Studies in pyrimidine chemistry.
BUCKLAND, David J.

Available from Sheffield Hallam University Research Archive (SHURA) at:
http://shura.shu.ac.uk/19405/

This document is the author deposited version. You are advised to consult the publisher's version if you wish to cite from it.

Published version

Copyright and re-use policy
See http://shura.shu.ac.uk/information.html
A thesis entitled

STUDIES IN PYRIMIDINE CHEMISTRY

by

DAVID J. BUCKLAND

Presented in partial fulfilment of the requirements of

THE COUNCIL FOR NATIONAL ACADEMIC AWARDS

for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry
Sheffield City Polytechnic

January 1978
'Life being very short, and the quiet hours of it few, we ought to waste none of them in reading valueless books!

John Ruskin (Sesame and Lilies)

'Why not?'

Kilgore Trout (Venus on the half shell)
I am indebted to Dr. D.W. Allen for his continual inspiration and guidance. Thanks are also due to Drs. J. B. Turner and E. G. Hutley for the many constructive comments made during the research and writing of this thesis. The assistance of Dr. I. Nowell in the course of the X-ray crystallographic studies proved invaluable and I would like to thank him for the time and advice he gave so freely. I am grateful to Dr. R. Newton of Allen and Hanbury Research Ltd. for helpful discussions during the course of this work.

Finally, I am beholden to Mr. P. Drabble and the Bally Corporation of Chicago for their respective contributions towards my wellbeing during my three years in Sheffield.
Summary

The synthesis of a series of 2-chloro-5-(hetero)arylpyrimidines and 5-(hetero)arylpyrimidines has been investigated. The aryl substituted pyrimidines are readily obtainable from $[3$-(dimethylamino)-2-aryl allylidene] dimethylammonium perchlorates whilst the heteroaryl substituted pyrimidines are best prepared by the photolysis of the appropriate 5-iodopyrimidine in the presence of a heteroarene.

The photolysis of a series of 5-iodopyrimidines in heteroarene solutions has been investigated, the reaction giving high yields except for the case of 4-chloro-5-iodopyrimidine, this result being apparently due to the high reactivity of the 4-chloro substituent.

The kinetics of the reaction between piperidine and a series of 2-chloro-5-(hetero)arylpyrimidines in aqueous dioxan has been investigated. The order of electron-withdrawing ability of the heteroaryl substituents was found to be 1-methylpyrrol-2-yl < phenyl < 2-thienyl < 2-furyl. This result is shown to be consistent with current ideas on the nature of these substituents.

The kinetics of the reaction between phenacylbromide and a series of 5-(hetero)-arylpyrimidines in acetonitrile was investigated. The order of electron-donating ability of the heteroaryl substituents was found to be 1-methylpyrrol-2-yl > 2-furyl > 2-thienyl > phenyl. An explanation is proposed for this order.

The molecular structure of 2,4-diazido-5-iodopyrimidine was determined by single crystal X-ray crystallographic studies. The molecule was found to exist in the diazido form rather than one of the several
possible tetrazolo tautomers. 2, 4-Diazidopyrimidines are usually found to exist in one of the tetrazolo forms, the 5-iodo substituent is shown to stabilize the diazido tautomer.

An attempt was made to determine the molecular structure of 2, 4-diazido-6-methylpyrimidine which has been the subject of some controversy but due to crystal twinning an X-ray crystallographic study could not be completed.
Index

Introduction 1

Chapter 1. The synthesis of 5-aryl and 5-heteroaryl pyrimidines

1.1 Introduction 29
1.2 5-monosubstitutedpyrimidines 30
1.3 2-chloro-5-substitutedpyrimidines 37
1.4 The photolysis of 5-iodopyrimidines 38

Experimental 47
References 84

Chapter 2. Nucleophilic substitution of 2-chloro-5-substituted pyrimidines

2.1 Aromatic nucleophilic substitution
   (a) Introduction 69
   (b) Unimolecular mechanism 70
   (c) Bimolecular mechanism 70
   (d) Elimination-addition mechanism 75
   (e) ANROC mechanism 78

2.2 The kinetics of the reaction of piperidine with 2-chloro-5-substituted pyrimidines 79

Experimental 88
References 91

Chapter 3. The Quaternization of 5-substituted pyrimidines

3.1 Introduction 94

3.2 The influence of substituents in the heterocyclic systems 95

3.3 Quaternization of pyrimidine derivatives 97
3.4 The kinetics of quaternization of 5-monosubstituted pyrimidines

Experimental 107
References 111

Chapter 4. The molecular structure of 2,4-diazido-5-
iodopyrimidine and 2,4-diazido-6-methyl pyrimidine

