>
<tr>
<td>296</td>
<td>322</td>
<td>38.19</td>
<td>84.8</td>
<td>16.0</td>
<td>DMSO</td>
</tr>
<tr>
<td>312</td>
<td>279</td>
<td>5.12</td>
<td>11.3</td>
<td>14.9</td>
<td>CD$_2$Cl$_2$</td>
</tr>
<tr>
<td>297</td>
<td>$&gt;$443</td>
<td>$&gt;$25</td>
<td></td>
<td></td>
<td>DMSO</td>
</tr>
<tr>
<td>301</td>
<td>299</td>
<td>5.92</td>
<td>13.2</td>
<td>16.0</td>
<td>CD$_2$Cl$_2$</td>
</tr>
<tr>
<td>298</td>
<td>286</td>
<td>5.96</td>
<td>13.2</td>
<td>15.3</td>
<td>CDCl$_3$</td>
</tr>
<tr>
<td>414</td>
<td>263</td>
<td>140.66</td>
<td>312.5</td>
<td>12.3</td>
<td>CDCl$_3$</td>
</tr>
<tr>
<td>313</td>
<td>283</td>
<td>19.31</td>
<td>42.9</td>
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<td>50.42</td>
<td>112.0</td>
<td>16.0</td>
<td>CDCl$_3$</td>
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From the results (Table 1) it can clearly be seen that increasing the electronegativity of the substituent (as assessed by the Hammett $\sigma_p$ values,$^{191}$ Table 2) attached to the imine nitrogen leads to an increase in the activation barrier, as would be expected on the basis of the nitrogen inversion model, since the $s$ character of the nitrogen lone pair is increased.
Table 2

<table>
<thead>
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<th>Functional Group</th>
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<tr>
<td>CONH₂</td>
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<tr>
<td>COCH₃</td>
<td>0.50</td>
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<tr>
<td>CN</td>
<td>0.66</td>
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<tr>
<td>COCF₃</td>
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<tr>
<td>OCOCH₃</td>
<td>0.31</td>
</tr>
<tr>
<td>OCOCF₃</td>
<td>&lt;0.80</td>
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</table>

However, other factors must also apply since the activation energies for the O-phenylisoureas 296, 312, and 301 are all very similar despite the large differences in electronegativity. This seems to suggest that other factors not present in 296 are leading to the increase in ΔG‡ for 312 and 301. One possibility is that hydrogen-bonding (H-bonding) is occurring between the NH and the carbonyl oxygen groups as shown.

\[
\begin{array}{c}
\text{R} \\
\text{N}^+ \\
\text{PhO} \\
\text{N} \equiv \text{H} \\
\text{Ph} \\
\end{array}
\]

This type of interaction would be expected to be much weaker, in comparison, for the N-cyano compound. This H-bonding would be expected to lead to an increase in the activation energy that must be supplied to convert one isomer to another. However, it would be expected that this would be reflected in the isomer ratio since this represents the stability of one isomer relative to the other, and we would expect that the H-bonded isomer would be more stable. That this is not the case is clearly seen since the isomer ratio for both 312 and 301 is close to unity. The fact that the ratio is not unity in 296 suggests that other factors also play a part. Thus the greater steric hindrance present when the CN group is cis to the benzyl group will lead to this being slightly disfavoured but for 312 and 301 this is counter-acted by the H-bonding which brings the isomer ratio back to unity.

The high electronegativity of the trifluoroacetyl group combined with strong H-bonding could explain why in the ¹H n.m.r. spectrum of 297 only one isomer is seen in the temperature range 193 - 443 K. Indeed at high temperatures product breakdown seemed to occur before any stereoisomerisation process. This suggests that the barrier to inversion in this compound is very high, probably greater than 25 Kcal/mol, leading to the conclusion that only the form 297a exists at ambient temperature.
Further support for the H-bonding theory comes from the fact that for the N-methyl O-phenylisoureas 313 and 314, the barriers to rotation are lower than for 296 and 297. In the case of 313 the decrease is small, as would be predicted since only weak H-bonding to the CN functional group is predicted. For 314 the decrease is dramatic, the energy changing from greater than 25 Kcal/mol for 297 to 16.0 Kcal/mol for 314. This seems to suggest that H-bonding plays a considerable role in stabilising one rotamer of 297 over the other. As would be expected the isomer ratio is also no longer 1:0 but 1.5:1, reflecting this loss of H-bonding. For 313, however, the isomer ratio has gone to unity from 1.2:1 but the change in solvent makes it difficult to interpret this.

Substitution of the methoxy for the phenoxy group in going from 296 to 414 leads to a decrease in activation energy which suggests that the electrons of the oxygen are more available to stabilise a transition state of the type 425, as would be expected.

Addition of the extra oxygen in going from 297 to the trifluoroacetoxy derivative 298 leads to a decrease in the activation energy. Based on the fact that acetoxy has a smaller $\sigma_p$ value than acetyl it is to be expected that trifluoroacetoxy has a smaller $\sigma_p$ value than trifluoroacetyl, which explains the observed decrease in $\Delta G^\ddagger$.

In going from the O-phenylisoureas to the corresponding guanidines a decrease in activation energy is seen (Table 3). This is to be expected since nitrogen has greater conjugative ability than oxygen and so is better able to stabilise the transition state, be it that of the rotation or the inversion mechanism. For N-cyano guanidine 299 this decrease leads to an inversion barrier of less than 5 Kcal/mol which cannot be detected by $^1$H n.m.r. spectroscopy, and no line broadening is seen even at temperatures as low as 193 K. For the guanidines 311 and 304 the decrease in activation energy is quite small (<2 Kcal/mol), which suggests that the decrease due to transition state stabilisation is offset by an increase due to H-bonding. However, for the trifluoroacetyl derivative 300 the decrease is apparently very dramatic. The reason for this is unclear, since it would be expected that this compound would also show increased H-bonding to compensate for the decrease of $\Delta G^\ddagger$ brought about by adding the second nitrogen. Possibly a steric factor, in that the more bulky trifluoroacetyl group now prefers to adopt a conformation more like the linear transition state of the inversion mechanism now exists.
Interestingly, the imidazolidinone 307 does not show rotamers in its $^1$H n.m.r. spectrum at temperatures down to 193 K. This could be taken as evidence for hindered rotation about the single bond in a similar manner to 427. Hobbs$^{83}$ found further evidence to support hindered rotation about the N-C single bond for the O-phenylisourea 430. In this case, competition for conjugation of the nitrogen lone pair between the cyanoimino and the o-methoxycarbonyl groups would be expected to lower the barrier to isomerisation. This was seen in that only one set of signals was observed in both the $^1$H and $^{13}$C n.m.r. spectra at ambient temperature. A similar argument can be made in comparing the O-phenylisoureas 398 and 432 (structures on p119), where competition for the nitrogen lone pair due to the presence of the benzyloxy carbonyl group in 432 leads to a lowering of the activation barrier, hence only one set of signals is seen in the $^1$H and $^{13}$C n.m.r. spectra, even at 213 K.
Benzoxazine 433 also exhibited only one set of peaks at ambient temperature which could be interpreted as being consistent with the mechanism involving hindered rotation about the C-N single bond.

For the N-cyano-guanidines (Table 4) the barrier to rotation is fairly constant at 15-16 Kcal/mol as would be expected if the attached side chains have no actual part in the rotation process. However, the isomer ratios seen at low temperature vary quite widely which indicates that in these cases the two isomers vary considerably in energy. For the relatively unhindered side chains in 395, 63, and 398 the ratios are quite close to unity, with the advantage one isomer gains by any H-bonding that is present being offset by the increased steric hindrance in that isomer. In the series 127, 131, and 134, however, the ratio decreases going from 1.3:1 to 1:1. As the steric bulk of the side chain as a whole is increasing down the series, with the steric bulk close to the rotating cyano group increasing most, this seems to suggest that the most stable conformation alters from one with the β-ester closer to the cyano group in 127 to one with the α-ester closer in 134. This removes the bulky t-butyl group to a more remote position, and simultaneously reduces the steric hindrance around the rotating group. The system apparently finds it much harder to accommodate a phenyl group, as seen for the high isomer ratio of 434. There must be some degree of steric hindrance no matter what orientation the phenyl group adopts. For the O-phenylisoureas 152 and 146 the bulk of the side chain groups could conceivably lead to a trans orientation of the cyano and nitrogen being favoured over cis despite the loss of H-bonding in this case, however, the isomer ratios suggest that the whole aspartate portion of the molecules are in positions which allows for both isomers with minimal steric constraint. For the carbocyclic analogues 256 and 254 this trans orientation should be favoured on steric grounds, since in the cis orientation steric hindrance from the methyl ester group at position 4 is to be expected. The large ratios seen for 402 and 403 are more difficult to explain since the steric bulk of the side chains is less than in the case for 134. Obviously an interaction, possibly H-bonding, is present in one isomer but not the other leading to the ratio seen. In these cases the side chain must be in positions such that the steric hinderance they present is minimal.
Table 4

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<th>Tc (°K)</th>
<th>ΔV (Hz)</th>
<th>K⁻¹ (s⁻¹)</th>
<th>ΔG⁺ (Kcal/mol)</th>
<th>Solvent</th>
<th>Isomer ratio</th>
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PhO \text{N} \text{C} \text{N} H \text{C} \text{O}_2 \text{Me}

PhO \text{N} \text{C} \text{N} H \text{C} \text{O}_2 \text{Me}

PhO \text{N} \text{C} \text{N} \text{C} \text{O}_2 \text{R}'

PhO \text{N} \text{C} \text{N} \text{C} \text{O}_2 \text{R}''

127 R'=Me, R''=Me
131 R'=tBu, R''=Me
134 R'=Me, R''=tBu

PhO \text{N} \text{C} \text{N} \text{C} \text{O}_2 \text{R}

152 R=CH₃CH₂CH₂
146 R=PhCH₂
7.3 Conclusion

It can clearly be seen that altering the electronegativity of the group attached to the imino nitrogen leads to a change in $\Delta G^\ddagger$ that can be predicted in a qualitative sense but not in a quantitative sense. Similarly, a prediction can be made on changing the substituent attached to the imino carbon. The actual size of the change depends, however, on both the degree of H-bonding possible, and the steric constraints present within the molecule, since these alter the minimum energies of the two rotamers. The contribution of these factors cannot be easily predicted, hence $\Delta G^\ddagger$ values are best obtained by experiment rather than by prediction based on previous work. The results do not point conclusively to any one mechanism. Indeed the complex nature of the variation of $\Delta G^\ddagger$ with functional groups seems to point to a spectrum of mechanisms, as first suggested by Raban.174
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<th>Section</th>
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<td>Preparation of urea 306</td>
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<td>Preparation of methyl 4-(5-methylamino-(3-amino-s-triazole)) butanoate 399</td>
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8.1 Apparatus and reagents

Microanalyses were carried out by the Microanalytical Section of the Chemistry Department, University College London, except for $^{19}$F analyses which were carried out by the microanalytical department of Sandoz, Basel, Switzerland. In cases where a microanalysis could not be obtained high resolution mass spectrometry was used. Melting points were determined on a Reicher melting point apparatus and are uncorrected. The infra-red (I.R.) spectra were recorded on a Perkin-Elmer PE-983 spectrophotometer using potassium bromide pellets (unless otherwise stated); absorptions are recorded in terms of frequency ($\nu_{\text{max}}$ in cm$^{-1}$). The proton nuclear magnetic resonance ($^1$H n.m.r.) spectra were recorded on a Varian Gemini-200 (200 MHz) or a Varian VXR-400 (400 MHz) spectrometer, and are reported in $\delta$ values relative to tetramethylsilane as internal standard. The spectra were recorded in deuterochloroform (C), methanol-d$_4$ (M), or dimethylsulphoxide (D) solution. The following abbreviations are used in signal assignments; s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), m (multiple), b (broad). $^{13}$C n.m.r. were recorded at 50 MHz on the Varian VXR-400 spectrometer. Mass spectra were recorded on a VG7070H mass spectrometer with Finnigan Incos II data system at University College, or on a VG ZAB-2F (E.I.) or VG 12-250 (C.l.) mass spectrometer at the London School of Pharmacy. Only molecular ions (M$^+$), if present, base peaks and the next two peaks due to ions of maximum abundance are reported. Optical activity measurements were made on an Optical Activity Ltd polarimeter using a 10 cm cell.

Commercially available Merck Kieselgel 60 F$_{254}$ plates were used for analytical thin layer chromatography (t.l.c.). They were visualised with ultra-violet light or iodine. Column chromatography was performed using Merck flash silica (200-400 mesh) as stationary phase.

t-Butyllithium (in hexanes) was obtained commercially from the Aldrich Chemical Co Ltd and periodically titrated with 2,5-dimethoxybenzylalcohol according to the literature method.$^{187}$ All experiments using water sensitive reagents were carried out under an atmosphere of dry argon. Solvents were purified by standard methods. In particular tetrahydrofuran was freshly distilled from sodium-benzophenone-ketyl. Glassware for such reactions was dried by flaming with a Bunsen burner under a vigorous stream of dry argon. All syringes were dried in an oven at 130 °C overnight and flushed with argon prior to use. Temperatures below 0 °C were obtained by cooling acetone with carbon dioxide ("cardice bath").

HPLC was carried out using an (R)-N-2,4-dinitrobenzoyl phenylglycine (CHI-D-PGC 250A, Anachem) stationary phase and a mobile phase composed of hexane:dichloromethane:propan-2-ol in the ratio 92:8:5.

8.2 Preparation of N-cyano-N'-1-t-butyloxycarbonyl-2-methoxycarbonylethyl-O-phenylisourea 131

To a stirred solution of $\alpha$-tBu-$\beta$-Me-aspartate 130 (2.15 g, 10 mmol) in propan-2-ol (200 ml) was added a slurry of diphenyl cyanocarbonimidate 53 (2.15 g, 10 mmol) and the mixture was stirred at room temperature for 72 h. The solvent was removed by evaporation in vacuo to yield a
yellow oil which was purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:4), to give 131 (3.00 g, 84%) as a pale yellow oil.

M.S. m/e : 348 (MH+), 260 (M+87), 246 (M+101), 94 (M+253).

1H n.m.r. (C), δ: 7.50-7.00 (m, Ph), 6.10 (bd, NH), 4.80 (m, CHCO2Me), 4.70 (m, CHCO2Me), 3.75 (s, OCH3), 3.60 (s, OCH3), 3.10-2.90 (m, CHCO2), 1.50 (s, C(CH3)3), 1.42 (s, C(CH3)3).

13C n.m.r. (C), δ: 171.15, 170.52, 167.91, 167.89, 159.40, 150.81, 150.11, 130.70, 129.65, 127.83, 126.92, 121.36, 115.20, 115.18, 83.83, 52.30, 36.19, 35.23, 27.83.

I.R.(neat): 2195, 1740, 1725, 1625 cm⁻¹.

[α]D: -6.14° (c=1.01, MeOH).

8.3 Preparation of 1-benzyl-2-cyanomino-4-methoxycarbonylmethyl-2-imidazolidin-5-one 128 and 3-benzyl-6-t-butyloxy carbonyl-2-cyanomino-5,6-dihydro-4(3H)-pyrimidinone 132

To a solution of O-phenylisourea 131 (0.24 g, 0.69 mmol) in propan-2-ol (20 ml) was added benzylamine (0.15 g, 1.43 mmol) and the resulting solution was stirred at room temperature for 25 h. During this time a white precipitate formed. The solvent was removed by evaporation in vacuo and the resulting solid dissolved in ethyl acetate and purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:2), to give imidazolidin-5-one 128 (0.051 g, 26%), and 4(3H)-pyrimidinone 132 (0.075 g, 38%). Both products were recrystallised from methanol for analytical purposes.

2-Imidazolidin-5-one 128


M.S. m/e : 287 (MH+), 286 (M+), 105 (M+182), 91 (M+195).

1H n.m.r. (C), δ: 8.49 (bs, NH), 7.42-7.28 (m, Ph), 4.70 (d, PhCH', JH'-H"=26.8 Hz), 4.69 (d, PhCH", JH'-H"=26.8 Hz), 4.41 (dd, CHCH2, JH'-H"=4.0 Hz, JH'-H'=7.2 Hz), 3.65 (s, OCH3), 3.01 (dd, CH'CO2, JH'-H"=4.0 Hz, JH'-H'=17.2 Hz), 2.96 (dd, CH"CO2, JH'-H"=7.2 Hz, JH'-H'=17.2 Hz).
\[ \delta \text{H n.m.r. (C), } \delta: \quad 7.70 \text{(bs, NH), 7.40-7.24 (m, Ph), 5.02 (s, PhCH}_2, \quad 4.17 \text{(t, CHCO}_2, \quad J_H\_H=6.0 \text{ Hz, } J_H\_H=6.4 \text{ Hz), 3.03 (dd, CH\''CH, } J_H\_H=16.8 \text{ Hz, } J_H\_H=6.4 \text{ Hz), 2.95 (dd, CH\''CH, } J_H\_H=16.8 \text{ Hz, } J_H\_H=6.0 \text{ Hz), } \\
\delta \text{C n.m.r. (C), } \delta:\quad 167.34, 165.51, 160.00, 136.19, 128.74, 128.44, 127.78, 115.25, \quad 84.51, 49.83, 44.96, 33.72, 27.76. \]

\[ \text{I.R.: } \quad 2183, 1730, 1700, 1590 \text{ cm}^{-1}. \]

\[ \alpha D: \quad -114^\circ \text{(c=0.30, MeOH).} \]

**Analysis:**
- Calculated for C\(_{14}\)H\(_{14}\)O\(_3\)N\(_4\): C, 58.74; H, 4.89; N, 19.58.
- Found: C, 58.95; H, 4.80; N, 19.44.

**4(3H)-pyrimidinone 132**

- **M.pt:** 143.5-145.5 °C.
- **M.S. m/e :** 329 (MH\(^+\)), 328 (M\(^+\)), 272 (M\(^+\)-56), 91 (M\(^+\)-237).

**Preparation of N-cyano-N\('\)-(1-methoxycarbonyl-2-t-butoxycarbonylethyl)-O-phenylisourea 134**

Triethylamine (0.42 g, 4 mmol) was added to a stirred suspension of α-Me-β-tBu-aspartate-hydrochloride 133 (1.00 g, 4 mmol) in propan-2-ol (30 ml). Diphenyl cyanocarbonimidate 53 (0.99 g, 4 mmol) dissolved in propan-2-ol (10 ml) was added and the resulting mixture stirred at room temperature for 12 h. The propan-2-ol was removed by evaporation in vacuo to give a yellow oil, which crystallised on standing for several hours. The crystals were removed by filtration, washed with ether, and dried in vacuo to give the O-
phenylisourea 134 (1.07 g, 3.1 mmol, 74%). This material was used for further reactions, but a sample was recrystallised from methanol for analytical purposes.

M.pt: 106-108 °C.

M.S. m/e: 348.1716 (C₁₇H₂₁N₃O₅ requires 348.3779)
348 (M⁺+1), 292 (M⁺-55), 170 (M⁺-177), 95 (M⁺-252).

¹H n.m.r. (C), δ: 7.50 (m, m-Ph), 7.30 (m, p-Ph), 7.00 (m, o-Ph), 6.14 (bd, NH), 4.80 (m, CHCO₂Me), 4.70 (m, CHCO₂Me), 3.80 (s, OCH₃), 3.75 (s, OCH₃), 2.95 (m, CH₂CO₂C(CH₃)₃), 1.40 (s, C(CH₃)₃), 1.30 (s, C(CH₃)₃).

¹³C n.m.r. (C), δ: 169.83, 169.78, 169.33, 168.91, 163.27, 159.39, 156.38, 150.84, 130.74, 129.44, 127.88, 126.87, 121.38, 121.24, 121.08, 119.99, 115.43, 114.31, 53.18, 51.90, 45.98, 37.18, 36.44, 28.00, 27.81.