4.1 Introduction 112

4.2 Crystal Data

(a) 2,4-diazido-5-iodopyrimidine 113
(b) 2,4-diazido-6-methylpyrimidine 114

4.3 Collection of data 115

4.4 Solution of the structure

(a) Patterson synthesis 116
(b) Fourier refinement 118

4.5 Discussion of structure 119

Experimental References 124 125

Appendix 1

Measured and calculated structure factors for 2,4-diazido
-5-iodopyrimidine 127

Appendix 2

Postgraduate courses and lectures attended 138
Pyrimidine (I) is classified as a 'π electron deficient' heterocycle. In accordance with this, its normal mode of reaction is by nucleophilic substitution or addition; the parent heterocycle reacts with hydrazine to give pyrazole (II) and with phenyl lithium to give (on subsequent oxidation) 4-phenylpyrimidine (III). Halogen and other good leaving groups in the 2-, 4- and 6- positions are particularly susceptible to nucleophilic replacement, whilst those in the 5-position can react with strong nucleophiles. The bromination of pyrimidine hydrobromide in the 5-position is the only known instance of electrophilic substitution of an unactivated pyrimidine. If the pyrimidine nucleus is activated by the presence of one or more electron-releasing groups in the 2-, 4- or 6- positions the number of electrophilic substitutions possible increases e.g., iodination, nitration and sulphonation.

![Pyrimidine (I)](image1)

![Pyrazole (II)](image2)

![4-phenylpyrimidine (III)](image3)
There has been considerable recent interest in the synthesis of 5-substituted pyrimidines, due mainly to their pharmacological properties. However, although it was pointed out in 1957 that little attention had been paid to kinetic and mechanistic aspects of the chemistry of 5-arylpyrimidines these aspects have largely been neglected. The only reported work has been by Brown et al. who investigated the kinetics of the thermal rearrangement of a series of 2-methoxy-5-(p-substituted phenyl) pyrimidines (IV) to give the corresponding N-methyl-2-oxopyrimidine (V). It was found that a good correlation exists between the rates of rearrangement and known para \( \sigma \) values. The \( \sigma \) values used were derived from a study of the hydrolysis of ethyl-4-substituted biphenyl-4-carboxylates which hence automatically include a reduced transmission factor to allow for diminished conjugation between the phenyl and pyrimidine rings resulting from imperfect coplanarity.

Since a group at Sheffield City Polytechnic has been investigating the steric and electronic effects of "\( \pi \) electron excessive" heterocycles
as substituents \(^{15-20}\), it was of interest to extend this work to an investigation of the electronic effects of such heteroaryl substituents at the 5-position of the pyrimidine ring, and to compare their effects with those observed for a series of related 5-aryl pyrimidines. Two systems were chosen for study (i) a series of 2-chloro-5-substituted pyrimidines (VI; \(X = 2\)-furyl, 2-thienyl, 1-methylpyrrol-2-yl or substituted aryl) for investigation of the rate of nucleophilic displacement of the chlorine atom, in order to investigate the ability of the 5-substituent to stabilise a negative charge on the pyrimidine ring in the transition state of the reaction and (ii) a series of 5-substituted pyrimidines (VII; \(X\) as above) for studies of the rate of quaternization at nitrogen, to determine the ability of the 5-substituent to stabilize a positive charge on the pyrimidine ring in the transition state of the quaternization reaction.

\[ X-\text{N} \quad \text{Cl} \quad X-\text{N} \]

\((\text{VI})\) \quad \((\text{VII})\)

In recent years, there have been a number of investigations of the behaviour of furan, thiophen and N-methylpyrrole as
substituents in a variety of situations, and the conclusions of these studies are reviewed in the remainder of this Introduction.