I.R: 2190, 1745, 1705, 1600 cm⁻¹.

[α]D: -16.19° (c=1.10, MeOH).

8.5 Preparation of 1-benzyl-2-cyanolmino-(4-t-butoxycarbonylmethyl)-2-imidazolidin-5-one 135

A solution of O-phenylisourea 134 (0.30 g, 0.86 mmol) and benzylamine (0.096 g, 0.89 mmol) in propan-2-ol (20 ml) was heated to reflux for 2 h. The volume was reduced, by evaporation in vacuo, to one half and then cooled (4 °C, 3 h). The resulting white crystals were removed by filtration, washed with ether, and dried in vacuo to give the imidazolidin-5-one 135 (0.11 g, 0.34 mmol, 40%).

M.pt: 161.5-163.0 °C.

M.S. m/e: 329 (M⁺+1), 328(M⁺), 255(M⁺-73), 91(M⁺-237).

¹H n.m.r. (C), δ: 7.40-7.25 (m, Ph), 4.75 (s, PhCH₂N), 4.40 (dd, CHCH₂, JH⁻H=8.4 Hz, JH⁻H=3.6 Hz), 2.94 (dd, CH²CO₂, JH⁻H=3.6 Hz, JH⁻H=17.2 Hz), 2.66 (dd, CH²CO₂, JH⁻H=8.4 Hz, JH⁻H=17.2 Hz), 1.45 (s, C(CH₃)₃).

¹³C n.m.r. (C), δ: 173.41, 167.95, 161.85, 135.47, 128.29, 127.44, 127.41, 115.18, 81.05, 54.94, 42.23, 35.13, 27.51.
I.R:
2194, 1778, 1728, 1645 cm\(^{-1}\).

[\alpha]D:
0.00°.

Analysis:
Calculated for \(\text{C}_{17}\text{H}_{20}\text{N}_{4}\text{O}_{3}\): C, 62.18; H, 6.10; N, 17.06.
Found: C, 62.03; H, 6.22; N, 16.56.

8.6 Preparation of 1-benzyl-2-cyanomino-4-carbamoylmethyl-2-imidazolidin-5-one 136

Aqueous ammonia (s.g.=0.880, 0.28 ml) was added to a solution of imidazolidin-5-one 128 (0.42 g, 1.47 mmol) in propan-2-ol (20 ml) and the resulting solution was heated to reflux for 3 h. The solvent was removed by evaporation \textit{in vacuo}, the resulting oil redissolved in ethyl acetate (20 ml) and cooled to 4 °C for 6 h. The resulting crystalline product was filtered, washed with ether and dried to give the title compound (0.30 g, 75%).

M.pt: 147-149 °C.

M.S. \(m/e\):
272.0945 (C\(_{13}\)H\(_{14}\)N\(_{5}\)O\(_{2}\) requires 272.0909)
272 (M\(^+\)), 226 (M\(^+\)-45), 169 (M\(^+\)-102), 91 (M\(^+\)-180).

\(^1\text{H}\) n.m.r. (D), \(\delta\):
7.33-7.23 (m, Ph), 4.58 (d, PhCH\(^\prime\), \(J_{H'-H''}=15.72\ \text{Hz}\)), 4.55 (d, PhCH\(^\prime\), \(J_{H'-H''}=15.72\ \text{Hz}\)), 4.32 (dd, CHCH\(_2\), \(J_{H'H''}=4.20\ \text{Hz}\), \(J_{H'-H''}=4.24\ \text{Hz}\)),
2.58 (dd, CH\(^\prime\)CH, \(J_{H'-H''}=4.20\ \text{Hz}\), \(J_{H'-H''}=16.80\ \text{Hz}\)), 2.54 (dd, CH\(^\prime\)CH, \(J_{H'H''}=4.24\ \text{Hz}\), \(J_{H'-H''}=16.80\ \text{Hz}\)).

\(^13\text{C}\) n.m.r. (D), \(\delta\):
174.93, 171.30, 161.99, 136.09, 128.27, 127.18, 127.13, 115.78, 56.51, 42.08, 37.06.

I.R:
3168, 2207, 1749, 1638, 1574 cm\(^{-1}\).

8.7 Preparation of N-cyano-N\(^'\)-(1-t-butyloxycarbonyl-2-benzoxy carbonyl ethyl)-O-phenylisourea 138

A solution of diphenyl cyanocarbonimidate 53 (0.90 g, 3.78 mmol) and \(\alpha\)-tBu-\(\beta\)-Bzl-Asp 137 (0.99g, 3.45 mmol) in propan-2-ol (50 ml) was stirred at room temperature for 15 h. The solvent was removed by evaporation \textit{in vacuo} and the resulting brown oil was purified by flash chromatography, eluting with dichloromethane:methanol (9:1), to give the O-phenylisourea 138 as a pale yellow oil (0.8 g, 53%).
M.S. m/e: 424 (MH+), 368 (M+-55), 188 (M+-235), 91 (M+-332).

$^1$H n.m.r. (C), $\delta$: 7.45-7.00 (m, Ph), 6.20 (bs, NH), 6.10 (bd, NH), 5.27 (m, PhCH$_2$), 5.05 (m, PhCH$_2$), 4.76 (m, CHCO$_2$Me), 4.45 (m, CHCO$_2$Me), 3.05 (m, CH$_2$CO$_2$tBu), 1.44 (bs, C(CH$_3$)$_3$), 1.36 (bs, C(CH$_3$)).

$^{13}$C n.m.r. (C), $\delta$: 170.30, 169.95, 167.73, 159.28, 156.10, 149.74, 135.00, 130.71, 129.76, 129.63, 128.79, 128.53, 128.45, 127.88, 126.84, 121.32, 121.14, 120.9, 120.63, 120.15, 115.39, 83.97, 67.38, 67.07, 52.31, 36.21, 35.37, 27.89, 27.79.


8.8 Preparation of 1-benzyl-2-cyanolimino-4-benzylxycarbonylmethyl-2-imidazolidin-5-one 139 and 3-benzyl-6-t-butoxycarbonyl-2-cyanolimino-5,6-dihydro-4(3H)-pyrimidinone 132

To a solution of O-phenylisourea 138 (0.4 g, 0.95 mmol) in propan-2-ol (10 ml) was added benzylamine (0.2 g, 1.89 mmol), and the resulting solution was stirred at room temperature for 8 h. The solvent was removed by evaporation in vacuo and the products separated by column chromatography, eluting with ethyl acetate:cyclohexane (1:2), to give a coeluting mixture of imidazolidin-5-one 139 and pyrimidinone 132.

2-imidazolidin-5-one 139

$^1$H n.m.r. (C), $\delta$: 8.77 (bs, NH), 7.40-7.20 (m, Ph), 5.15 (d, PhCH$^+$CO$_2$, J$_{H^+-H^p}$=12 Hz), 5.10 (d, PhCH$^+$CO$_2$, J$_{H^+-H^p}$=12 Hz), 4.61 (s, PhCH$_2$N), 4.40 (dd, CHCH$_2$, J$_{H^+-H^p}$=6.8 Hz, J$_{H^+-H^p}$=4.0 Hz), 3.00 (dd, CH$^+$CH, J$_{H^+-H^p}$=4.0 Hz, J$_{H^+-H^p}$=17.6 Hz), 2.86 (dd, CH$^+$CH, J$_{H^+-H^p}$=6.8 Hz, J$_{H^+-H^p}$=17.6 Hz).

8.9 Preparation of t-Butyl 2-benzylxycarbonylamino-3-methoxycarbonyl-4-phenyl-(2S)-butanoate 144

The title compound was prepared by the method of Baldwin. The two diastereoisomers of the product were separated by column chromatography eluting initially with hexane, and then gradually increasing the polarity with ether to a final concentration of 15%.
**Major diastereoisomer 144a**

Yield: 42%.

M.pt: 68-70 °C.

$^1$H n.m.r. (C, $\delta$):

- 7.41-7.18 (m, Ph), 5.76 (bd, NH, J_{NH,CH}=9.6 Hz), 5.16 (d, PhCH'0, J_{H',H}=12.4 Hz), 5.15 (PhCH''O, J_{H,H''}=12.4 Hz), 4.45 (dd, NHCH, J_{H,CH}=3.6 Hz, J_{NH,CH}=9.6 Hz), 3.63 (s, OCH$_3$), 3.36 (ddd, CHCO$_2$Me, J_{H,H''}=8.0 Hz, J_{H,H''}=7.2 Hz, J_{H,H''}=13.8 Hz), 2.81 (dd, CHCH''Ph, J_{H,H''}=8.0 Hz, J_{H,H''}=13.8 Hz), 1.50 (s, C(CH$_3$)$_3$).

**Minor diastereoisomer 144b**

Yield: 15.3%.

M.pt: 51-53 °C.

$^1$H n.m.r. (C, $\delta$):

- 7.40-7.18 (m, Ph), 5.61 (bd, NH, J_{NH,CH}=8.4 Hz), 5.11 (s, PhCH$_2$O), 4.58 (dd, NHCH, J_{H,H}=4.4 Hz, J_{NH,CH}=8.4 Hz), 3.62 (s, OCH$_3$), 3.18 (ddd, CHCO$_2$Me, J_{H,H}=4.4 Hz, J_{H,H''}=4.7 Hz, J_{H,H''}=5.2 Hz), 3.13 (dd, CHCH''Ph, J_{H,H''}=4.7 Hz, J_{H,H''}=13.2 Hz), 2.86 (dd, CHCH''Ph, J_{H,H''}=5.2 Hz, J_{H,H''}=13.2 Hz), 1.50 (s, C(CH$_3$)$_3$).

### 8.10 Preparation of t-butyl 2-amino-3-methoxycarbonyl-4-phenyl-(2S)-butanoate 145a

The title compound was prepared by the method of Baldwin$^{70}$ using the purified diastereoisomer 144a.

$^1$H n.m.r. (C, 200 Mhz, $\delta$): 7.40-7.14 (m, Ph), 3.70-3.65 (m, NHCH), 3.53 (s, OCH$_3$), 3.25-2.85 (m, PhCH$_2$CH and CHCO$_2$Me), 1.46 (s, C(CH$_3$)$_3$).

### 8.11 Preparation of t-butyl 2-amino-3-methoxycarbonyl-4-phenyl-(2S)-butanoate 145b

The title compound was prepared by the method of Baldwin$^{70}$ using the purified diastereoisomer 144b.
8.12 Preparation of N-cyano-N’-(t-butyl 3-methoxycarbonyl-4-phenyl-(2S)-butanoate)-O-phenylisourea 146a

To a stirred solution of aspartate 145a (0.78 g, 2.66 mmol) in propan-2-ol (40 ml) was added diphenyl cyanocarbonimidate 53 (0.69 g, 2.89 mmol) and the resulting solution was stirred at room temperature for 8 h. The solvent was removed by evaporation in vacuo to yield a yellow oil which was purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:3), to give the O-phenylisourea 146a (0.97 g, 83%) as a pale yellow oil.

M.S.(C.I.) m/e : 438 (MH+), 382 (M+-55), 281 (M+-156), 162(M+-275).

\(^1\)H n.m.r. (C), δ: 7.52-6.94 (m, PhO and PhCH₂), 6.31 (bd, NH), 4.47 (dd, NHCH), 4.40 (dd, NHCH), 3.72 (bs, OCH₃), 3.48 (bs, OCH₃), 3.31 (m, CHCO₂Me), 3.25 (m, CHCO₂Me), 2.95 (m, PhCH'), 2.70 (dd, PhCH'), 1.44 (s, C(CH₃)₃), 1.39 (s, C(CH₃)₃).

\(^13\)C n.m.r. (C), δ: 173.81, 168.86, 164.79, 160.80, 137.49, 137.43, 131.25, 130.12, 129.47, 129.32, 128.36, 127.79, 127.32, 121.68, 84.12, 56.17, 55.31, 52.88, 52.49, 47.70, 47.59, 35.36, 35.04, 28.16, 28.03.

I.R.(neat): 2197, 1738, 1621, 1581 cm⁻¹.

8.13 Preparation of N-cyano-N’-(t-butyl 3-methoxycarbonyl-4-phenyl-(2S)-butanoate)-O-phenylisourea 146b

The O-phenylisourea 146b was prepared in an analogous manner to O-phenylisourea 146a, from aspartate 145b (0.27 g, 9.22 mmol), to give the title compound (0.18 g, 45%).

M.S.(C.I.) m/e : 438 (MH+), 382 (M+-55), 305 (M+-132), 91 (M+-346).

\(^1\)H n.m.r. (C), δ: 7.43-6.80 (m, PhO and PhCH₂), 5.95 (bd, NH), 4.65 (m, NHCH), 4.50 (m, NHCH), 3.64 (s, OCH₃), 3.57 (s, OCH₃), 3.30-2.75 (m, PhCH₂ and CHCO₂Me), 1.46 (s, C(CH₃)₃), 1.40 (s, C(CH₃)₃).

\(^13\)C n.m.r. (C), δ: 172.52, 172.30, 168.17, 133.13, 131.21, 130.30, 130.05, 129.46, 129.17, 128.32, 127.51, 127.42, 121.73, 121.15, 84.58, 60.67, 56.26, 56.08, 52.49, 49.89, 49.07, 34.61, 34.34, 28.15, 28.02.
8.14 Preparation of 3,5-dibenzyl-6-t-butyloxy carbonyl-2-cyanolimino-5,6-dihydro-4(3H)-pyrimidinone 148a, 1-benzyl-2-cyanolimino-4-ethyl-(1'-methoxy carbonyl-2'-phenyl)-2-imidazolidin-5-one 147 and N-benzyl-N'-cyano-N''-(2-t-butoxy carbonyl-3-methoxycarbonyl-4-phenyl)-(2S)-butanoate)-guanidine 149

Benzylamine (0.14 g, 1.31 mmol) was added to a stirred solution of O-phenylisourea 146a (0.53 g, 1.21 mmol) in propan-2-ol (30 ml) and the resulting solution stirred at 40 °C for 6 days. The solvent was removed by evaporation in vacuo and the resulting yellow oil was purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:3), to yield pure pyrimidinone 148a and a mixture of imidazolidin-5-one 147 and guanidine 149. Imidazolidin-5-one 147 was isolated by fractional crystallisation from the mixture by slow evaporation of the column eluant. The guanidine 149 was then purified from all remaining impurities by flash chromatography, eluting with ethyl acetate:cyclohexane (1:4).

4(3H)-Pyrimidinone 148a

Yield: 0.22g (44%).

M.pt: 186-188 °C.

M.S. m/e: 418.2017 (C\textsubscript{24}H\textsubscript{26}N\textsubscript{4}O\textsubscript{3} requires 418.2005)
418 (M\textsuperscript{+}), 362 (M\textsuperscript{+}-56), 336 (M\textsuperscript{+}-82), 91 (M\textsuperscript{+}-327).

\(^1\)H n.m.r. (C), \(\delta\): 8.30 (bd, NH, \(J_{NH-H}=4.2\) Hz), 7.40-7.17 (m, Ph), 5.02 (s, PhCH\textsubscript{2}), 5.01 (s, PhCH\textsubscript{2})\textsuperscript{*}, 3.79 (dd, NH\textsubscript{2}CHCO\textsubscript{2}, \(J_{H-H}=4.8\) Hz, \(J_{H-NH}=4.2\) Hz), 3.76 (m, NH\textsubscript{2}CHCO\textsubscript{2})\textsuperscript{*}, 3.38 (m, CH\textsubscript{2}CHCO\textsubscript{2})\textsuperscript{*}, 3.26 (ddd, CH\textsubscript{2}CHCO, \(J_{H-H}=4.8\) Hz, \(J_{H-H}=4.8\) Hz, \(J_{H-H}=10.8\) Hz), 3.11 (dd, PhCH\textsubscript{2}, \(J_{H-H}=4.8\) Hz, \(J_{H-H}=13.6\) Hz), 3.00-2.90 (m, PhCH\textsubscript{2})\textsuperscript{*}, 2.82 (dd, PhCH\textsubscript{2}, \(J_{H-H}=10.8\) Hz, \(J_{H-H}=13.6\) Hz), 2.72-2.64 (m, PhCH\textsubscript{2})\textsuperscript{*}, 1.42 (s, C(CH\textsubscript{3})\textsubscript{3})\textsuperscript{*}, 1.28 (s, C(CH\textsubscript{3})\textsubscript{3}).

*Peaks of the minor diastereoisomer present.

\(^{13}\)C n.m.r. (C), \(\delta\): 168.31, 168.04, 159.04, 136.16, 135.57, 129.11, 128.97, 128.78, 128.73, 128.64, 128.34, 127.77, 127.67, 127.63, 127.45, 115.75, 83.81, 52.43, 45.25, 44.89, 35.82, 27.54.
I.R.: 2184, 1738, 1721, 1611 cm⁻¹.

2-Imidazolidin-5-one 147

Yield: 0.09 g (20%).

M.pt: 173-175 °C.

M.S. m/e: 376 (M⁺), 345 (M⁺-31), 214 (M⁺-162), 91 (M⁺-285).

¹H n.m.r. (C), δ: 9.07 (bs, NH), 8.52 (bs, NH), 7.54-7.19 (m, Ph), 4.69 (d, PhCH'), 4.67 (d, PhCH⁺, J_H-H⁺=14.4 Hz)', 4.53 (d, PhCH⁺, J_H-H⁺=14.4 Hz), 4.46 (d, PhCH⁺, J_H-H⁺=14.4 Hz), 4.33 (d, NHCHCO, J_H-H=3.6 Hz), 4.06 (d, NHCHCO, J_H-H=3.2 Hz), 3.64 (s, OCH₃), 3.42 (dd, PhCH', J_H'-H'=14.0 Hz), 4.35 (d, NHCHCO, J_H-H=3.6 Hz), 3.17 (dd, PhCH², J_H-H=6.8 Hz, J_H-H=14.0 Hz), 3.07-3.00 (m, PhCH₂). Peaks of minor diastereoisomer present.

¹³C n.m.r. (C), δ: 172.63, 171.74, 171.61, 170.21, 162.52, 162.35, 137.36, 136.75, 134.83, 134.71, 130.89, 129.33, 129.23, 129.11, 129.01, 128.96, 128.87, 128.79, 128.68, 128.60, 128.22, 127.16, 127.13, 115.37, 57.86, 57.59, 52.54, 52.19, 48.19, 47.96, 43.35, 43.23, 38.69, 33.45, 30.33, 28.91, 23.72, 22.99.

I.R.: 2197, 1761, 1735, 1638, 1601 cm⁻¹.

Analysis: Calculated for C₂₁H₂₀N₄O₃: C, 67.00; H, 5.30; N, 14.90. Found: C, 66.35; H, 5.64; N, 14.37.

Guanidine 149

(The guanidine was prepared using a racemic sample of O-phenyisourea 146, hence it contains both diastereoisomers).

M.S. m/e: 451 (MH⁺), 377 (M⁺-73), 214 (M⁺-236), 91 (M⁺-359).

¹H n.m.r. (C), δ: 7.42-7.21 (m, Ph), 5.91 (bd, NH), 4.51 (d, PhCH'), 4.50 (d, PhCH⁺), 4.45 (m, PhCH₂), 4.35 (d, NHCH), 4.32 (d, NHCH), 4.25 (d, NHCH).
3.61 (s, OCH₃), 3.58 (s, OCH₃), 3.20-3.01 (m, CHCO₂Me), 2.74 (m, PhCH'), 2.45 (m, PhCH"'), 1.38 (s, C(CH₃)₃), 1.26 (s, C(CH₃)₃).

¹³C n.m.r. (C), δ: 173.57, 171.85, 171.68, 168.98, 162.29, 160.02, 137.39, 136.94, 135.84, 134.85, 129.29, 129.25, 129.11, 129.02, 128.94, 128.88, 128.68, 128.35, 127.48, 127.06, 126.88, 121.19, 118.00, 115.99, 82.96, 57.85, 54.78, 52.44, 52.06, 48.32, 47.83, 45.70, 43.17, 35.55, 33.51, 31.72, 30.14, 29.69, 27.82, 27.74.

I.R: 2184, 1762, 1715, 1635 cm⁻¹.

8.15 Preparation of 3,5-dibenzyl-6-t-butyloxy carbonyl-2-cyanolimino-5,6-dihydro-4(3H)-pyrimidinone 148b

The title compound was prepared in an analogous manner to pyrimidinone 148a from O-phenylisourea 146b (0.16 g, 0.37 mmol).

Yield: 0.08 g (52%).

M.S. m/e: 418 (M+), 362 (M+-56), 336 (M+-82), 91 (M+-327).

¹H n.m.r. (C), δ: 7.83 (bs, NH), 7.30-7.10 (m, Ph), 4.96 (s, PhCH₂), 3.71 (bs, NHCHCO), 3.22 (ddd, CHCO, J₉.H=5.12 Hz, J₉.H'=5.20 Hz, J₉.H"=10.88 Hz), 3.07 (dd, PhCH', J₉.H"=5.20 Hz, J₉.H"'=13.68 Hz), 2.75 (dd, PhCH"', J₉.H"'=10.88 Hz, J₉.H""=13.68 Hz), 1.28 (s, C(CH₃)₃).

¹³C n.m.r. (C), δ: 168.24, 167.96, 159.01, 136.12, 135.58, 129.10, 129.04, 128.71, 127.74, 127.53, 115.37, 84.02, 52.56, 45.21, 44.93, 35.82, 27.58.

I.R: 2184, 1735, 1718, 1608 cm⁻¹.

8.16 Preparation of t-butyl-2-amino-3-methoxycarbonyl-(2S)-hexanoate 151

To a solution of t-butyl-2-benzylxycarbonylamino-3-methoxycarbonyl-(2S)-5-hexenoate 15070 (2.13 g, 5.6mmol) in ethanol (60 ml) was added Pd/C (0.2 g, 10%). The resulting mixture was stirred under an atmosphere of hydrogen (1 atm) for 6 h, diluted with ether (100 ml), filtered through celite and the solvent removed by evaporation in vacuo to give the hexanoate 151 as a colourless oil (1.38 g, 99%).
8.17 Preparation of N-cyano-N’-(t-butyl-3-methoxycarbonyl-(2S)-hexanoate)-O-phenylisourea 152

To a stirred solution of aspartate 151 (0.95 g, 3.89 mmol) in propan-2-ol (40 ml) was added diphenyl cyanocarbonimidate 53 (1.11 g, 4.68 mmol) and the resulting mixture stirred at room temperature for 16 h. The solvent was removed by evaporation in vacuo and the resulting yellow oil was purified by flash chromatography, eluting with dichloromethane:methanol (99:1), to give O-phenylisourea 152 as a pale yellow oil (1.50 g, 70%).

M.S. m/e: 390.2073 (C20H28N4O3 requires 390.4583)
390 (MH+), 334 (M+-55), 302 (M+-87), 94 (M+-295).

1H n.m.r. (C), δ: 7.55-7.00 (m, PhO), 6.33 (bd, NH), 4.68-4.52 (m, NHCH), 3.74 (s, OCH3), 3.53 (s, OCH3), 3.21-2.97 (m, CHCO2Me), 1.90-1.10 (m, CH2CH2), 1.49 (s, C(CH3)3), 1.44 (s, C(CH3)3).

13C n.m.r. (C), δ: 174.51, 174.10, 168.68, 168.55, 164.47, 160.91, 131.11, 130.15, 129.69, 128.22, 127.25, 121.66, 121.48, 121.02, 115.83, 81.90, 56.75, 56.23, 52.47, 52.23, 45.48, 31.26, 31.12, 27.89, 21.66, 20.47, 13.82, 13.72.

I.R.(CHCl3): 2198, 1738, 1621, 1591 cm⁻¹.
8.18 Preparation of 3-benzyl-5-propyl-6-t-butoxycarbonyl-2-cyanoimino-5,6-dihydro-4(3H)-pyrimidinone 153, 1-benzyl-2-cyanoimino-4-butyl-(1'-methoxycarbonyl)-2-imidazolidin-5-one 154 and N-benzyl-N'-cyano-N''-(2-t-butyl-3-methoxycarbonyl-(2S)-hexanoate)-guanidine 155

Benzylamine (0.47 g, 4.45 mmol) was added to a stirred solution of O-phenylosourea 152 (1.65 g, 4.24 mmol) in propan-2-ol (40 ml) and the resulting solution stirred at 40 °C for 6 days. The solvent was removed by evaporation in vacuo and the resulting yellow oil purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:4), to yield pure pyrimidinone 153 and a mixture of imidazolidin-5-one 154 and guanidine 155. Imidazolidin-5-one 154 was isolated by fractional crystallisation from the mixture by slow evaporation of the column eluant. The guanidine 155 was then purified from all remaining impurities by flash chromatography, eluting with ethyl acetate:cyclohexane (1:4).

4(3H)-Pyrimidinone 153

Yield: 0.85 g (54%).
M.pt: 147-150 °C.
M.S. (C.l.) m/e:
371 (MH⁺), 315 (M⁺-55), 269 (M⁺-101), 227 (M⁺-143).

¹H n.m.r. (C), δ:
8.14 (bs, NH), 7.34-7.23 (m, Ph), 5.03 (d, PhCH', JH⁺H⁺=14.4 Hz), 5.00 (d, PhCH", JH⁺H⁺=14.4 Hz), 3.91 (dd, NHCH, JH⁺NH=1.8 Hz, JH⁺H⁺=4.0 Hz), 2.96 (bt, CHCO₂, J=7.4 Hz), 1.71-1.63 (m, CH₂CH₂), 1.47-1.32 (m, CH₂CH₂), 1.35 (s, C(CH₃)₃), 0.94 (t, CH₃, JH⁺H⁺=7.2 Hz).

¹³C n.m.r. (C), δ:
168.75, 168.23, 159.01, 136.25, 128.64, 128.38, 127.54, 116.00, 83.82, 53.92, 44.85, 43.17, 32.18, 27.79, 27.65, 19.70, 13.38.

I.R: 2184, 1735, 1718, 1614 cm⁻¹.

Analysis: Calculated for C₂₀H₂₆N₄O₃: C, 64.85; H, 7.07; N, 15.12.
            Found:     C, 64.62; H, 7.03; N, 14.86.

2-Imidazolidin-5-one 154

Yield: 0.14 g (10%).
M.pt: 153-155 °C.
M.S. (C.I.) m/e : 329 (MH⁺), 215 (M⁺-113), 185 (M⁺-143), 91 (M⁺-237).

\(^1H\) n.m.r. (C), δ: 8.76 (bs, NH), 8.37 (bs, NH), 7.44-7.26 (m, Ph), 4.70 (d, PhCH', J_H-H' = 14.8 Hz), 4.68 (d, PhCH", J_H-H" = 14.8 Hz), 4.41 (dd, NHCH, J_H-NH = 1.6 Hz, J_H-H = 4.4 Hz), 3.69 (s, OCH₃), 3.42 (s, OCH₃), 3.01-2.92 (m, CHCO₂), 2.05-1.90 (m, CH₂CH₂), 1.77-1.62 (m, CH₂CH₂), 1.44-1.24 (m, CH₂CH₂), 0.97 (t, CH₃, J_H-H = 7.2 Hz), 0.84 (t, CH₃, J_H-H = 7.2 Hz).

*Peaks of the minor diastereoisomer present.

\(^{13}C\) n.m.r. (C), δ: 172.56, 172.41, 171.65, 171.25, 162.44, 162.11, 134.84, 134.67, 129.12, 129.00, 128.95, 128.70, 128.67, 128.36, 128.27, 115.23, 115.09, 59.18, 58.64, 52.43, 52.07, 46.31, 45.81, 43.33, 29.80, 29.22, 20.59, 20.31, 13.69.

I.R: 2191, 1755, 1728, 1681, 1638 cm⁻¹.

Analysis: Calculated for C₁₇H₂₀N₄O₃: C, 61.99; H, 6.43; N, 17.01.
Found: C, 61.90; H, 6.06; N, 16.82.

Guanidine 155

Yield: 0.13 g (8%).

M.pt: 144-146 °C.

M.S. (C.I.) m/e : 403 (MH⁺), 371 (M⁺-31), 346 (M⁺-56), 329(M⁺-73).

\(^1H\) n.m.r. (C), δ: 7.44-7.26 (m, Ph), 5.83 (bd, NH, J_NH-H = 8.8 Hz), 4.70 (d, PhCH', J_H-H' = 14.4 Hz), 4.68 (d, PhCH", J_H-H" = 14.4 Hz), 4.55-4.26 (m, NHCH), 3.65 (s, OCH₃), 3.59 (s, OCH₃), 3.02-2.88 (m, CHCO₂), 1.79-1.72 (m, CH₂CH₂), 1.53-1.21 (m, CH₂CH₂), 1.42 (s, C(CH₃)₃), 0.86 (t, CH₃, J_H-H = 7.2 Hz), 0.81 (t, CH₃, J_H-H = 7.2 Hz).

\(^{13}C\) n.m.r. (C), δ: 174.40, 172.00, 169.22, 162.24, 160.25, 134.99, 134.86, 129.86, 128.93, 128.90, 128.24, 128.20, 128.01, 127.35, 121.70, 115.76, 115.61, 82.64, 59.19, 58.77, 54.88, 52.29, 51.96, 51.90, 46.69, 45.75,
I.R: 2184, 1755, 1735, 1635, 1588 cm\(^{-1}\).

8.19 Preparation of 2-cyanoimino-4-methoxycarbonylmethyl-2-imidazolidin-5-one 159

To a solution of N-(1,2-dimethoxycarbonylethyl)-N'-cyano-O-phenylisourea 12724 (0.70 g, 2.30 mmol) in propan-2-ol (30 ml) was added aqueous ammonia solution (0.880 s.g., 5 ml) and the resulting solution was stirred at room temperature for 2.5 h. The solvent was removed by evaporation \textit{in vacuo} and the product purified by flash chromatography, eluting with ethyl acetate:cyclohexane (7:3), to give the title compound (0.14 g, 31%).

M.pt: 188-190 °C.

M.S. \textit{m/e}:

196.0596 (C\(_7\)H\(_8\)N\(_4\)O\(_3\) requires 196.0596)
196 (M\(^+\), 181 (M\(^+\)-15), 137 (M\(^+\)-59), 94 (M\(^+\)-102).

\(^1\)H n.m.r. (M), \(\delta\):

4.89 (t, CH, \(J_{H-H}=5.08 \) Hz), 3.70 (s, OCH\(_3\)), 2.91 (d, CH\(_2\), \(J_{H-H}=5.08 \) Hz).

\(^1\)C n.m.r. (M), \(\delta\):

176.26, 171.34, 164.48, 116.66, 57.57, 52.60, 35.51.

I.R:

3132, 2207, 1776, 1724, 1672 cm\(^{-1}\).

8.20 Preparation of 6-carboxy-5,6-dihydro-4(3H)-pyrimidinone 162

A solution of imidazolidin-5-one 159 (0.205 g, 1.05 mmol) in 2 M sodium hydroxide (2 ml) was stirred at room temperature for 15 min. The solution was acidified to pH 1 with concentrated hydrochloric acid. The solvent was reduced to a small volume by evaporation \textit{in vacuo} and ether/methanol (1:1, 5 ml) added. The precipitated product was collected by filtration, washed with ether and dried to give the title compound (0.12 g, 63%).

M.pt: 192-194 °C.

M.S. \textit{m/e}:

182.0445 (C\(_6\)H\(_6\)N\(_4\)O\(_3\) requires 182.0440)
182 (M\(^+\)), 154 (M\(^+\)-28), 129 (M\(^+\)-53), 111 (M\(^+\)-71).

\(^1\)H n.m.r. (D/D\(_2\)O), \(\delta\):

4.53 (dd, CH, \(J_{H-H}=4.52 \) Hz, \(J_{H-H}=4.30 \) Hz), 4.38 (dd, CH, \(J_{H-H}=4.48\), \(J_{H-H}=4.56 \) Hz), 3.01 (dd, CH\(^\prime\), \(J_{H-H}=17.97 \) Hz, \(J_{H-H}=4.52 \) Hz), 2.93
(dd, CH\textsuperscript{\textprime\textprime}, J\textsubscript{H-\textprime\textprime-H}=17.97 Hz, J\textsubscript{H-H-\textprime\textprime}=4.30 Hz), 2.76 (dd, CH\textsuperscript{\textprime}, J\textsubscript{H-\textprime-H}=17.86 Hz, J\textsubscript{H-\textprime-H}=4.48 Hz), 2.74 (dd, CH\textsuperscript{\textprime\textprime}, J\textsubscript{H-\textprime\textprime-H}=17.86 Hz, J\textsubscript{H-\textprime\textprime-H}=4.56 Hz).

\textsuperscript{13}C n.m.r. (D/D\textsubscript{2}O), \textgreek{\delta}: 173.89, 170.63, 156.09, 152.27, 115.90, 55.55, 34.22, 33.55.

I.R: 3510, 3425, 2207, 1785, 1761, 1706, 1648 cm\textsuperscript{-1}.

\textbf{8.21 Preparation of 3,5-dibenzyl-6-carboxy-2-cyanomino-5,6-dihydro-4(3H)-pyrimidinone 164}

A solution of imidazolidin-5-one 147 (0.017 g, 0.04 mmol) in 2 M sodium hydroxide solution (0.6 ml) was stirred at room temperature for 10 min. The solution was acidified to pH 1 with concentrated hydrochloric acid and the precipitated product collected and washed with ether to give the carboxylic acid 164 (0.008 g, 50%).

M.pt: 145-147 °C.

M.S. m/e : 362 (M\textsuperscript{+}), 316 (M\textsuperscript{+}-46), 225 (M\textsuperscript{+}-137), 91 (M\textsuperscript{+}-271).

\textsuperscript{1}H n.m.r. (D), \textgreek{\delta}: 10.69 (s,CO\textsubscript{2}H), 10.60 (s,CO\textsubscript{2}H), 7.30-7.05 (m,Ph), 4.70-4.30 (m,PhCH\textsubscript{2} and NHCH), 3.20-2.97 (m, PhCH\textsubscript{2} and CHCHCO\textsubscript{2}H).

I.R: 3418, 2195, 1770, 1718, 1635 cm\textsuperscript{-1}.

\textbf{8.22 Preparation of 3-benzyl-5-propyl-6-carboxy-2-cyanomino-5,6-dihydro-4(3H)-pyrimidinone 165}

A solution of imidazolidin-5-one 154 (0.045 g, 0.14 mmol) in 2 M sodium hydroxide solution (1 ml) was stirred at room temperature for 7 min. The solution was acidified to pH 1 with concentrated hydrochloric acid and the precipitated product collected and washed with ether to give the carboxylic acid 165 (0.035 g, 82%).

M.pt: 165-167 °C.

M.S. m/e : 314.1388 (C\textsubscript{16}H\textsubscript{18}N\textsubscript{4}O\textsubscript{3} requires 314.1379)

314 (M\textsuperscript{+}), 270 (M\textsuperscript{+}-32), 212 (M\textsuperscript{+}-102), 200 (M\textsuperscript{+}-114).
1H n.m.r. (D), δ: 10.09 (s, CO₂H), 9.95 (s, CO₂H), 7.31-7.24 (m, Ph), 4.67-4.51 (m, PhCH₂ and CHCO₂H), 2.85-2.82 (m, COCH₂), 1.80-1.52 (m, CH₂), 1.40-1.29 (m, CH₂), 0.90-0.80 (m, CH₃).

13C n.m.r. (D), δ: 173.46, 172.89, 172.35, 162.01, 161.71, 135.65, 135.61, 128.29, 127.44, 127.33, 126.93, 115.26, 115.10, 58.25, 58.21, 46.30, 46.06, 42.30, 42.20, 29.40, 29.25, 20.19, 20.04, 13.79, 13.65.

I.R: 3412, 2176, 1767, 1718, 1633 cm⁻¹.

8.23 Preparation of 1-cyclopentyl-2-cyanimino-4-methoxycarbonylmethyl-2-imidazolidin-5-one 181

Cyclopentylamine (0.20 g, 2.35 mmol) was added to a solution of O-phenylisourea 127 (0.70 g, 2.30 mmol) in propan-2-ol (20 ml) and the resulting solution was heated to reflux for 8 h. The solvent was removed by evaporation in vacuo and the residue purified by flash chromatography, eluting with ethyl acetate:cyclohexane (2:3), to give the title compound (0.25 g, 41%).

M.pt: 132-133 °C.

M.S. m/e: 264.1221 (C₁₂H₁₆N₄O₃ requires 264.1222) 264 (M⁺), 237 (M⁺-27), 208 (M⁺-56), 197 (M⁺-67).

1H n.m.r. (C), δ: 8.71 (bs,NH), 4.44 (m, NCH), 4.27 (dd, NHCH, J₇-H=4.00 Hz, J₇-H=6.00 Hz), 3.69 (s, OCH₃), 2.93 (dd, CH'CO₂, J₇-H=4.00 Hz, J₇-H=17.60 Hz), 2.82 (dd, CH'CO₂, J₇-H=6.00 Hz, J₇-H=17.60 Hz), 2.03-2.01 (m, 2H, CH₂), 1.99-1.83 (m, 3H, CH₂), 1.54-1.52 (m, 3H, CH₂).

13C n.m.r. (C), δ: 172.76, 169.23, 163.08, 115.83, 54.44, 53.01, 52.33, 34.80, 28.61, 28.34, 24.99.

I.R: 3412, 2195, 1758, 1736, 1635 cm⁻¹.

8.24 Preparation of 3-cyclopentyl-6-carboxy-2-cyanimino-5,6-dihydro-4(3H)-pyrimidinone 187

A solution of imidazolidin-5-one 181 (0.09 g, 0.35 mmol) in 2 M sodium hydroxide (2 ml) was stirred at room temperature for 10 min. The solution was acidified to pH 1 with concentrated
hydrochloric acid and the precipitated product collected and washed with ether to give the carboxylic acid 187 (0.06 g, 68%).

M.pt: 225-227 °C.

M.S. m/e: 250.1066 (C_{11}H_{14}N_{4}O_{3} requires 250.1071)  
250 (M^+), 223 (M^+ -23), 194 (M^+ -56), 183 (M^+ -67).

$^1$H n.m.r. (D), δ: 9.70 (s, CO$_2$H), 4.38-4.29 (m, CH$_2$CH$_2$CH and CHCO$_2$H), 2.83 (dd, CH''CH, J$_{CH''}$-CH'=3.96 Hz, J$_{CH''}$-CH''=17.44 Hz), 2.73 (dd, CH''''CH, J$_{CH''''}$-H'=4.28 Hz, J$_{CH''''}$-H''=17.44 Hz), 2.01-1.97 (m, CH$_2$), 1.85-1.63 (m, 4H, CH$_2$), 1.55-1.45 (m, CH$_2$).

$^{13}$C n.m.r. (D), δ: 173.79, 170.63, 162.48, 115.56, 54.20, 51.86, 34.21, 28.17, 27.91, 24.81.

I.R: 3327, 2195, 1745, 1710, 1638 cm$^{-1}$.

8.25 Preparation of N-benzyl-N'-cyano-N''-(1-carboxyethylcarbamate)-guanidine 190

To a solution of imidazolidin-5-one 128 (0.47 g, 1.64 mmol) in dry THF (15 ml) under an atmosphere of argon was added sodium amide (0.38 g, 9.74 mmol) and the resulting solution was stirred at room temperature for 75 min. Ethanol (10 ml) and water (15 ml) were then added sequentially and the resulting mixture extracted with chloroform (3x20 ml). The aqueous layer was then acidified to pH 1.0 with 2M hydrochloric acid solution and extracted with chloroform. The chloroform extracts were dried (MgSO$_4$), the solvent removed by evaporation in vacuo and the residue redissolved in methanol (5 ml). Cyclohexane (0.5 ml) was added and the solution cooled to 4 °C for 12 h. The resulting crystalline product was filtered, washed with ether and dried to give the title compound (0.20 g, 42 %).