By virtue of their chemical reactivity furan, thiophen and pyrrole are appropriately grouped as "π electron excessive" heteroaromatics. This classification implies a pronounced ability to stabilize an electron deficient transition state or intermediate, as in electrophilic aromatic substitution and side-chain carbonium ion reactions. A recent paper has summarised much of the available data on the relative reactivities of these systems in electrophilic substitution, the observed order of reactivity being pyrrole > furan > thiophen > benzene. The ease of electrophilic substitution of these compounds is not of necessity an indication of an increased ground-state electron density at the ring carbon atoms; if this were the case it would be found that the preference for 2- substitution would be reflected in the net charges on the 2- and 3- carbon atoms in these molecules as calculated by various semiempirical or ab initio methods. However, the correlations sought have not been found and it is the 3- carbons that appear to have the more negative charges. Recently, the interactions of furan, pyrrole and N- methylpyrrole with electrophiles have been investigated by means of the calculated molecular electrostatic potentials, obtained from INDO wave functions, which indicate the most attractive sites and pathways of attack for an approaching electrophile. The preference for 2- substitution in furan can be interpreted if it is assumed that the 2- hydrogen moves out of the plane of the molecule as an initial step in the reaction. For pyrrole and N- methylpyrrole it is necessary to assume out-of-plane bending of the N-H, N-CH₃ and C-H bonds to satisfactorily explain
both the preference for 2- substitution, and also the relative selectivities of furan, pyrrole and N-methylpyrrole. The reactivity of these "π electron excessive heteroaromatics" has been attributed to the low localisation energies of these systems, and also as suggested by Dewar to the fact that the Wheland intermediate in the electrophilic substitution reaction has the same number of covalent bonds as the starting molecule.

![Diagram](attachment:image.jpg)

(VIII)

(IX)

The most widely accepted mechanism for electrophilic substitution involves a change from sp² to sp³ hybridisation of the carbon under attack, with the formation of an intermediate (the Wheland intermediate or σ complex (VIII)). Prior to and perhaps also after the formation of the σ complex, a π complex (IX) (with the aromatic ring behaving as an electron-donor) can form,
although it has not been proved that the formation of the $\pi$ complex is a necessary step in the reaction path $^{31}$.

The ability of the heterocyclic ring systems of furan, thiophen and pyrrole to direct electron density to an electron deficient site is illustrated by the ready hydrolysis of their halomethyl derivatives (i.e. the analogues of benzyl halides), and their migratory behaviour in the pinacol-pinacolone rearrangement. In the former reaction the stability of the intermediate carbonium-ion (X) can be understood in terms of $\pi-\pi$ overlap between the $\pi$ system of the ring and the vacant $p$ orbital of the carbonium ion centre $^{32}$.

\[
\begin{array}{c}
\text{\includegraphics[width=0.2\textwidth]{image}} \\
(X)
\end{array}
\]

A consequence of the resonance stabilization of the carbonium ion is the formation of a mixture of 2- furylacetonitrile (XII) and 2- cyano- 5- methylfuran (XIII) in the reaction of furfurylchloride (XI) and cyanide ion in protic solvents, for which the following mechanism has been suggested $^{32}$ (Scheme A).
Kegelman et al. have studied the course of the pinacolone rearrangement of the mixed pinacols 1,2-di-(2-thienyl)-1,2-diphenylethane-1,2-diol (XIV) and 1,2-di-(2-furyl)-1,2-diphenylethane-1,2-diol (XV) both of which proceed with exclusive migration of the heterocycle to give the ketones (XVI) and (XVII) respectively.
The preferential migration of the 2- furyl and 2- thienyl groups thus indicates the ability of the "\( \pi \) excessive" heterocycles to stabilize the non-classical carbonium intermediate (XVIII) in the reaction to a greater extent than the phenyl group. In contrast the rearrangement of mixed pinacols bearing 2- and 3- pyridyl substituents (XIX) proceeds with preferential migration of phenyl, since the "\( \pi \) deficient" pyridyl group is less able to stabilize the intermediate than phenyl\(^{34}\).
Recently a number of workers have studied the capabilities of heteroaryl groups to promote reactions involving electron-deficient transition states by studying the rates of solvolysis of a variety of derivatives of furan and thiophen. Noyce et al.\(^{35}\) examined the solvolysis of 1-(2-furyl)-ethyl p-nitrobenzoate (XX) in 80% ethanol. The reaction proceeds via a carbonium ion intermediate (Scheme B) to give 1-(2-furyl) ethanol (XXI) (16%) and its ethyl ether (XXII) (18%) at a rate which was estimated to be some 10\(^4\) times faster than for phenylethyl- p-nitrobenzoate\(^{36}\). Further work by Noyce et al.\(^{37}\) has revealed that the solvolysis of (XX) proceeds at a rate some five times faster than for the 2-thienyl analogue.
In contrast, an extension of the study to the solvolysis of arylethyl-tosylates has revealed that the solvolysis of 2-(2-furyl)-ethyl tosylate (XXIII), shows a moderate increase in the rate compared with 2-phenyl ethyl tosylate (XXIV), whereas 2-(2-thienyl)-ethyl tosylate (XXV) shows a somewhat greater rate acceleration. Separation of the observed rate constants into direct substituent constants ($k_s$) and a constant for a participating rearrangement mechanism ($k_a$) in which the substituent contributes to an unsymmetrically bridged transition state (XXVI) revealed that both the 2-thienyl and 2-furyl tosylates show a greater proportion of participating
rearrangement than does 2-phenylethyltosylate.