M.pt: 168-170 °C.

M.S. m/e: 289 (M^+), 226 (M^+ -63), 103 (M^+ -186), 91 (M^+ -198).

$^1$H n.m.r. (D), δ: 9.87 (s, CO$_2$H), 7.31-7.24 (m, Ph), 4.63 (d, PhCH', J$_{H'-H''}$=15.72 Hz), 4.57 (d, PhCH'', J$_{H''}$-H''=15.72 Hz), 4.55 (m, NHCH), 3.15 (s, 1.2H, NH$_2$), 2.89 (dd, CH''CO$_2$, J$_{H''}$-H''=17.68 Hz, J$_{H''}$-H'=4.32 Hz), 2.77 (dd, CH''''CO$_2$, J$_{H''''}$-H''=17.68 Hz, J$_{H''''}$-H'=4.64 Hz).
8.26 Preparation of N-cyclopentyl-N'-cyano-N''-(methyl propionate)-guanidine 244

To a solution of O-phenylisourea 63 (0.300 g, 1.21 mmol) in propan-2-ol (20 ml) was added cyclopentylamine (0.103 g, 1.21 mmol) and the resulting solution heated to reflux for 8 h. The solvent was removed by evaporation in vacuo and the product purified by flash chromatography, eluting with ethyl acetate:cyclohexane (3:2), to give the title compound (0.090 g, 30%) as a pale yellow oil.

M.S. m/e: 238.1433 (C_{11}H_{18}N_{4}O_{2} requires 238.1430)
238 (M+), 215 (M+-23), 207 (M+-31), 197 (M+-41).

{^1}H n.m.r. (C), δ: 5.85 (bs, NH), 5.60 (bs, NH), 3.77 (m, NCH), 3.67 (s, OCH$_3$), 3.48 (q, NCH$_2$, J$_{H-H}$=5.89 Hz), 2.56 (t, CH$_2$, J$_{H-H}$=5.89 Hz), 2.00-1.90 (m, CH$_2$), 1.71-1.20 (m, 6H, CH$_2$).

{^{13}}C n.m.r. (C), δ: 173.63, 159.44, 119.40, 53.45, 52.14, 37.33, 33.83, 33.15, 23.72.


8.27 Preparation of N-cyclopentyl-N'cyano-N''-(t-butyl 3methoxycarbonyl-4-phenyl-(2S)-butanoate)-guanidine 245

Cyclopentylamine (0.036 g, 0.42 mmol) was added to a stirred solution of O-phenylisourea 146 (0.155 g, 0.35 mmol) in propan-2-ol (10 ml) and the resulting solution heated to reflux for 12 h. The solvent was removed by evaporation in vacuo and the product purified by flash chromatography eluting with ethyl acetate:cyclohexane (1:2), to give the title compound (0.036 g, 20%) as a pale yellow oil.

M.S. m/e: 428.2411 (C$_{23}$H$_{32}$N$_{4}$O$_{4}$ requires 428.2423)
428 (M+), 327 (M+-101), 266 (M+-162), 91 (M+-337).

{^1}H n.m.r. (C), δ: 7.26-7.08 (m, Ph), 5.93 (d, NH, J$_{H-H}$=8.72 Hz), 5.47 (d, NH, J$_{H-H}$=6.12 Hz), 4.53 (dd, NCHCO$_2$, J$_{H-H}$=3.12 Hz, J$_{H-NH}$=8.72 Hz), 3.67-3.63 (m, CHNH), 3.58 (s, OCH$_3$), 3.26 (ddd, CHCO$_2$Me, J$_{H-H}$=3.12 Hz,
$J_{H,H'}=7.28\ \text{Hz}$, $J_{H,H''}=7.96\ \text{Hz}$, $2.97\ \text{(dd, CH'}\text{CH, } J_{H,H'}=13.76\ \text{Hz,} \ J_{H,H''}=7.28\ \text{Hz)}$, $2.76\ \text{(dd, CH'}\text{CH, } J_{H,H'}=13.76\ \text{Hz,} \ J_{H,H''}=7.96\ \text{Hz)}$, $2.03\text{-}1.40\ \text{(m, 8H, CH$_2$)}, 1.36\ \text{(s, C(CH$_3$)$_3$).}$

$^13$C n.m.r. (C), $\delta$: $174.06$, $172.05^*$, $171.81^*$, $169.21$, $162.76^*$, $159.99$, $137.37$, $137.05^*$, $128.93^*$, $128.84$, $128.71^*$, $128.67$, $126.99^*$, $126.93$, $117.69$, $115.90^*$, $83.07$, $57.08$, $54.87$, $53.45^*$, $52.84$, $52.15^*$, $48.44^*$, $47.91$, $35.20$, $33.27^*$, $33.23$, $27.77$, $26.84^*$, $24.98^*$, $23.91^*$.

*Peaks of minor diastereoisomer present.

I.R.(CHCl$_3$): $3400$, $2170$, $1733$, $1629$, $1589\ \text{cm}^{-1}$.

8.28 Preparation of $N$-cyano-$N'$-(1-benzyloxy carbonyl-2-phenylethyl)-O-phenylisourea 246

A solution of S-phenylalanine benzylester hydrochloride (0.60 g, 2.05 mmol) and diethylamine (0.22 g, 2.76 mmol) in benzene (20 ml) was stirred for 20 min. Ether (50 ml) was added and the precipitated diethylamine hydrochloride removed by filtration. The filtrate was evaporated in vacuo to give S-phenylalanine benzylester (0.52 g, 99%) as a colourless oil. The oil was dissolved in propan-2-ol (20 ml) and diphenyl cyanocarbonimidate 53 (0.48 g, 2.05 mmol) was added. The solution was heated to reflux for 5 h and the solvent removed by evaporation. The residual oil was purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:4), to give the title compound as a colourless oil (0.75 g, 75%).

M.S. $m/e$: $399.1586$ (C$_{24}$H$_{21}$N$_3$O$_3$ requires 399.1583) $399$ (M$^+$), $354$ (M$^+$-45), $308$ (M$^+$-91), $91$ (M$^+$-308).

$^1$H n.m.r. (C), $\delta$: $7.40$-$7.10$ (m, 12H, Ph), $6.98$-$6.80$ (m, 2H, Ph), $6.75$-$6.60$ (m, 2H, Ph), $5.58$ (bd, NH), $5.23$ (bs, CH$^'$Ph), $5.15$ (bd, CH$^''$Ph), $4.85$-$4.78$ (m, NHCH), $3.40$-$3.00$ (m, CH$_2$Ph).

$^{13}$C n.m.r. (C), $\delta$: $170.64$, $163.75$, $151.36$, $136.33$, $135.54$, $131.11$, $130.32$, $129.95$, $129.26$, $128.95$, $128.17$, $127.58$, $127.16$, $121.82$, $121.20$, $116.03$, $68.10$, $57.37$, $56.46$, $38.13$, $37.96$, $36.84$, $27.17$.

I.R.(CHCl$_3$): $3680$, $2197$, $1745$, $1621\ \text{cm}^{-1}$.

Analysis: Calculated for C$_{24}$H$_{21}$O$_3$N$_3$: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.43; H, 5.54; N, 10.23.
8.29 Preparation of 1-cyclopentyl-2-cyanoimino-4-benzyl-2-imidazolidin-5-one 247

To a solution of O-phenylisourea 246 (0.35 g, 0.88 mmol) in propan-2-ol (20 ml) was added cyclopentylamine (0.15 g, 1.75 mmol) and the resulting solution heated to reflux for 8 h. The solvent was removed by evaporation in vacuo and the resulting oil purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:1), to give the title compound (0.17 g, 70%).

M.pt: 152-154 °C.

M.S. m/e: 282.1489 (C16H18N4O requires 282.1481)
282 (M+), 255 (M+-27), 215 (M+-67), 91 (M+-191).

1H n.m.r. (C), δ: 8.93 (bs, NH), 7.25-7.15 (m, Ph), 4.28 (m, CHCH2Ph, JH-H'=4.0 Hz, JH-H"=4.4 Hz), 4.20 (qn, CHN, JH-H'=8.4 Hz), 3.11 (dd, PHCH', JH'-H'=4.4 Hz, JH'-H"=4.0 Hz), 3.09 (dd, PHCH", JH"-H'=14.4 Hz, JH"-H"=4.4 Hz), 1.73-1.35 (m, 8H, CH2).

13C n.m.r. (C), δ: 172.93, 162.62, 133.27, 129.86, 128.42, 127.44, 115.90, 58.48, 36.57, 28.37, 28.07, 24.80.

I.R.(CHCl3): 3414, 2189, 1755, 1632 cm⁻¹.

8.30 Preparation of 1-cyclopentyl-2-cyanoimino-4-benzylloxycarbonylmethyl-2-imidazolidin-5-one 248 and N-cyclopentyl-N'-cyano-N"-(1-t-butyloxycarbonyl-2-benzoxy carbonylethyl)-guanidine 249

A solution of O-phenylisourea 138 (0.22 g, 0.52 mmol) and cyclopentylamine (0.05 g, 0.59 mmol) in propan-2-ol (20 ml) was heated to reflux for 8 h. The solvent was removed by evaporation in vacuo and the resulting oil was purified by flash chromatography, eluting with ethyl acetate:cyclohexane (2:3), to give the imidazolidin-5-one 248 (0.10 g, 57%), and the guanidine 249 (0.05 g, 23%) as an oil.

2-Imidazolidin-5-one 248.

M.pt: 110-112 °C.

M.S. m/e: 340.1535 (C18H20N4O3 requires 340.1535)
340 (M+), 273 (M+-67), 183 (M+-157), 91 (M+-249).
\[^1\text{H n.m.r. (C), } \delta: \ 7.35-7.24 \text{ (m, Ph), 5.15 (d, CH'Ph, J_{H'-H} = 12.0 \text{ Hz}), 5.10 (d, CH''Ph, J_{H''-H''} = 12.0 \text{ Hz}), 4.45 (qn, CHN, J_{H-CHN} = 8.4 \text{ Hz}), 4.32-4.29 \text{ (m, CH}_2\text{CHN), 3.00 (dd, PhCH', J_{H'-H''} = 17.44 \text{ Hz, } J_{H''-H} = 3.9 \text{ Hz), 2.86 (dd, PhCH'', J_{H''-H''} = 17.44 \text{ Hz, } J_{H'-H'} = 6.4 \text{ Hz), 2.03-1.99 (m, 2H, CH}_2\text{), 1.87-1.79 (m, 4H, CH}_2\text{). } \]

\[^{13}\text{C n.m.r. (C), } \delta: \ 172.63, 168.87, 162.96, 134.98, 128.62, 128.49, 128.40, 115.77, 67.29, 54.49, 53.05, 35.12, 28.35, 24.99. \]

I.R. (CHCl\textsubscript{3}): 3412, 2189, 1755, 1733, 1635 \text{ cm}^{-1}.

**Guanidine 249**

M.S. m/e : 414.2278 (C\textsubscript{22}H\textsubscript{30}N\textsubscript{4}O\textsubscript{4} requires 414.2267)
414 (M\textsuperscript{+}), 358 (M\textsuperscript{+}-56), 341 (M\textsuperscript{+}-73), 91 (M\textsuperscript{+}-323).

\[^1\text{H n.m.r. (C), } \delta: \ 7.34-7.24 \text{ (m, Ph), 5.73 (bd, NH), 5.35 (bd, NH), 5.14 (d, PhCH'), J_{H'-H} = 12.4 \text{ Hz), 5.04 (d, PhCH'', J_{H''-H''} = 12.4 \text{ Hz), 4.61-4.57 (m, NHCH), 3.63 (qn, NHCH, J_{H-CHN} = 6.0 \text{ Hz), 2.97 (dd, CH'Ph, J_{H'-H''} = 16.4 \text{ Hz, J_{H''-H} =2.0 \text{ Hz), 2.96 (dd, CH''Ph, J_{H''-H''} = 16.4 \text{ Hz, J_{H'-H'} =2.4 \text{ Hz), 2.08-1.85 (m, 2H, CH}_2\text{), 1.79-1.49 (m, 6H, CH}_2\text{), 1.40 (s, C(CH}_3\text{)_3). } \]

\[^{13}\text{C n.m.r.(C), } \delta: \ 170.82, 170.77, 169.17, 135.22, 128.59, 128.49, 128.40, 118.90, 83.27, 66.85, 53.40, 51.04, 36.42, 33.29, 27.76, 23.74. \]

I.R. (CHCl\textsubscript{3}): 3400, 2170, 1736, 1589 \text{ cm}^{-1}.

**8.31 Preparation of N-cyano-N'-(4-methoxycarbonyl)cyclopent-2-enyl) O-phenylisourea 254**

Triethylamine (0.65 g, 6.47 mmol) was added to a stirred suspension of cyclopentylamine hydrochloride 250 (1.10 g, 6.41 mmol) in propan-2-ol (50 ml). Diphenyl cyanocarbonimidate 53 (1.54 g, 6.47 mmol) was added and the resulting solution was stirred at room temperature for 8 h. The solvent was removed by evaporation in vacuo and the product purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:1), to give the title compound as a white solid (1.62 g, 89%).

M.S. m/e : 285.1127 (C\textsubscript{15}H\textsubscript{15}N\textsubscript{3}O\textsubscript{3} requires 285.1113)
285 (M\textsuperscript{+}), 226 (M\textsuperscript{+}-59), 125 (M\textsuperscript{+}-160), 94 (M\textsuperscript{+}-191).
8.32 Preparation of N-cyano-N'-(3-hydroxymethylcyclopentyl) O-phenylisourea

To a stirred suspension of cyclopentylamine 253 (0.63 g, 4.19 mmol) in propan-2-ol (25 ml) was added triethylamine (0.82 g, 8.11 mmol) and diphenyl cyanocarbonimidate 53 (0.99 g, 4.19 mmol) and the resulting solution was heated to reflux for 8 h. The solvent was removed by evaporation in vacuo and the residue purified by flash chromatography, eluting with ethyl acetate:cyclohexane (3:2), to give the title compound as a white solid (0.91 g, 84%).

M.pt: 82-84 °C.

M.S. m/e: 259.1321 (C_{14}H_{17}N_3O_2 requires 259.1321) 259 (M^+), 225 (M^+-34), 118 (M^+-114), 94 (M^+-165).

$^1$H n.m.r. (C), δ: 8.69 (bd, NH), 7.40-7.37 (m, 2H, Ph), 7.28-7.24 (m, 1H, Ph), 7.09-7.07 (m, 2H, Ph), 4.39 (bs, OH), 4.28 (bs, CHN), 3.64-3.57 (m, CH₂O), 2.40-2.20 (m, CHCHO), 2.16-2.00 (m, CHCH₂O), 1.90-1.75 (m, 6H, CH₂).

$^{13}$C n.m.r. (C), δ: 162.63, 151.16, 130.16*, 129.35, 126.70*, 126.24, 121.43, 115.40, 64.13*, 63.86, 54.08, 37.94, 35.42, 34.08, 25.06.

I.R.(CHCl₃): 3393, 2183, 1621, 1428 cm⁻¹.
8.33 Preparation of N-cyano-N'-[(3-methoxycarbonylcyclopentyl) O-phenylisourea 256

To a stirred solution of O-phenylisourea 254 (0.25 g, 0.87 mmol) in degassed ethanol (10 ml) was added palladium on charcoal (10%, 0.01 g) and the resulting suspension was stirred under an atmosphere of hydrogen (1 atm) for 8 h. The reaction mixture was diluted with ethanol (20 ml), filtered through celite, and the solvent removed by evaporation in vacuo to give the title compound as a white solid (0.24 g, 95%).

M.S. m/e : 288.1361 (C\textsubscript{15}H\textsubscript{18}N\textsubscript{3}O\textsubscript{3} requires 288.1348)
288 (MH\textsuperscript{+}), 256 (M\textsuperscript{+}-31), 127 (M\textsuperscript{+}-160), 67 (M\textsuperscript{+}-220).

\(^1\text{H}\) n.m.r. (C), \(\delta\) : 7.47-7.38 (m, 2H, Ph), 7.36-7.25 (m, 1H, Ph), 7.14-7.08 (m, 2H, Ph), 4.44-4.32 (m, NCH), 3.76 (s, OCH\(_3\)), 3.54 (s, OCH\(_3\)), 3.01-2.85 (m, CHCO\(_2\)), 2.32-1.65 (m, 6H, CH\(_2\)).

\(^1\text{C}\) n.m.r. (C), \(\delta\) : 176.83, 163.09, 150.99, 130.43, 129.58, 127.24, 126.65, 121.43, 121.35, 115.15, 114.90, 54.98, 54.47, 52.52, 52.49, 41.85, 41.48, 35.90, 35.32, 33.37, 33.28, 28.65, 28.15.

*Peaks for minor stereoisomer present

I.R.(CHCl\(_3\)) : 3286, 2191, 1722, 1615 cm\(^{-1}\).

8.34 Preparation of N-cyano-N'-(4-hydroxymethylcyclopent-2-enyl) O-phenylisourea 257

To a solution of O-phenylisourea 254 (0.80 g, 2.79 mmol) in dry THF at 0 °C under an atmosphere of N\(_2\) was added lithium triethylborohydride (8.37 ml, 1M, 8.37 mmol). The resulting solution was stirred at 0 °C for 3 h. The solvent was removed by evaporation in vacuo and the residue was dissolved in methanol (15 ml), and treated with 1M HCl at 0 °C to destroy any remaining lithium triethylborohydride. The methanol and resulting trichloroborane were removed by evaporation in vacuo and the residue was purified by flash chromatography, eluting with chloroform:methanol (33:1) to give the title compound as a white solid (0.47 g, 66%).

M.S. m/e : 259 (M\textsuperscript{+}), 241 (M\textsuperscript{+}-18), 165 (M\textsuperscript{+}-94), 94 (M\textsuperscript{+}-165).

\(^1\text{H}\) n.m.r. (C), \(\delta\) : 7.90 (bd, NH), 7.40-7.34 (m, 2H, Ph), 7.27-7.23 (m, 1H, Ph), 7.10-7.07 (m, 2H, Ph), 5.91-5.71 (m, CH=CH), 4.89 (bt, 0.50H, CHN), 4.81 (bt, 0.15H, CHN), 4.65 (bt, 0.35H, CHN), 4.18 (bs, 0.55H, OH), 3.94 (bs,
1H n.m.r. (C), δ: 7.81 (bs, NH), 5.08 (m, CHN), 3.72-3.68 (m, CHCO2), 3.70 (s, OCH3), 3.50 (dt, NHCH2, JH-H=6.87 Hz, JH-NH=3.21 Hz), 2.74 (t, CH2CO, JH-H=6.87 Hz), 2.50-2.01 (m, 6H, CH2).

13C n.m.r. (C), δ: 175.09, 167.71, 159.97, 116.05, 54.43, 51.87, 43.30, 35.84, 32.05, 29.68, 27.93, 27.79.

I.R.(CHCl3): 3145, 2178, 1792, 1718, 1601 cm⁻¹.

8.36 Preparation of N-(4-hydroxymethylcyclopent-2-enyl)-N'-cyano-N''-(methyl propionate) guanidine 260

To a solution of O-phenylisourea 257 (0.11 g, 0.43 mmol) and β-alanine-methyl ester hydrochloride 62 (0.078 g, 0.56 mmol) in dry THF (10 ml) was added sodium hydride (0.032 g,
1.07 mmol) and the resulting suspension was heated to 40 °C for 24 h. Water (10 ml) was added and the pH brought to 7.0 with 2M HCl solution. The reaction mixture was extracted with chloroform (3x10 ml), dried (MgSO₄), and the solvent removed by evaporation in vacuo. The residue was purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:2), to give the title compound as a pale yellow oil (0.02 g, 15%).

M.S. m/e: 266.1407 (C₁₂H₁₈N₄O₃ requires 266.1379) 266 (M⁺), 249 (M⁺-17), 236 (M⁺-30), 162 (M⁺-104).

¹H n.m.r. (C), δ: 6.37 (bd, NH, J₉-H=7.92 Hz), 5.91-5.76 (m, 2H, CH=CH), 4.60(bs, CHN), 3.71 (dd, CH’OH, JH'-H“=10.56 Hz, JH‘.H“=3.08 Hz), 3.70 (s, OCH₃), 3.62 (dd, CH”OH, JH‘.H“=10.56 Hz, JH‘.H“=3.68 Hz), 3.47 (dt, NHCH₂, JH.H=5.96 Hz, JH.H=6.12 Hz), 2.89-2.87 (m, CHCH₂O), 2.62-2.58 (m, CH₂CO₂), 2.49-2.41 (m, CH), 1.61 (d, CH”, JH.H=14.00 Hz).

¹³C n.m.r. (C), δ: 173.14, 158.61, 136.17, 131.68, 118.58, 63.18, 56.96, 52.10, 46.48, 37.27, 33.70.

I.R.(CHCl₃): 3399, 2171, 1722, 1588 cm⁻¹.

8.37 Preparation of 1-(3-methoxycarbonyl-cyclopentyl)-2-cyanolimino-4-benzyl-2-imidazolidin-5-one 261

A solution of O-phenylisourea 246 (0.90 g, 2.25 mmol), 3-carboxymethyl-cyclopentylamine hydrochloride 251 (0.44 g, 2.45 mmol) and triethylamine (0.29 g, 2.87 mmol) in propan-2-ol (40 ml) was heated to reflux for 48 h. The solvent was removed by evaporation in vacuo and the resulting oil purified by flash chromatography, eluting with ethyl acetate:cyclohexane (2:3), to give the title compound (0.20 g, 26%) as a pale yellow oil.

M.S. m/e: 340.1539 (C₁₈H₂₀N₄O₃ requires 340.1535) 340 (M⁺), 309 (M⁺-31), 281 (M⁺-59), 91 (M⁺-249).

¹H n.m.r. (C), δ: 9.06 (bd, NH, J₉-H=2.8 Hz), 7.33-7.22 (m, Ph), 4.38 (m, NHCH₂CH₂, JH.H=4.24 Hz, JH.H=4.48 Hz), 4.24 (m, CHN), 3.71 (s, OCH₃), 3.69 (s, OCH₃), 3.18 (dd, CH’Ph, JH.H=12.0 Hz, JH.H=2.0 Hz), 3.16 (dd, CH”Ph, JH.H=12.0 Hz, JH.H=2.4 Hz), 2.67 (m, CHCO₂Me), 2.22-2.04 (m, 2H,CH₂), 1.98-1.75 (m, 3H, CH₂), 1.70-1.52 (m, CH₂).
13C n.m.r. (C), δ: 174.86, 172.71, 162.29, 133.16, 129.85, 128.46, 127.52, 115.62, 58.92, 51.87, 51.72, 51.60, 42.42, 36.59, 36.52, 31.42, 31.22, 27.35, 27.11, 26.93.

I.R.(CHCl3): 3149, 2195, 1758, 1727, 1635 cm\(^{-1}\).

8.38 Preparation of 1-(3'-hydroxymethylcyclopentyl)-2-cyanimino-4-benzyl-2-imidazolidin-5-one 262

A solution of O-phenylisourea 246 (0.52 g, 1.30 mmol), 3-hydroxymethylcyclopentylamine hydrochloride 253 (0.12 g, 1.35 mmol) and triethylamine (0.15 g, 1.50 mmol) in propan-2-ol (20 ml) was heated to reflux for 48 h. The solvent was removed by evaporation in vacuo and the resulting oil was purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:3), to give the title compound (0.10 g, 25%) as a pale yellow oil.

M.S. m/e: 313.1666 (C\(_{17}\)H\(_{21}\)N\(_4\)O\(_2\) requires 313.1664) 312 (M+), 241 (M+-71), 215 (M+-97), 91 (M+-221).

1H n.m.r. (C), δ: 8.50 (bd, NH), 7.25-7.08 (m, Ph), 4.36 (t, NHCHCH\(_2\), \(J_{\text{H-H}}=4.54\) Hz), 4.26-4.21 (m, CHNH), 3.56 (dd, CH'OH, \(J_{\text{H'-H''}}=5.64\) Hz, \(J_{\text{H-H}}=1.60\) Hz), 3.54 (dd, CH''OH, \(J_{\text{H''-H'='}}=5.64\) Hz, \(J_{\text{H-H}}=1.56\) Hz), 3.20 (dd, CH'Ph, \(J_{\text{H-H'='}}=14.1\) Hz, \(J_{\text{H''-H'=}}=4.4\) Hz), 3.10 (dd, CH''Ph, \(J_{\text{H''-H'=}}=14.1\) Hz, \(J_{\text{H-H}}=2.8\) Hz), 2.30-1.95 (m, 2H, CH\(_2\)), 1.75-1.50 (m, 5H, CH\(_2\)).

13C n.m.r. (C), δ: 172.83, 162.40, 133.33, 129.74, 128.60, 127.59, 115.66, 66.60, 58.99, 52.38, 40.57, 36.78, 27.33, 27.05, 26.88.

I.R.(CHCl3): 3412, 2189, 1751, 1702, 1629 cm\(^{-1}\).

8.39 Preparation of 1-(4'-hydroxymethylcyclopent-2'-enyl)-2-cyanimino-4-benzyl-2-imidazolidin-5-one 263

A solution of O-phenylisourea 246 (0.55 g, 1.38 mmol), 4-hydroxymethylcyclopent-2-enylamine hydrochloride 252 (0.24 g, 1.61 mmol) and triethylamine (0.20 g, 1.98 mmol) in propan-2-ol (20 ml) was heated to reflux for 72 h. The solvent was removed by evaporation in vacuo and the resulting oil purified by flash chromatography, eluting with ethyl acetate:cyclohexane (4:1), to give the title compound (0.05 g, 12%).

M.pt: 145-147 °C.
M.S. m/e: 311.1519 ($C_{17}H_{19}N_{4}O_{2}$ requires 311.1508)
311 (MH$^+$), 310 (M$^+$), 280 (M$^{+}$-30), 91 (M$^{+}$-219).

$^1$H n.m.r. (C), $\delta$: 9.07 (s, NH), 7.34-7.10 (m, Ph), 5.86-5.84 (m, CHCHNH), 5.26-5.24 (m, CH$_2$CHCH), 5.03-4.98 (m, CHN), 4.39 dd, CH$_2$CH$_2$Ph, J$_{H-H}$=4.92 Hz, J$_{H-H}$=4.48 Hz), 3.73 (dd, CH$^\prime$OH, J$_{H-H}$=10.60 Hz, J$_{H-H}$=4.60 Hz), 3.63 (dd, CH$^\prime$OH, J$_{H-H}$=10.60 Hz, J$_{H-H}$=4.28 Hz), 3.17 (dd, CH$^\prime$Ph, J$_{H-H}$=14.10 Hz, J$_{H-H}$=4.48 Hz), 3.11 (dd, CH$^\prime$Ph, J$_{H-H}$=14.10 Hz, J$_{H-H}$=4.92 Hz), 2.93-2.88 (m, CHCH$_2$OH), 2.27-2.19 (m, CH$^\prime$), 1.65 (bs, OH), 1.56-1.49 (m, CH$^\prime$).

$^{13}$C n.m.r. (C), $\delta$: 172.98, 162.33, 135.79, 133.20, 129.90, 129.45, 128.64, 127.66, 115.26, 64.99, 58.98, 57.69, 47.30, 36.70, 29.20.

I.R. (CHCl$_3$): 3942, 2189, 1752, 1727, 1635 cm$^{-1}$.

8.40 Preparation of 1-(3'-methoxycarboxylicpicyclopentyl)-2-cyanolmino-4-methyloxyxcarbonyl-methyl-2-imidazolidin-5-one 264

To a solution of 13-methoxycarboxylicpicyclopentylamine hydrochloride 251 (0.20 g, 1.14 mmol) and O-phenylisourea 127 (0.34 g, 1.11 mmol) in propan-2-ol (20 ml) was added triethylamine (0.14 g, 1.38 mmol) and the resulting solution was heated to reflux for 48 h. The solvent was removed by evaporation in vacuo and the residue was purified by flash chromatography, eluting with chloroform:methanol (99:1), to give the title compound (0.05 g, 13.6 %) as a pale yellow oil.

M.S. m/e: 323.1369 ($C_{14}H_{17}N_{4}O_{5}$ requires 323.1355)
322 (M$^+$), 291 (M$^+$-31), 263 (M$^{+}$-59), 165 (M$^{+}$-167).

$^1$H n.m.r. (C), $\delta$: 8.25 (bs, NH), 4.49 (m, NCH), 4.30 (m, NHCH), 3.71 (s, OCH$_3$), 3.68 (s, OCH$_3$), 2.96 (dd, CH$^\prime$CO$_2$, J$_{H-H}$=3.76 Hz, J$_{H-H}$=17.56 Hz), 2.82 (dd, CH$^\prime$CO$_2$, J$_{H-H}$=6.44 Hz, J$_{H-H}$=17.56 Hz), 2.80-2.74 (m, CHCO$_2$), 2.51-2.41 (m, 1H, CH$_2$), 2.27-2.09 (m, 3H, CH$_2$), 1.92-1.82 (m, 2H, CH$_2$).

$^{13}$C n.m.r. (C), $\delta$: 174.92, 172.40, 169.50, 162.65, 117.98, 54.49, 52.38, 52.35, 51.95, 42.76, 42.67, 35.01, 31.85, 31.62, 27.65, 27.58, 27.30.

I.R. (CHCl$_3$): 3418, 2195, 1758, 1730, 1635 cm$^{-1}$.
84.1 Preparation of N-benzyl-N-methyl-N'-cyano-N''-(1-benzyloxy carbonyl-2-phenylethyl) guanidine 284

N-methyl-benzylamine (10 ml) was added to O-phenylisourea 246 (0.30 g, 7.51 mmol) and the resulting solution stirred at room temperature for 8 h. Chloroform (30 ml) was added and the chloroform extracted with 5% citric acid solution (2×15 ml), dried (MgSO4), and the solvent removed by evaporation in vacuo. The residue was purified by flash chromatography, eluting with ethyl acetate:cyclohexane (2:1), to give the title compound (0.18 g, 56%).

M.S. m/e : 426.2087 (C26H26N4O2 requires 426.4916) 426 (M+), 335 (M+-91), 291 (M+-135), 91 (M+-335).

1H n.m.r (C), δ: 7.39-7.08 (m, 13H, Ph), 6.84 (d, 2H, Ph), 5.20 (d, PhCH', JH'-H'=11.90 Hz), 5.21-5.18 (m, NHCH), 5.12 (d, PhCH'', JH''-H'=11.90 Hz), 5.08 (d, NH, JNH-H=7.87 Hz), 4.49 (s, PhCH2), 3.23 (dd, PhCH', JH'-H'=14.04 Hz, JH'-H=5.89 Hz), 3.18 (dd, PhCH'', JH''-H'=14.04 Hz, JH''-H=4.93 Hz), 2.88 (s, NCH3).

13C n.m.r. (C), δ: 171.25, 158.23, 135.14, 134.75, 134.64, 129.18, 128.98, 128.70, 128.66, 128.59, 128.01, 127.22, 127.02, 116.88, 67.75, 55.61, 54.39, 37.81, 36.51.

I.R: 3399, 2171, 1735, 1668, 1638 cm⁻¹.

84.2 Preparation of 2-(N-methylbenzylamine)-4-benzyl-imidazolidin-5-one 287

To a solution of guanidine 284 (0.15 g, 0.35 mmol) in degassed ethanol (10 ml) was added Pd/C (0.10 g, 5%) and the resulting suspension was stirred under an atmosphere of hydrogen (1 atm) for 48 h. The solution was filtered through celite, the solvent was removed by evaporation in vacuo and the residue was purified by flash chromatography, eluting with chloroform:methanol, (12.5:1) to give the title compound (0.08 g, 78%).

M.pt: 172-174 °C.

M.S. m/e : 293 (M+), 278 (M+-15), 202 (M+-91), 91 (M+-202).

1H n.m.r. (D), δ: 8.28 (bs, 0.3H, NH), 8.14 (bs, 0.7H, NH), 7.25-7.15 (m, 8H, Ph), 7.00-6.80 (m, 2H, Ph), 4.81 (bd, 0.7H, PhCH'), 4.65 (bd, 0.3H, PhCH'), 4.30
1H n.m.r. (D, 140°C), δ: 7.68 (bs, NH), 7.30-7.16 (m, 8H, Ph), 7.07 (d, 2H, Ph), 4.57 (d, PhCH', J_H-H=15.37 Hz), 4.50 (d, PhCH', J_H-H=15.37 Hz), 4.06 (dd, NHCH, J_H-NH=4.78 Hz), 3.03 (dd, PhCH', J_H-H=14.11 Hz, J_H-H=4.78 Hz), 2.86 (dd, PhCH', J_H-H=14.11 Hz, J_H-H=5.97 Hz), 2.84 (s, NCH3).

13C n.m.r. (D), δ: 187.96, 171.58, 137.26, 137.02, 130.14, 128.92, 128.30, 127.54, 126.71, 62.34, 53.10, 51.50, 37.23, 33.83.

I.R.(CHCl3): 3500, 2925, 1715, 1595, 1578, 1458 cm⁻¹.

Analysis: Calculated for C18H19N₃O: C, 73.69; H, 6.25; N, 14.32.

Found: C, 73.31; H, 6.58; N, 14.38.

8.43 Alternative preparation of 287

To potassium t-butoxide (0.55 g, 4.95 mmol) in dry ether (10 ml) cooled to 0 °C was added water (0.02 g, 1.28 mmol) and the suspension was stirred for 5 min. Guanidine 291 (0.20 g, 0.57 mmol) was added and the suspension stirred at room temperature for 2 h. Iced water (30 ml) was added to dissolve all the solid, the solution was acidified to pH 1.0 with 2M hydrochloric acid solution, extracted with ether (3x20 ml), and dried (MgSO4). The solvent was removed by evaporation in vacuo to give a white foam. This was dissolved in ethyl acetate:methanol (19:1, 5 ml) and cooled to 4 °C for 6 h. The white crystalline product was filtered, washed with ether and dried to give the title compound (0.07 g, 44%), that was identical in all respects to imidazolidin-5-one 287.

8.44 Preparation of N-cyano-N'-{1-carboxy-2-phenylethyl}-O-phenylisourea 288

To a solution of O-phenylisourea 246 (0.70 g, 1.75 mmol) in degassed ethanol (30 ml) was added Pd/C (10%, 0.10 g) and the resulting suspension stirred under an atmosphere of hydrogen (1 atm) for 8 h. The Pd/C was removed by filtration through celite and the solvent was removed by evaporation in vacuo. The residue was purified by flash chromatography, eluting with chloroform:methanol (9:1), to give the title compound (0.40 g, 74%).

M.S. m.e.: 264.1146 (M⁺-CO₂H, C₁₆H₁₄N₃O requires 264.2897)

264 (M⁺-45), 215 (M⁺-94), 149 (M⁺-160), 94 (M⁺-215).
$^1$H n.m.r. (M), $\delta$: 7.35-7.17 (m, Ph), 6.90 (d, 1H, Ph), 6.62 (d, 1H, Ph), 4.63 (m, 0.5 H, CHCO$_2$), 4.49 (m, 0.5 H, CHCO$_2$), 3.47-3.39 (m, CH$^\prime$Ph), 3.06-3.00 (m, CH$^\prime$Ph).

$^{13}$C n.m.r. (M), $\delta$: 177.77, 164.10, 161.03, 152.49, 152.38, 139.26, 138.67, 131.41, 130.73, 130.56, 130.32, 129.67, 129.60, 129.47, 127.82, 127.73, 127.49, 127.43, 122.48, 121.34, 116.28, 115.90, 60.26, 59.80, 40.35, 38.01.

I.R: 3627, 2189, 1715, 1614 cm$^{-1}$.

8.45 Preparation of benzylamine salt of O-phenylisourea 288

Benzyamine (10 ml) was added to O-phenylisourea 288 (0.50 g, 1.62 mmol) and the resulting solution stirred at room temperature for 12 h. Chloroform (20 ml) was added and the reaction mixture was extracted with 5% citric acid solution (2x10 ml). The organic layer was dried (MgSO$_4$) and reduced to half its original volume by evaporation in vacuo. On cooling to 4 $^\circ$C for 12 h the product 289 crystallised from solution (0.50 g, 74%).

$^1$H n.m.r. (D), $\delta$: 7.80 (bs, NH), 7.44-7.04 (m, 15H, Ph), 4.30 (dd, PhCH$^\prime$, J$_{H'\cdot-H}$=15.84 Hz, J$_{H'\cdot-H}$=6.18 Hz), 4.28 (dd, PhCH$^\prime$, J$_{H'\cdot-H}$=15.84 Hz, J$_{H'\cdot-H}$=5.80 Hz), 4.10 (m, NHCH), 3.06 (dd, PhCH$^\prime$, J$_{H'\cdot-H}$=13.57 Hz, J$_{H'\cdot-H}$=5.18 Hz), 3.00 (dd, PhCH$^\prime$, J$_{H'\cdot-H}$=13.57 Hz, J$_{H'\cdot-H}$=5.40 Hz).

$^{13}$C n.m.r. (D), $\delta$: 172.01, 158.54, 138.50, 138.07, 135.74, 129.58, 128.59, 128.50, 128.27, 128.01, 127.90, 126.98, 126.82, 118.05, 56.47, 56.44, 44.25, 42.53, 39.09, 38.88.

I.R: 3364, 3229, 2170, 1602, 1553 cm$^{-1}$.

8.46 Reaction of benzylamine salt of O-phenylisourea 288 with benzylamine

Benzyamine (10 ml) was added to the benzylamine salt 289 (0.50 g, 1.20 mmol) and the resulting solution was heated to 100 $^\circ$C for 48 h. Chloroform (30 ml) was added and the mixture was extracted with 5% citric acid solution (3x20 ml). The chloroform layer was dried (MgSO$_4$), the solvent removed by evaporation in vacuo and the residue purified by flash chromatography, eluting with chloroform:methanol (9:1), to give 290 (0.31 g, 63%).

M.S. $m/e$: 412 (M$^+$), 320 (M$^+$-92), 277 (M$^+$-135), 91 (M$^+$-321).
1H n.m.r. (C), δ: 7.32-7.21 (m, 3H, Ph), 7.19-7.12 (m, 10H, Ph), 6.94-6.92 (m, 2H, Ph), 4.60 (d, PhCH', JH'-H''=14.88 Hz), 4.52 (d, PhCH'', JH'-H''=14.88 Hz), 4.36 (dd, NCH, JH-H'=4.56 Hz, JH-H''=6.50 Hz), 4.30 (s, PhCH₂), 3.22 (dd, PhCH', JH'-H''=13.68 Hz, JH*-H=4.56 Hz), 2.98 (dd, PhCH'', JH'-H=13.68 Hz, JH-H'=6.50 Hz).

13C n.m.r. (C), δ: 174.80, 160.01, 159.35, 137.80, 136.80, 136.63, 129.72, 128.75, 128.27, 128.06, 127.60, 127.35, 127.09, 126.96, 126.49, 65.32, 45.23, 42.70, 37.51.

I.R: 3437, 1755, 1712, 1620, 1586 cm⁻¹.

8.47 Preparation of N-cyano-N'-(1-benzylxycarbonylpropyl)-O-phenylisourea 293

To diphenyl cyanocarbonimidate 53 (1.89 g, 7.98 mmol) in propan-2-ol (40 ml) was added 2-aminobutyric acid benzyl ester 292 (1.54 g, 7.98 mmol) and the resulting solution was stirred at room temperature for 3 h. The solvent was reduced to half by evaporation in vacuo, and the reaction mixture was cooled to 4 °C for 2 h. The product that crystallised from solution was filtered, washed with ether and dried to give the title compound (2.10 g, 78%).

M.pt: 95-96 °C.

M.S. m/e: 337.1437 (C₁₉H₁₉N₃O₃ requires 337.1426) 337 (M⁺), 214 (M⁺-123), 145 (M⁺-192), 91 (M⁺-246).

1H n.m.r. (C, -20 °C), δ: 7.47-7.08 (m, 8H, Ph), 6.90 (d, 2H, Ph), 5.21 (s, PhCH₂), 5.15 (d, PhCH', JH'-H''=11.60 Hz)*, 5.10 (d, PhCH'', JH'-H''=11.60 Hz)*, 4.50-4.23 (m, NHCH), 2.04-1.85 (m, 1.5H, CH₂CH₃), 1.73-1.69 (m, 0.5H, CH₂CH₃)*, 1.02 (t, CH₃, JH-H=7.20 Hz), 0.75 (t, CH₃, JH-H=7.20 Hz)*.

13C n.m.r. (C, -20 °C), δ: 170.75*, 170.59, 163.19, 161.24*, 150.39, 149.49*, 134.69, 134.35, 130.71, 129.95, 129.49, 128.69, 128.58, 128.48, 128.30, 127.85, 127.52, 127.46, 126.42, 121.99, 120.96, 120.58, 114.49, 114.14, 67.70*, 67.43, 56.78, 56.23*, 24.75, 24.35*, 10.15, 9.01*.

*Peaks of minor stereoisomer present.

I.R: 3180, 3045, 2195, 1733, 1635 cm⁻¹.
8.48 Preparation of N-benzyl-N-methyl-N'-cyano-N"-(1-carboxybenzylpropyl) guanidine 294

N-methyl benzylamine (7 ml) was added to O-phenylisourea 293 (0.63 g, 1.87 mmol) and the resulting solution stirred at room temperature for 12 h. Chloroform (30 ml) was added and the reaction mixture extracted with 5% citric acid solution (2x20 ml). The chloroform layer was dried (MgSO$_4$), the solvent removed by evaporation in vacuo, and the product purified by flash chromatography, eluting with ethyl acetate:cyclohexane (2:1), to give the title compound (0.41 g, 60%).

M.S. $m/e$: 364 (M$^+$), 273 (M$^+$-91), 229 (M$^+$-135), 91 (M$^+$-273).

$^1$H n.m.r. (C), $\delta$: 7.37-7.29 (m, 8H, Ph), 7.21-7.20 (m, 2H, Ph), 5.31 (bd, NH, $J_{NH-H}$=7.68 Hz), 5.18 (d, PhCH', $J_{H'-H''}$=12.20 Hz), 5.13 (d, PhCH'', $J_{H''-H'}$=12.20 Hz), 4.87 (dt, NHCH, $J_{H-NH}$=7.68 Hz, $J_{H-H}$=11.30 Hz), 4.64 (d, PhCH', $J_{H-H}$=16.00 Hz), 4.57 (d, PhCH'', $J_{H''-H'}$=16.00 Hz), 3.05 (s, NCH$_3$), 2.02-1.91 (m, CH'CH$_3$), 1.84-1.74 (m, CH''CH$_3$), 0.78 (t, CH$_3$, $J_{H-H}$=7.44 Hz).

$^{13}$C n.m.r. (C), $\delta$: 172.13, 158.41, 135.26, 134.88, 129.02, 128.60, 128.54, 128.25, 128.05, 127.04, 116.82, 67.51, 56.05, 54.58, 36.81, 25.66, 8.73.

I.R: 3406, 2992, 2171, 1731, 1578 cm$^{-1}$.

8.49 Preparation of 2-(N-methylbenzylamine)-4-ethyl-imidazolidin-5-one 295

To a solution of guanidine 294 (0.40 g, 1.10 mmol) in degassed ethanol (30 ml) was added Pd/C (0.10 g, 10%) and the resulting suspension was stirred under an atmosphere of hydrogen (1 atm) for 12 h. The solution was filtered through celite, the solvent was removed by evaporation in vacuo and the residue was purified by flash chromatography, eluting with chloroform:methanol (9:1), to give the title compound (0.20 g, 79%).

M.pt: 124-126 °C.

M.S. $m/e$: 231.1365 (C$_{13}$H$_7$N$_3$O requires 231.1372)

231 (M$^+$), 216 (M$^+$-15), 202 (M$^+$-29), 91 (M$^+$-140).

$^1$H n.m.r. (C), $\delta$: 8.19 (bs, NH), 7.27-7.21 (m, 3H, Ph), 7.16-7.14 (m, 2H, Ph), 4.62 (bs, PhCH$_2$), 3.95 (bs, NHCH), 3.00 (bs, NCH$_3$), 2.93 (bs, NCH$_3$), 1.90-1.72 (m, CH"CH$_3$), 1.70-1.66 (m, CH"CH$_3$), 0.85 (bs, CH$_3$).
$^{13}$C n.m.r. (C), δ: 190.41, 171.14, 136.12, 128.96, 128.54, 127.63, 127.10, 63.71, 54.05, 52.65, 36.37, 33.93, 24.64, 8.72.

I.R: 3284, 2978, 1702, 1592, 1451 cm$^{-1}$.

8.50 Preparation of N-trifluoroaceto-N'-benzyl-O-phenylisourea 297 and N-trifluoroacetoxy-N'-benzyl-O-phenylisourea 298

A solution of O-phenylisourea 296 (0.40 g, 1.59 mmol) and trifluoroacetic acid (1.11 g, 9.74 mmol) in THF (20 ml) was heated to reflux for 8 h. The solvent was removed by evaporation in vacuo and the resulting oil purified by flash chromatography, eluting with chloroform:methanol (9:1) to give the O-phenylisourea 297 (0.20 g, 39%) and O-phenylisourea 298 (0.12 g, 22%). A sample of each was recrystallised from cyclohexane for analytical purposes.

O-phenylisourea 297

M.pt: 94-96 °C.

M.S. m/e: 189 (M+-133), 94 (M+-228), 91 (M+-231).

$^1$H n.m.r. (C), δ: 10.00 (bs, NH), 7.47-7.37 (m, 6H, Ph), 7.32-7.28 (m, 2H, Ph), 7.13 (d, 2H, PhO, J$_{H-H}$=1.2 Hz), 4.76 (d, PhCH$_2$, J$_{H-NH}$=5.6 Hz).

$^{13}$C n.m.r. (C), δ: 168.44 (q, COCF$_3$, J$_{C-F}$=36.92 Hz), 163.87, 150.89, 135.58, 129.25, 129.09, 128.33, 127.62, 126.30, 121.48, 116.13 (q, COCF$_3$, J$_{C-F}$=284.55 Hz), 42.04.

I.R: 3419, 1657, 1608, 1427 cm$^{-1}$.

Analysis: Calculated for C$_{16}$H$_{13}$N$_2$O$_2$F$_3$: C, 59.62; H, 4.03; N, 8.69; F, 17.69.

Found: C, 59.24; H, 3.88; N, 8.58; F, 16.90.

O-phenylisourea 298

M.pt: 110-112 °C.

M.S. m/e: 225 (M+-113), 133 (M+-205), 91 (M+-245).
\(^1\)H n.m.r. (C), \(\delta\): 7.46-7.32 (m, 8H, Ph), 7.01 (d, 2H, PhO, J\text{H-H}=7.6 Hz), 6.00 (bs, NH), 4.58 (s, PhCH\(_2\)).

\(^{13}\)C n.m.r. (C), \(\delta\): 163.19 (q, COCF\(_3\), J\text{C-F}=35.07 Hz), 160.05, 148.61, 136.25, 130.86, 128.80, 128.44, 127.94, 127.48, 120.79, 116.34 (q, COCF\(_3\), J\text{C-F}=290.46 Hz), 44.95.

I.R: 3336, 1684, 1531, 1440 cm\(^{-1}\).

Analysis: Calculated for C\(_{16}\)H\(_{13}\)N\(_2\)O\(_3\)F\(_3\): C, 56.80; H, 3.85; N, 8.28; F, 16.20.

Found: C, 56.51; H, 4.15; N, 8.26; F, 16.80.

8.51 Preparation of N-benzyl-N’-benzyl-N”-trifluoroacetyl guanidine 300

A solution of guanidine 299 (0.50 g, 1.89 mmol) and trifluoroacetic acid (1.32 g, 11.60 mmol) in THF (20 ml) was stirred at room temperature for 8 h. The solvent was removed by evaporation \textit{in vacuo} and the resulting oil purified by flash chromatography, eluting with chloroform:methanol (49:1), to give the guanidine 300 (0.41 g, 65%). A sample was recrystallised from cyclohexane for analytical purposes.

M.pt: 135-137\(^\circ\)C.

M.S. \(m/e\) : 267 (M\(^\text{+}-68\)), 266 (M\(^\text{+}-69\)), 244 (M\(^\text{+}-91\)), 91 (M\(^\text{+}-244\)).

\(^1\)H n.m.r. (C, 0\(^\circ\)C), \(\delta\): 10.06 (bs, NH), 7.37-7.27 (m, 8H, Ph), 7.12 (bs, 2H, Ph), 5.08 (bs, NH), 4.61 (bs, 2H, PhCH\(_2\)), 4.39 (bs, 2H, PhCH\(_2\)).

\(^{13}\)C n.m.r. (C, 45\(^\circ\)C), \(\delta\): 167.38 (q, COCF\(_3\), J\text{C-F}=35.23 Hz), 160.89, 129.09, 128.12, 127.37, 116.93 (q, COCF\(_3\), J\text{C-F}=285.15 Hz), 45.54.

I.R: 3321, 1608, 1568, 1436 cm\(^{-1}\).

Analysis: Calculated for C\(_{17}\)H\(_{16}\)N\(_3\)O\(_3\)F\(_3\): C, 60.89; H, 4.81; N, 12.53.

Found: C, 61.04; H, 4.75; N, 12.39.
8.52 Preparation of N-aceto-N'-benzyl-O-phenylisourea 301 and isourea 302

A solution of O-phenylisourea 296 (0.40 g, 1.59 mmol) and glacial acetic acid (0.57 g, 9.56 mmol) in THF (20 ml) was heated to reflux for 48 h. The solvent was removed by evaporation in vacuo and the resulting oil purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:3), to give the O-phenylisourea 301 (0.12 g, 26%) as an oil, and the isourea 302 (0.08 g, 26%).

O-phenylisourea 301

M.S. m/e: 
268.1211 (C₁₆H₁₆N₂O₂ requires 268.1212)
268 (M⁺), 253 (M⁺-15), 226 (M⁺-42), 191 (M⁺-77).

¹H n.m.r. (C), δ: 
7.36-7.18 (m, 8H, Ph), 7.05-7.03 (m, 2H, Ph), 4.63 (bs, PhCH₂), 1.99 (s, OCH₃).

¹³C n.m.r. (C), δ: 
185.80, 161.57, 151.48, 137.13, 129.09, 128.80, 127.72, 127.40, 125.52, 121.78, 45.33, 28.18.

I.R: 
3217, 1703, 1623, 1596 cm⁻¹.

Isourea 302

M.pt: 
125-127 °C.

M.S. m/e: 
192.0894 (C₁₀H₁₂N₂O₂ requires 192.0899)
192 (M⁺), 149 (M⁺-43), 133 (M⁺-59), 91 (M⁺-101).

¹H n.m.r. (C), δ: 
9.96 (bs, OH), 8.85 (bt, NH), 7.40-7.21 (m, Ph), 4.64 (d, PhCH₂ JₗH-H=6.00 Hz), 4.46 (d, PhCH₂, JₗH-H=6.00 Hz), 2.26 (s, OCH₃), 2.07 (s, OCH₃).

¹³C n.m.r. (C), δ: 
172.36, 162.52, 160.80, 154.78, 151.22, 137.99, 136.81, 129.22, 128.89, 128.60, 127.91, 127.47, 127.42, 127.39, 125.95, 121.83, 45.65, 43.51, 24.23, 23.91.

I.R: 
3302, 1730, 1693, 1666 cm⁻¹.
8.53 Preparation of N-benzyl-N'-benzyl-N''-acetyl guanidine 304

A solution of guanidine 299 (0.79 g, 2.99 mmol) and glacial acetic acid (1.07 g, 17.83 mmol) in THF (30 ml) was heated to reflux for 72 h. The solvent was removed by evaporation in vacuo and the resulting oil purified by flash chromatography, eluting with dichloromethane:ethyl acetate (1:1), to give the guanidine 304 (0.45 g, 54%).

M.pt: 75-76 °C.

M.S. m/e: 281.1537 (C17H19N3O requires 281.1528)
281 (M+), 266 (M+-15), 222 (M+-59), 91 (M+-190).

1H n.m.r. (C), δ: 7.30-7.24 (m, 6H, Ph), 7.17 (bs, 4H, Ph), 4.42 (bs, PhCH2), 2.10 (s, OCH3).

13C n.m.r. (C), δ: 181.50, 159.60, 128.80, 127.65, 127.06, 44.88, 28.36.

I.R: 3327, 3217, 1596, 1565 cm⁻¹.

8.54 Preparation of 1-aminO' 2-cyanomimino-4-ethylimidazolidin-5-one 305

A solution of O-phenylisourea 403 (0.22 g, 0.84 mmol) and hydrazine (0.035 g, 1.10 mmol) in propan-2-ol (7 ml) was stirred at room temperature for 75 min. The resulting precipitate was collected by filtration, washed with ether and dried to give imidazolidin-5-one 305 (120 mg, 85%).

M.pt: 137-139 °C.

M.S. m/e: 168.0892 (C6H10N5O requires 168.0885)
167 (M+), 139 (M+-28), 124 (M+-43), 110 (M+-47).

1H n.m.r. (D), δ: 9.67 (bs, NH), 4.94 (s, NH2), 4.18 (t, NHCH, JH-NH=5.84 Hz), 1.77-1.61 (m, CH2CH3), 0.84 (t, CH3, JH-H=7.52 Hz).

13C n.m.r. (D), δ: 172.59, 162.01, 115.51, 57.22, 28.82, 8.42.

I.R: 3413, 2187, 1761, 1752, 1654 cm⁻¹.
8.55 Preparation of urea 306

A solution of imidazolidin-5-one 166 (0.38 g, 1.25 mmol), trifluoroacetic acid (0.86 g, 7.54 mmol) and water (0.14 g, 7.54 mmol) in THF (10 ml) was heated to reflux for 6 h. The solvent was removed by evaporation in vacuo and the resulting oil triturated with ether to give the title compound as white crystals (0.25 g, 76%).

M.pt: 107-109 °C.

M.S. m/e: 322.1431 (C\textsubscript{18}H\textsubscript{18}N\textsubscript{4}O\textsubscript{2} requires 322.1430)
322 (M\textsuperscript{+}), 305 (M\textsuperscript{+}-17), 231 (M\textsuperscript{+}-91), 91 (M\textsuperscript{+}-231).

\textsuperscript{1}H n.m.r. (C), δ: 9.40 (bs, NH), 7.29-7.20 (m, 6H, Ph), 7.13-7.10 (m, 2H, Ph), 7.02-6.99 (m, 2H, Ph), 5.75 (bs, NH), 4.84 (d, PhCH\textsuperscript{′}, J\textsubscript{H-H\textsuperscript{′}}=15.40 Hz), 4.82 (d, PhCH\textsuperscript{″}, J\textsubscript{H-H\textsuperscript{″}}=15.40 Hz), 4.45 (dd, CHCH\textsubscript{2}, J\textsubscript{H-H\textsuperscript{′}}=4.48 Hz, J\textsubscript{H-H\textsuperscript{″}}=6.72 Hz), 3.26 (dd, PhCH\textsuperscript{′}, J\textsubscript{H-H\textsuperscript{′}}=14.32 Hz, J\textsubscript{H-H\textsuperscript{″}}=4.48 Hz), 3.05 (dd, PhCH\textsuperscript{″}, J\textsubscript{H-H\textsuperscript{″}}=14.32 Hz, J\textsubscript{H-H\textsuperscript{′}}=6.72 Hz).

\textsuperscript{13}C n.m.r. (C), δ: 171.74, 160.69, 158.64, 133.96, 133.23, 129.33, 129.05, 128.71, 128.06, 127.91, 127.58, 59.13, 42.86, 36.87.

I.R: 3266, 1788, 1755, 1740, 1693 cm\textsuperscript{-1}.

8.56 Preparation of urea 307

A solution of imidazolidin-5-one 128 (0.41 g, 1.43 mmol), trifluoroacetic acid (0.98 g, 8.60 mmol) and water (0.15 g, 8.60 mmol) in THF (10 ml) was heated to reflux for 3 h. The solvent was removed in vacuo and the resulting oil purified by flash chromatography, eluting with chloroform:methanol (49:1), to give the urea 307 (0.30 g, 69%).

M.pt: 106-108 °C.

M.S. m/e: 304.1176 (C\textsubscript{14}H\textsubscript{16}N\textsubscript{4}O\textsubscript{4} requires 304.1171)
304 (M\textsuperscript{+}), 287 (M\textsuperscript{+}-17), 261 (M\textsuperscript{+}-43), 91 (M\textsuperscript{+}-213).

\textsuperscript{1}H n.m.r. (C), δ: 9.50 (bs, NH\textsubscript{2}), 7.39-7.26 (m, Ph), 6.06 (bs, NH), 4.95 (d, PhCH\textsuperscript{′}, J\textsubscript{H-H\textsuperscript{′}}=15.00 Hz), 4.91 (d, PhCH\textsuperscript{″}, J\textsubscript{H-H\textsuperscript{″}}=15.00 Hz), 4.45 (dd, CHCH\textsubscript{2}, J\textsubscript{H-H\textsuperscript{′}}=3.62 Hz, J\textsubscript{H-H\textsuperscript{″}}=7.90 Hz), 3.66 (s, OCH\textsubscript{3}), 3.04 (dd, CH\textsuperscript{′}CO\textsubscript{2}.}
\( J_H: H^* = 17.68 \text{ Hz}, J_H: H = 3.62 \text{ Hz}, \) 2.80 (dd, CH\(^\text{CO}_2\), \( J_H: H^* = 17.68 \text{ Hz}, J_H: H = 7.90 \text{ Hz} \)).

\( ^{13}C \text{n.m.r. (C), } \delta: \) 171.71, 169.55, 161.42, 158.96, 134.37, 128.80, 128.39, 128.32, 54.27, 52.60, 43.26, 35.09.

I.R: 3315, 1785, 1742, 1684 cm\(^{-1}\).

### 8.57 Preparation of urea 308

A solution of imidazolidin-5-one 247 (0.12 g, 0.45 mmol), trifluoroacetic acid (0.28 g, 2.46 mmol) and water (0.04 g, 2.46 mmol) in THF (6 ml) was heated to reflux for 3 h. The solvent was removed by evaporation in vacuo and the product purified by flash chromatography, eluting with ethyl acetate:cyclohexane (4:1), to give the urea 308 (0.10 g, 74%).

M.pt: 100-102 °C.

M.S. m/e: 301.1675 (C\(_{16}\)H\(_{21}\)N\(_4\)O\(_2\) requires 301.1664)

\( 300 (\text{M}^+), 283 (\text{M}^+ - 17), 233 (\text{M}^+ - 67), 91 (\text{M}^+ - 209) \).

\( ^1H \text{n.m.r. (C), } \delta: \) 8.83 (bs, NH), 7.28-7.15 (m, Ph), 5.02 (bs, NH\(_2\)), 4.38 (m, CHN), 4.18 (dd, CHCH\(_2\), \( J_H: H^* = 3.92 \text{ Hz}, J_H: H = 7.32 \text{ Hz} \)), 3.14 (dd, PhCH\(_2\), \( J_H: H^* = 3.92 \text{ Hz}, J_H: H = 14.04 \text{ Hz} \)), 2.90 (dd, PhCH\(_3\), \( J_H: H^* = 14.04 \text{ Hz}, J_H: H = 7.32 \text{ Hz} \)), 1.98-1.04 (m, 8H, CH\(_2\)).

\( ^{13}C \text{n.m.r. (C), } \delta: \) 173.07, 165.87, 159.77, 134.66, 129.35, 128.66, 127.29, 58.47, 51.98, 37.82, 28.40, 28.19, 24.90.

I.R: 3541, 1739, 1647, 1617 cm\(^{-1}\).

### 8.58 Preparation of 5,6-dihydro-4(3H)pyrimidinone 309

A solution of imidazolidin-5-one 307 (0.127 g, 0.42 mmol) in 2 M sodium hydroxide solution (2 ml) was stirred at room temperature for 6 min. The solution was acidified to pH 1.0 with concentrated hydrochloric acid and the solvent volume reduced to one half by evaporation in vacuo when the product precipitated from solution. The product was collected by filtration and dried to give the title compound (0.090 g, 74%).

M.pt: 188-190 °C.
M.S. m/e : 290 (M+), 261 (M+ -29), 227 (M+ -63), 91 (M+ -199).

$^1$H n.m.r. (D), $\delta$: 8.93 (bs, CO$_2$H), 7.34-7.22 (m, Ph), 6.50 (bs, NH), 6.24 (bs, NH), 4.66 (d, PhCH', $J_{H'-H}=15.36$ Hz), 4.61 (d, PhCH'', $J_{H''-H}=15.36$ Hz), 4.38 (m, CHCO$_2$), 2.85 (dd, CHCH', $J_{H'-H}=4.64$ Hz, $J_{H'-H''}=17.36$ Hz), 2.77 (dd, CHCH'', $J_{H''-H}=5.46$ Hz, $J_{H''-H''}=17.36$ Hz).

$^{13}$C n.m.r. (D), $\delta$: 173.52, 171.15, 164.74, 157.99, 136.60, 128.26, 127.40, 127.33, 127.27, 54.00, 53.83, 41.66, 34.69.

I.R: 3480, 1746, 1700, 1632 cm$^{-1}$.

8.59 Preparation of urea 310

A solution of imidazolidin-5-one 305 (0.088 g, 0.52 mmol), trifluoroacetic acid (0.36 g, 3.15 mmol) and water (0.06 g, 3.15 mmol) in THF (10 ml) was heated to reflux for 2 h. The solvent was removed by evaporation in vacuo and ether (6 ml) added. The resulting solution was cooled to 4°C for 8 h during which the product crystallised from solution. The product was collected by filtration and recrystallised from methanol/ether to give the title compound (0.060 g, 62%).

M.pt: 215-217 °C.

M.S. m/e : 185.0918 (C$_6$H$_{11}$N$_5$O$_2$ requires 185.0913)
185 (M+), 167 (M+ -18), 139 (M+ -46), 96 (M+ -89).

$^1$H n.m.r. (D), $\delta$: 8.59 (bs, NH), 6.17 (bs, NH$_2$), 4.33 (dt, CHCH$_2$, $J_{H'-H}=5.48$ Hz, $J_{H-NH}=1.56$ Hz), 3.40 (bs, NH$_2$), 1.84-1.77 (m, CH'CH$_3$), 1.70-1.59 (m, CH''CH$_3$), 0.87 (t, CH$_3$, $J_{H-H}=7.20$ Hz).

$^{13}$C n.m.r. (D), $\delta$: 170.62, 165.49, 163.72, 65.76, 24.26, 8.93.

I.R: 3339, 1739, 1653, 1565 cm$^{-1}$.

8.60 Preparation of urea 311

A solution of guanidine 299 (0.50 g, 1.89 mmol), trifluoroacetic acid (1.32 g, 11.60 mmol) and water (0.20 g, 11.60 mmol) in THF (12 ml) was heated to reflux for 4 h. The solvent was removed by evaporation in vacuo and the resulting oil purified by flash chromatography, eluting with chloroform/methanol (19:1) to give the urea 311 (0.40 g, 75 %). A sample was recrystallised from chloroform/cyclohexane for analytical purposes.
M.pt: 111-113 °C.

M.S. m/e: 282.1489 (C_{16}H_{18}N_{4}O requires 282.1481)
282 (M^+), 239 (M^+-43), 169 (M^+-113), 91 (M^+-191).

^1H n.m.r. (C), δ: 10.02 (bs, NH), 7.28-7.16 (m, Ph), 4.86 (bs, NH and NH_2), 4.36 (bs, PhCH_2).

^13C n.m.r. (C), δ: 167.11, 159.23, 139.00, 128.61, 127.34, 126.88, 44.69.

I.R: 3474, 1724, 1629, 1617 cm^-1.

8.61 Preparation of urea 312

A solution of O-phenylisourea 296 (0.60 g, 2.39 mmol) and trifluoroacetic acid (1.63 g, 14.29 mmol) in THF (20 ml) was stirred at room temperature for 13 days. The solvent was removed by evaporation *in vacuo* and the resulting oil purified by flash chromatography, eluting with ethyl acetate:cyclohexane (2:3), to give the title compound (0.40 g, 62%).

M.pt: 138-140 °C.

M.S. m/e: 269.1179 (C_{15}H_{15}N_{3}O requires 269.1164)
269 (M^+), 253 (M^+-16), 226 (M^+-43), 91 (M^+-178).

^1H n.m.r. (C), δ: 9.90 (bs, NH), 7.78-7.19 (m, 8H, Ph), 7.01 (d, 2H, PhO, J_{H,H}=7.60 Hz),
5.80 (bs, NH), 4.85 (bs, NH), 4.61 (s, PhCH_2).

^13C n.m.r. (C), δ: 163.99, 160.88, 151.26, 137.09, 129.39, 128.81, 127.75, 127.34,
125.99, 121.56, 45.47.

I.R: 3474, 1739, 1641, 1617 cm^-1.

8.62 Preparation of N-cyano-N'-benzyl-N'-methyl-O-phenylisourea 313

To a solution of diphenyl cyanocarbonimidate 53 (0.11 g, 0.46 mmol) in propan-2-ol (10 ml) was added N-methyl benzylamine (0.07 g, 0.58 mmol) and the resulting solution was stirred at room temperature for 2 h. The solvent volume was reduced to one half by evaporation *in vacuo* and the reaction mixture cooled to 4 °C for 2 h. The crystalline product was filtered, washed with ether and dried to give the title compound (0.10 g, 85%).
M.pt: 122-124 °C.

M.S. m/e: 265.1240 (C₁₆H₁₅N₃O requires 265.1215)
265 (M⁺), 250 (M⁺-15), 208 (M⁺-57), 91 (M⁺-174).

¹H n.m.r. (C), δ: 7.45-7.25 (m, 8H, Ph). 7.12 (d, 2H, Ph), 4.69 (bs, CH₂), 3.12 (bs, CH₃).

¹³C n.m.r. (C), δ: 157.99, 157.80, 134.79, 129.95, 128.87, 128.19, 127.71, 127.63, 125.86, 118.80, 54.15, 36.64, 34.19.

I.R: 2990, 2187, 1617, 1476 cm⁻¹.

8.63 Preparation of N-trifluoroaceto-N'-benzyl-N'-methyl-O-phenylisourea 314

A solution of O-phenylisourea 313 (0.34 g, 1.28 mmol) and trifluoroacetic acid (0.88 g, 7.69 mmol) in THF (15 ml) was stirred for 12 h at room temperature. The solvent was removed by evaporation in vacuo and the resulting oil purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:1) to give the O-phenylisourea 314 (0.25 g, 58%). A sample was recrystallised from cyclohexane for analytical purposes.

M.pt: 60-62 °C.

M.S m/e: 279 (M⁺-57), 267 (M⁺-69), 243 (M⁺-93), 91 (M⁺-245).

¹H n.m.r. (C), δ: 7.33-7.24 (m, 7H, Ph), 7.16-7.12 (m, 1H, Ph), 7.06-7.05 (m, 2H, Ph), 4.71 (bs, 1.3H, CH₂), 4.62 (bs, 0.7H, CH₂), 3.06 (bs, 3H, CH₃), 3.02 (bs, 1.7H, CH₃).

¹³C n.m.r. (C), δ: 163.96, 159.57 (q, J_C·F=35.91 Hz), 159.51 (q, J_C·F=38.09 Hz), 151.81, 151.71, 133.95, 129.41, 129.08, 128.41, 127.46, 126.31, 120.15, 119.97, 116.36 (q, J_C·F=285.60 Hz), 55.22, 54.26, 37.24, 34.84.

I.R: 2953, 1721, 1617, 1589 cm⁻¹.

8.64 Preparation of N-benzyl-N-methyl-N'-cyano-N''-(methyl propionate)-guanidine 326

To a solution of O-phenylisourea 638 (0.40 g, 1.62 mmol) in propan-2-ol (25 ml) was added N-methyl-benzylamine (1.95 g, 16.12 mmol) and the solution was stirred for 12 h. The solvent was removed by evaporation in vacuo and the residue redissolved in chloroform (20 ml).
The chloroform was extracted with 5% citric acid solution (2x10 ml), dried (MgSO₄) and the solvent removed by evaporation in vacuo. The residue was purified by flash chromatography, eluting with ethyl acetate:cyclohexane (1:1) to give the title compound (0.40 g, 90 %) as an oil.

M.S. m/e : 274 (M⁺), 259 (M⁺-15), 215 (M⁺-59), 91 (M⁺-183).

¹H n.m.r. (C), δ: 7.34-7.00 (m, Ph), 5.77 (bs, NH), 4.57 (s, PhCH₂), 3.76 (dt, CH₂N, JH-H=6.04 Hz, JH-H=5.88 Hz), 3.62 (s, OCH₃), 2.95 (s, NCH₃), 2.62 (t, CH₂, JH-H=5.88 Hz).

¹³C n.m.r. (C), δ: 173.06, 158.89, 135.60, 128.87, 127.87, 127.14, 117.42, 54.35, 51.88, 38.62, 36.41, 33.89.

I.R: 3217, 2164, 1739, 1544 cm⁻¹.

8.65 Preparation of N-benzyl-N-methyl-N'-cyano-N''-(2-carboxyethyl)-guanidine 327

To guanidine 326 (0.20 g, 0.73 mmol) in methanol (10 ml) was added sodium hydroxide solution (0.36 ml, 2M, 0.73 mmol) and the solution was stirred for 3 h. The solvent was removed by evaporation in vacuo and the residue was purified by flash chromatography, initially eluting with chloroform:methanol (9:1) and increasing the polarity to a final value of 6:4. Fractions containing the product were pooled to give the title compound as a white foam (0.15 g, 79 %). A sample was recrystallised from methanol for analytical purposes.

M.pt: 116-118 °C.

M.S. m/e : 188 (M⁺-72), 173 (M⁺-83), 91 (M⁺-169).

¹H n.m.r. (C), δ: 7.60 (bs, NH), 7.35-7.20 (m, Ph), 4.58 (s, PhCH₂), 3.55 (m, NCH₂), 2.84 (s, NCH₃), 2.25 (t, CH₂, JH-H=6.67 Hz).

¹³C n.m.r. (C), δ: 177.09, 158.82, 137.17, 128.58, 127.25, 117.45, 53.23, 39.75, 36.72, 36.03.

I.R: 3315, 2164, 1708, 1562 cm⁻¹.
8.66 Preparation of 3-amino-5-phenoxy-s-triazole 390

A solution of diphenyl cyanocarbonimidate 53 (0.50 g, 2.10 mmol) and hydrazine (0.08 g, 2.50 mmol) in propan-2-ol (15 ml) was heated to reflux for 3 h. The volume of the solvent was reduced to half by evaporation in vacuo and cooled to 4 °C. The resulting precipitate was removed by filtration to give s-triazole 390 (0.22 g, 59%).

M.pt: 128-130 °C.

M.S. m/e: 176.0704 (C_8H_8N_4O requires 176.0698)
          176 (M^+), 148 (M^+-27), 119 (M^+-56), 77 (M^+-98).

^1H n.m.r. (D), δ: 11.49 (bs, NH), 7.35-7.31 (m, 2H, Ph), 7.11-7.07 (m, 3H, Ph), 6.09 (bs, NH_2).

^13C n.m.r. (D), δ: 163.59, 156.08, 155.39, 129.39, 123.44, 118.37.

I.R: 3437, 3149, 1651, 1590 cm\(^{-1}\).

Analysis: Calculated for C_8H_8N_4O: C, 54.55; H, 4.54; N, 31.82.
          Found: C, 53.88; H, 4.38; N, 32.21.

8.67 Preparation of 1-methyl-3-amino-5-phenoxy-s-triazole 391

A solution of diphenyl cyanocarbonimidate 53 (0.50 g, 2.1 mmol) and methylhydrazine (0.13 g, 2.8 mmol) in propan-2-ol (15 ml) was stirred at room temperature for 2 h. The solvent was removed by evaporation in vacuo and the resulting oil purified by flash chromatography, eluting with chloroform:methanol (49:1). Product fractions were collected and reduced to a small volume. Cyclohexane was added until the solution became cloudy and the mixture was cooled to 4 °C when precipitation occurred. The crystalline product was removed by filtration and dried to give s-triazole 391 (0.22 g, 63%).

M.pt: 109-110 °C.

M.S. m/e: 190.0855 (C_9H_10N_4O requires 190.0855)
          190 (M^+), 119 (M^+-71), 91 (M^+-99), 77 (M^+-113).

^1H n.m.r. (D), δ: 7.43-7.41 (m, 2H, Ph), 7.39-7.20 (m, 3H, Ph), 5.23 (bs, NH_2), 3.47 (s, NCH_3).
170

13C n.m.r. (D), δ: 159.73, 154.64, 154.03, 129.74, 125.06, 119.24, 32.39.

I.R: 3364, 1641, 1580, 1516 cm⁻¹.

Analysis: Calculated for C9H10N4O: C, 56.54; H, 5.26; N, 29.47.
Found: C, 56.73; H, 5.13; N, 28.88.

8.68 Preparation of 1-phenyl-3-amino-5-phenoxy-s-triazole 392

A solution of diphenyl cyanocarbonimidate 53 (0.30 g, 1.26 mmol) and phenylhydrazine (0.10 g, 1.51 mmol) in propan-2-ol (15 ml) was heated to reflux for 6 h. The solution was cooled and the resulting precipitate removed by filtration to give s-triazole 392 (0.20 g, 63%).

M.pt: 165-167 °C.

M.S. m/e: 252.1021 (C14H12N4O requires 252.1011)
252 (M⁺), 235 (M⁺-17), 134 (M⁺-118), 91 (M⁺-161).

1H n.m.r. (D), δ: 7.50-7.45 (m, 4H, Ph), 7.40-7.30 (m, 2H, Ph), 7.23-7.10 (m, 2H, Ph), 6.62 (bs, NH2).

13C n.m.r. (D), δ: 163.85, 154.65, 154.03, 136.97, 129.52, 129.37, 126.73, 124.09, 122.52, 119.14.

I.R: 3382, 3119, 1641, 1562 cm⁻¹.

8.69 Preparation of methyl 2-(5-amino-(3-amino-s-triazole))ethanoate 396

A solution of O-phenylisourea 395 (0.25 g, 1.07 mmol) and hydrazine (0.04 g, 1.25 mmol) in propan-2-ol (20 ml) was heated to reflux for 8 h. The solution was then reduced to half volume by evaporation in vacuo, cooled to 4⁰ C and the resulting precipitate collected by filtration. The precipitate was washed with ether to give s-triazole 396 (0.14 g, 95%).

M.pt: 162-163⁰ C.

M.S. m/e: 171 (M⁺), 139 (M⁺-32), 119 (M⁺-52), 112 (M⁺-59).

1H n.m.r. (D), δ: 10.75 (bs, NH), 5.65 (bs, NH2), 3.76 (d, NHCH, JH-NH=6.0 Hz), 3.59 (s, OCH3).
13C n.m.r. (D), δ: 172.07, 161.67, 156.08, 51.36, 44.33.

I.R: 3406, 1724, 1654, 1571 cm⁻¹.

Analysis: Calculated for C₅H₉N₅O₂: C, 35.08; H, 5.26; N, 40.94. Found: C, 34.90; H, 5.29; N, 42.46.

8.70 Preparation of methyl 3-(5-amino-(3-amino-s-triazole))propionate 397

A solution of O-phenylisourea 63 (0.42 g, 1.70 mmol) and hydrazine (0.07 g, 2.20 mmol) in propan-2-ol (10 ml) was stirred at room temperature for 6 h. The solvent volume was reduced to one half by evaporation in vacuo and ether added. On cooling to 4 °C the product crystallised from solution and was collected by filtration to give the s-triazole 397 (0.29 g, 93%).

M.pt: 135-137 °C.

M.S. m/e: 185.0911 (C₆H₁₁N₅O₂ requires 185.0913)
185 (M⁺), 153 (M⁺-32), 126 (M⁺-59), 112 (M⁺-73).

¹H n.m.r. (D), δ: 10.70 (bs, NH), 5.40 (bs, NH₂), 3.57 (s, OCH₃), 3.22 (q, NHCH₂, Jₜ-H=6.80 Hz, Jₜ-H=6.96 Hz), 2.52 (t, CH₂CO₂Me, Jₜ-H=6.96 Hz).

¹³C n.m.r. (D), δ: 172.23, 161.90, 158.50, 51.27, 38.84, 34.05.

I.R: 3443, 1718, 1608, 1565 cm⁻¹.

Analysis: Calculated for C₆H₁₁N₅O₂: C, 38.92; H, 5.94; N, 37.84. Found: C, 39.08; H, 5.99; N, 37.91.

8.71 Preparation of methyl 4-(5-methylamino-(3-amino-s-triazole))butanoate 399

A solution of O-phenylisourea 39883 (0.82 g, 2.98 mmol) and hydrazine (0.11 g, 3.43 mmol) in propan-2-ol (40 ml) was heated to reflux for 7 h. Cyclohexane was then added until the solution just became cloudy and the mixture was kept at 15° C for 8 h. The precipitated crystalline material was collected by filtration, washed with ether and dried to give s-triazole 399 (0.60 g, 94%).

M.pt: 76-78 °C.
M.S. m/e: 213.1226 (C₈H₁₅N₅O₂ requires 213.1219)
213 (M⁺), 181 (M⁺-32), 140 (M⁺-73), 126 (M⁺-87).

¹H n.m.r. (D), δ: 10.83 (bs, NH), 5.48 (bs, NH₂), 3.56 (s, OCH₃), 3.18 (t, N(Me)CH₂,
J_H_H=7.10 Hz), 2.75 (s, NCH₃), 2.25 (t, CH₂CO₂Me, J_H_H=7.58 Hz), 1.72 (tt, CH₂CH₂CH₂, J_H_H=7.1 Hz, J_H_H=7.58 Hz).

¹³C n.m.r. (D), δ: 173.21, 161.20, 157.40, 51.30, 49.51, 35.56, 30.80, 22.15.

I.R: 3406, 1721, 1654, 1605 cm⁻¹.

8.72 Preparation of 3-amino-7-benzyl-1,2,4,6-tetraazabicyclo[3.3.0]octan-8-one 400

A solution of O-phenylisourea 246 (0.26 g, 0.65 mmol) and hydrazine (0.025 g, 0.78
mmol) in propan-2-ol (20 ml) was stirred at 40 °C for 1 h. The solution was cooled to 4 °C and the
precipitate collected by filtration and dried to give the octan-8-one 400 (0.10 g, 67%).

M.pt: 152-154 °C.

M.S. m/e: 229.0975 (C₁₁H₁₁N₅O requires 229.0964)
229 (M⁺), 170 (M⁺-59), 110 (M⁺-119), 91 (M⁺-138).

¹H n.m.r. (D), δ: 10.69 (bs, NH), 9.04 (bs, NH), 7.26-7.22 (m, 4H, Ph), 7.16-7.14 (m, 1H,
Ph), 4.17-4.11 (m, NH₂ and CHCH₂), 2.89 (dd, PhCH', J_H_H=13.72 Hz,
J_H_H=4.68 Hz), 2.79 (dd, PhCH'', J_H_H=13.72 Hz, J_H_H=9.24 Hz).

¹³C n.m.r. (D), δ: 172.11, 161.01, 156.00, 138.61, 129.24, 127.98, 126.08, 56.70,
38.88.

I.R: 3314, 1641, 1565, 1534 cm⁻¹.

8.73 Preparation of 3-amino-7-methoxycarbonylmethyl-1,2,4,6-
tetraazabicyclo[3.3.0]octan-8-one 401

A solution of O-phenylisourea 127 (0.30 g, 0.98 mmol) and hydrazine (0.039 g, 1.22
mmol) in propan-2-ol (25 ml) was heated to 60 °C for 2 h. The volume of the solution was reduced
to one half by evaporation *in vacuo* and ether was added. On cooling to 4 °C the product precipitated from solution and was collected by filtration, washed with ether and dried to give octan-8-one 401 (0.090 g, 43%).

**M.pt:** 117-119 °C.

**M.S. *m/e*:**
- 211.0700 (C7H9N5O3 requires 211.0705)
- 211 (M+), 184 (M+-27), 152 (M+-59), 124 (M+-87).

**1H n.m.r. (D), δ:**
- 10.78 (bs, NH), 5.55 (bs, NH₂), 4.46-4.27 (m, CHCH₂), 3.58 (s, OCH₃), 2.82-2.73 (m, CH₂).

**13C n.m.r. (D), δ:**
- 173.09, 170.87, 159.90, 156.50, 51.90, 51.04, 36.49.

**I.R:** 3449, 3370, 1736, 1565 cm⁻¹.

**8.74 Preparation of N-cyano-N'-(methyl 2-propionate)-O-phenylisourea 402**

Triethylamine (0.86 g, 8.85 mmol) was added to a stirred suspension of S-alanine-methyl ester hydrochloride (1.0 g, 7.17 mmol) and diphenyl cyanocarbonimidate 53 (1.71 g, 7.17 mmol) in propan-2-ol (40 ml) and the resulting solution heated to reflux for 3 h. The solvent was removed by evaporation *in vacuo* and the residue dissolved in chloroform (30 ml) and washed with saturated sodium bicarbonate (2x20 ml). The organic layer was dried (MgSO₄) and the solvent removed by evaporation *in vacuo*. The residue was redissolved in propan-2-ol (20 ml) and cooled to 4° C for 4 h. The resulting crystalline product was collected by filtration to give the O-phenylisourea 402 (1.0 g, 56%).

**M.pt:** 108-110 °C.

**M.S. *m/e* :**
- 188 (M+-59), 153 (M+-94), 126 (M+-121), 118 (M+-129).

**1H n.m.r. (C), δ:**
- 7.45-7.02 (m, PhO), 5.70 (bs, NH), 4.53 (m, NHCH), 3.78 (bs, OCH₃), 1.55 (bd, CH₃, J_H-H=6.8 Hz), 1.42 (bs, CH₃).

**13C n.m.r. (C), δ:**
- 171.60, 163.07, 150.79, 130.63, 129.53, 127.70, 126.73, 121.30, 121.00, 114.49, 52.89, 51.20, 17.62.

**I.R:** 3437, 2189, 1730, 1635 cm⁻¹.
8.75 Preparation of N-cyano-N’-(methyl 2-butanoate)-O-phenylisourea 403

Triethylamine (1.75 g, 17 mmol) was added to methyl 2-amino-butanoate hydrochloride (2.05 g, 13 mmol) in benzene (20 ml), with stirring. Dry ether was added and the resulting precipitate of triethylamine hydrochloride was removed by filtration. The solvent was removed from the filtrate to give methyl 2-amino-butanoate 404 as a yellow oil (0.46 g, 3.93 mmol). N-cyanocarbonimidate 53 (0.94 g, 3.93 mmol) was added to a solution of 404 (0.46 g, 3.93 mmol) in propan-2-ol (20 ml) and the mixture stirred at room temperature for 8 h. The resulting white precipitate was removed by filtration and a second crop was obtained by a similar method (2.1 g, 62%).

M.S. m/e: 262.1189 (C13H15N3O3 requires 262.1191)
261 (M+), 202 (M+-59), 140 (M+-120), 94 (M+-167).

1H n.m.r. (C), δ:
7.47-7.04 (m, Ph), 6.77 (bs, NH), 4.46 (m, NHCH), 3.79 (s, OCH3), 3.73 (s, OCH3), 2.04-1.70 (m, CH2CH3), 1.04 (t, CH3, JH-H=7.30 Hz), 0.82 (t, CH3, JH-H=7.30 Hz).

13C n.m.r. (C), δ:
170.95, 163.23, 150.76, 130.70, 129.56, 127.78, 126.79, 121.98, 121.17, 114.41, 113.67, 56.72, 56.61, 52.86, 52.75, 25.31, 24.63, 9.93, 9.06.

I.R: 3443, 2200, 1730, 1645 cm⁻¹.

Analysis: Calculated for C13H15N3O3: C, 59.77; H, 5.75; N, 16.09.
Found: C, 60.01; H, 5.71; N, 15.99.

8.76 Preparation of methyl 2-(5-amino-(3-amino-s-triazole))propionate 404

A solution of O-phenylisourea 402 (0.140 g, 0.57 mmol) and hydrazine (0.023 g, 0.70 mmol) in propan-2-ol (6 ml) was heated to reflux for 20 min. Cyclohexane was added and the mixture cooled to 4° when precipitation occurred. The precipitate was collected by filtration, washed with ether and dried to give the s-triazole 404 (0.075 g, 71%).

M.pt: 189-191 °C.
M.S. \( m/e \): 186.0996 (C\(_6\)H\(_{11}\)N\(_5\)O\(_2\) requires 186.0991)
186 (MH\(^+\)), 185 (M\(^+\)), 126 (M\(^+\)-59).

\( ^1H \) n.m.r. (D), \( \delta \): 10.73 (bs, NH), 5.84 (bs, NH), 5.53 (bs, NH\(_2\)), 4.01 (m, NHCH), 3.57 (s, OCH\(_3\)), 1.27 (d, CH\(_3\), \( J_{H-H}=7.6 \) Hz).

\( ^13C \) n.m.r. (D), \( \delta \): 175.05, 160.01, 157.30, 50.84, 50.71, 18.12.

I.R: 3437, 1724, 1654, 1568 cm\(^{-1}\).

8.77 Preparation of methyl 2-(5-amino-(3-amino-s-triazole))butanoate 405

A solution of O-phenylisourea 403 (0.28 g, 1.07 mmol) and hydrazine (0.040 g, 1.25 mmol) in propan-2-ol (20 ml) was heated to reflux for 3.5 h. The solvent volume was reduced to half in vacuo, ether was added and mixture was cooled to 4 °C. The resulting precipitate was collected by filtration and washed with ether to give the s-triazole 405 (0.15 g, 70%).

M.pt: 169-171 °C.

M.S. \( m/e \): 199.1076 (C\(_7\)H\(_{13}\)N\(_5\)O\(_2\) requires 199.1069)
199 (M\(^+\)), 170 (M\(^+\)-29), 140 (M\(^+\)-59).

\( ^1H \) n.m.r. (D), \( \delta \): 10.71 (bs, NH), 5.65 (bs, NH\(_2\)), 3.91-3.89 (m, NHCH), 3.57 (s, OCH\(_3\)), 1.70 -1.60 (m, CH\(_2\)CH\(_3\)), 0.89 (t, CH\(_3\), \( J_{H-H}=7.60 \) Hz).

\( ^13C \) n.m.r. (D), \( \delta \): 172.45, 159.50, 154.01, 54.90, 49.32, 22.99, 8.51.

I.R: 3425, 1724, 1651, 1568 cm\(^{-1}\).

8.78 Preparation of 3-amino-7-ethyl-1,2,4,6-tetraazabicyclo[3.3.0]octan-8 one 407

To a solution of O-phenylisourea 293 (1.00 g, 2.97 mmol) in propan-2-ol (40 ml) was added hydrazine (0.11 g, 3.56 mmol) and the resulting solution stirred at room temperature for 2 h. The solvent volume was reduced to one half by evaporation in vacuo and the resulting solution cooled to -10 °C for 2 h. The precipitated solid was collected by filtration, washed with ether and recrystallised from a large volume of propan-2-ol to give title compound (0.35 g, 71%).

M.pt: 200-202 °C.
8.79 Preparation of 1-amino-2-cyanolmino-4-methyl-2-imidazolidin-5-one 408

A solution of O-phenylisourea 402 (0.23 g, 0.93 mmol) and hydrazine (0.09 g, 1.25 mmol) in propan-2-ol (15 ml) was stirred at room temperature for 3 h. A precipitate formed which, at the end of this period, was collected by filtration, washed with ether and dried to give the imidazolidin-5-one 408 (0.11 g, 77%).

M.pt: 155-157° C.

M.S. m/e: 168.0881 (C₆H₉N₅O requires 167.0807)
168 (M⁺), 140 (M⁺-28), 126 (M⁺-42), 99 (M⁺-69).

¹H n.m.r. (D), δ: 8.95 (bs, NH), 5.50 (bs, NH₂), 3.79 (dd, CHCH₂, J=7.28 Hz, J=15.04 Hz), 1.66-1.48 (m, CH₂), 0.83 (t, CH₃, J=7.60 Hz).

¹³C n.m.r. (D), δ: 172.36, 56.56, 25.97, 10.35.

I.R: 3394, 1620, 1596, 1546 cm⁻¹.

Analysis: Calculated for C₅H₇N₅O: C, 39.22; H, 4.58; N, 45.75.
Found: C, 39.54; H, 4.85; N, 44.35.

8.80 Preparation of methyl 2-(5-amino-(3-amino-1-methyl-s-triazole))butanoate 410

A solution of O-phenylisourea 403 (0.26 g, 1.0 mmol) and methylhydrazine (0.059 g, 1.2 mmol) in propan-2-ol (20 ml) was heated to reflux for 6 h. After removal of the solvent by evaporation in vacuo the residue was purified by flash chromatography, eluting with chloroform:methanol (9:1), to give the s-trazole 410 as an oil (0.155 g, 73%).
M.S. m/e : 214.1305 (C₈H₁₅N₅O₂ requires 214.1304)
214 (MH⁺), 213 (M⁺), 154 (M⁺-59).

¹H n.m.r. (C), δ: 4.75 (d, NH, JₙH-NH=8.40 Hz), 4.32 (ddd, CHCH₂, Jₖ-NH=8.40 Hz, Jₖ-
H=6.92 Hz, Jₖ-N-H=6.22 Hz), 3.91 (bs, NH₂), 3.69 (s, OCH₃), 3.37 (s, NCH₃), 1.92-1.83 (m, CH'CH₃), 1.87-1.67 (m, CH''CH₃), 0.91 (t, CH₃, Jₗ-H=7.56 Hz).

¹⁳C n.m.r. (C), δ: 174.11, 159.64, 153.66, 57.49, 52.33, 32.61, 25.73, 9.57.

I.R: 3363, 1733, 1608, 1543 cm⁻¹.

8.8.1 Reaction of O-phenylisourea 246 with methylhydrazine

A solution of O-phenylisourea 246 (0.38 g, 0.95 mmol) and methylhydrazine (0.048 g, 1.14 mmol) in propan-2-ol (30 ml) was heated to reflux for 6 h. The solvent was removed by evaporation in vacuo and the residue was purified by chromatography, eluting with chloroform:methanol (19:1), to give 2-methyl-s-triazole 409 (0.110 g, 32%) and 1-methyl-s-triazole 411 (0.120 g, 35%).

2-Methyl-s-triazole 409

M.S. m/e : 351.1671 (C₁₉H₂₁N₅O₂ requires 351.1695)
351 (M⁺), 260 (M⁺-91), 216 (M⁺-135), 91 (M⁺-260).

¹H n.m.r. (C), δ: 7.34-7.17 (m, 8H, Ph), 6.99-6.97 (m, 2H, Ph), 5.13 (d, PhCH', Jₖ-H-
H=12.12 Hz), 5.08 (d, PhCH", Jₖ-H=12.12 Hz), 4.78 (d, NH, JₙH-N-H=8.72 Hz), 4.74-4.69 (m, CHCO₂), 3.75 (bs, NH₂), 3.23 (s, NCH₃), 3.16 (dd, PhCH", Jₖ-H=13.80 Hz, Jₖ-H=5.84 Hz), 3.09 (dd, PhCH", Jₖ-H=13.80 Hz, Jₖ-H=5.68 Hz).

¹³C n.m.r. (C), δ: 172.53, 159.66, 153.12, 135.62, 134.92, 129.16, 128.43, 128.34,
126.88, 67.14, 57.12, 37.80, 32.40.

I.R: 3400, 1733, 1617, 1589 cm⁻¹.

1-Methyl-s-triazole 411

M.pt: 124-126 °C.
M.S. \textit{m/e} : 351.1678 (C\textsubscript{19}H\textsubscript{21}N\textsubscript{5}O\textsubscript{2} requires 351.1695)  
351 (M\textsuperscript{+}), 260 (M\textsuperscript{+}-91), 216 (M\textsuperscript{+}-135), 91 (M\textsuperscript{+}-260).

\textsuperscript{1}H\textit{n.m.r. (C), \textit{\delta}:} 7.30-7.05 (m, Ph), 5.07 (d, PhCH\textsuperscript{\prime}, J\textsubscript{H-\textit{H}}\textsuperscript{\prime}=12.36 Hz), 5.05 (d, PhCH\textsuperscript{\prime\prime}, J\textsubscript{H-\textit{H}}\textsuperscript{\prime\prime}=12.36 Hz), 4.70 (bs, NH\textsubscript{2}), 4.54 (m, CHCO\textsubscript{2}), 3.25 (s, NCH\textsubscript{3}), 3.10 (dd, PhCH\textsuperscript{\prime}, J\textsubscript{H-\textit{H}}\textsuperscript{\prime}=13.12 Hz, J\textsubscript{H-\textit{H}}=6.10 Hz), 3.06 (dd, PhCH\textsuperscript{\prime\prime}, J\textsubscript{H-\textit{H}}\textsuperscript{\prime\prime}=13.12 Hz, J\textsubscript{H-\textit{H}}=6.40 Hz).

\textsuperscript{13}C\textit{n.m.r. (C), \textit{\delta}:} 173.22, 159.58, 153.58, 136.30, 135.50, 129.30, 129.23, 128.29, 128.09, 126.66, 66.55, 56.89, 38.39, 32.82.

I.R: 3406, 1721, 1635, 1599 cm\textsuperscript{-1}.

\textbf{8.82 Preparation of methyl 4-(5-methylamino-(3-amino-1-methyl-s-triazole))butanoate 412 and methyl 4-(5-methylamino-(3-amino-2-methyl-s-triazole))butanoate 413}

A solution of O-phenylisourea 398 (1.16 g, 4.22 mmol) and methylhydrazine (0.30 g, 6.52 mmol) in propan-2-ol (50 ml) was heated to reflux for 6 h. The solvent was removed by evaporation \textit{in vacuo} and the residue was purified by flash chromatography eluting with chloroform:methanol (99:1), to give 412 (0.35 g, 1.54 mmol) and 413 (0.30 g, 1.32 mmol). Each product was recrystallised from chloroform:cyclohexane for analytical purposes.

\textbf{1-methyl-s-triazole 412}

M.pt: 112-114 °C.

M.S. \textit{m/e} : 227.1319 (C\textsubscript{9}H\textsubscript{17}N\textsubscript{5}O\textsubscript{2} requires 227.1382)  
227 (M\textsuperscript{+}), 196 (M\textsuperscript{+}-30), 154 (M\textsuperscript{+}-73), 140 (M\textsuperscript{+}-87).

\textsuperscript{1}H\textit{n.m.r. (C), \textit{\delta}:} 4.99 (bs, NH\textsubscript{2}), 3.64 (s, OCH\textsubscript{3}), 3.43 (s, NCH\textsubscript{3}), 3.28 (t, NCH\textsubscript{2}, J\textsubscript{H-\textit{H}}=7.25 Hz), 2.86 (s, NCH\textsubscript{3}), 2.32 (t, CH\textsubscript{2}CO\textsubscript{2}, J\textsubscript{H-\textit{H}}=7.42 Hz), 1.87 (tt, CH\textsubscript{2}, J\textsubscript{H-\textit{H}}=7.25 Hz, J\textsubscript{H-\textit{H}}=7.42 Hz).

\textsuperscript{13}C\textit{n.m.r. (C), \textit{\delta}:} 174.05, 162.57, 153.71, 51.46, 49.84, 35.49, 32.93, 31.30, 22.65.

I.R: 3406, 3125, 1733, 1663, 1608, 1454 cm\textsuperscript{-1}. 
2-methyl-s-triazole 413

M.pt: 78-80 °C.

M.S. m/e: 227.1382 (C9H17N5O2 requires 227.1382)
227 (M+), 196 (M+-30), 154 (M+-73), 140 (M+-87).

1H n.m.r. (C), δ: 3.86 (bs, NH2), 3.64 (s, OCH3), 3.49 (s, NCH3), 3.10 (t, NCH2,
JH-H=7.21 Hz), 2.78 (s, NCH3), 2.32 (t, CH2CO2, JH-H=7.30 Hz), 1.87 (tt, CH2, JH-H=7.30 Hz, JH-H=7.21 Hz).

13C n.m.r. (C), δ: 173.44, 159.88, 158.65, 53.36, 51.57, 39.60, 34.62, 31.11, 22.69.

I.R: 3333, 3186, 1733, 1635, 1586, 1541 cm⁻¹.

Analysis: Calculated for C9H17N5O2: C, 47.56; H, 7.54; N, 30.82.
Found: C, 47.53; H, 7.50; N, 30.84.

8.83 Preparation of N-(methyl butanoate)-N-benzyloxycarbonyl-N'-cyano-O-
phenylisourea 432

To a solution of O-phenylisourea 431 (0.500 g, 1.92 mmol) and benzyloxycarbonyl
chloride (0.530 g, 3.12 mmol) in dry THF (30 ml) was added sodium hydride (0.058 g, 1.92 mmol,
80%) and the resulting suspension was stirred at room temperature for 1.5 h. Chloroform (30 ml)
was added and the reaction mixture was washed with water (2×20 ml). The organic layer was dried
(MgSO4), the solvent removed by evaporation in vacuo and the residue purified by flash
chromatography, eluting with ethyl acetate:cyclohexane (1:8), to give the title compound as a
colourless oil (0.37 g, 56%).

M.S. m/e: 396.1526 (C21H22N3O5 requires 396.1559)
396 (MH+), 352 (M+-43), 320 (M+-75), 302 (M+-93).

1H n.m.r. (C), δ: 7.42-7.20 (m, 8H, Ph), 7.12-7.02 (m, 2H, Ph), 5.30 (s, PhCH2), 3.92 (t, 
NCH2, JH-H=6.80 Hz), 3.62 (s, OCH3), 2.41 (t, CH2CO2, JH-H=7.20 Hz), 
2.04 (tt, CH2, JH-H=6.80 Hz, JH-H=7.20 Hz).

13C n.m.r. (C), δ: 172.92, 161.03, 152.22, 151.40, 134.13, 129.84, 128.88, 128.64, 
120.35, 119.58, 69.99, 47.83, 30.28, 26.55, 23.47.

I.R.(CHCl3): 2996, 2947, 2207, 1736, 1626 cm⁻¹.
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