\[
\begin{align*}
(XXIII) & \quad (XXIV) \\
\begin{array}{c}
\text{F} \\
\text{C} \\
\text{H}_2 \text{C} \\
\text{H}_2 \text{OTs}
\end{array} & \begin{array}{c}
\text{C} \\
\text{H}_2 \text{CH}_2 \text{OTs}
\end{array}
\end{align*}
\]

The rate of solvolysis via the participating rearrangement pathway \( k_\alpha \) is greater for the 2-thienyl than the 2-furyl system. However, the ratio of participating rearrangement to direct substitution solvolysis \( k_\alpha / k_\beta \) is higher for the 2-furyl system, a result more in accord with the generally accepted greater
susceptibility of furan to electrophilic attack. Noyce suggested that some explanation of the apparent deviation of these results from the behaviour expected on the basis of normal electrophilic reactivities is possibly obtained from the fact that in the transition state (XXVI) for the reaction, an appreciable proportion of the carbonium ion properties are maintained, and the stabilising influences of the aromatic moiety are not fully developed.

From a study of the solvolysis of a number of substituted t-cumylchlorides, Brown et al. obtained substituent (±) constants which proved quite successful in correlating rate and equilibrium constants for a wide range of reactions involving electron-deficient transition states or intermediates. In order to obtain a similar set of ± constants for a number of "electron-rich" aromatics other than substituted benzenes, and to examine their applicability to available data in the published literature, Hill et al. studied the solvolysis of a series of 1-arylethyl acetates (XXVII; X = O, S and N-CH^).

Earlier studies of the solvolysis of 1-ferrocenylethylacetate had shown that the reaction occurs via a carbonium ion intermediate
(XXVIII), formed as a result of alkyl-oxygen fission rather than the alternative mechanisms of acyl-oxygen fission or direct displacement solvolysis.

The rates of solvolysis of the arylethyl acetates were found to decrease in the order 1-methylpyrrol-2-y1->2-furyl->2-thienyl>phenylethylacetate, the relative rates being $6 \times 10^4 : 2 \times 10^5 : 5 \times 10^4 : 1$ and $\sigma^+$ constants of -1.96, -0.94 and -0.84 respectively, were derived for the heteroaryl substituents. Attempts to correlate the solvolysis derived $\sigma^+$ constant with kinetic data obtained for other similar "electron-deficient" reactions, received a limited degree of success when viewed on a broad scale of aromatic reactivity. Significant deviations from $\sigma^+$ correlations were, however, apparent in reactions where minor effects may obscure the broad trend of aromatic electron-release. In particular, the solvent is important in determining the exact relative reactivities in a given reaction.

The substituent $\sigma^+$ values derived from the above reactions were, however, in reasonable agreement with those obtained by Taylor from the gas-phase pyrolysis of heteroaryl ethyl acetates (XXVII; X = 0, S), a reaction taking place in the absence of solvent. The rates of the reaction were found to decrease in the order 2-furyl>2-thienyl>phenyl, and substituent $\sigma^+$ values of -0.89 and -0.79 were derived for the 2-furyl and 2-thienyl substituents respectively. Since the pyrolysis reaction of 1-arylethylacetates proceeds via a partial carbonium ion on a carbon atom adjacent to the aromatic ring, increased stabilization of the electron-deficient centre due to conjugative electron-release by the heterocycle is important in the determination of the order of reactivity. Thus the observation that 1-phenyl-
ethyl acetate (XXIX) undergoes pyrolysis more quickly than 2-, 3- and 4- pyridylethylacetates (XXX) appears as further evidence of the major difference in the electron character of the 5- and 6-membered heterocycles.

\[
\textbf{\text{(XXIX)}}
\]

\[
\textbf{\text{(XXX)}}
\]

(XXXI)

As an extension to a detailed study of substituent effects on the intensity of the \(\text{C} = \text{N}\) infrared stretching vibrations of a series of benzonitriles, Deady et al.\textsuperscript{43} investigated the 2- and 3- cyanoderivatives of furan, thiophen and pyrrole (XXXI; \(X = \text{O}, \text{S}, \text{NH}\)). A series of substituent (\(\sigma^+\)) constants were obtained from this study and compared with \(\sigma^+\) constants obtained from electrophilic substitution and the above pyrolysis reactions. It was shown that in each case the heterocycle acts as an electron donor. For the 2- and 3- pyrrolyl systems the effect is very strong, in accordance with the ease of electrophilic substitution. The substituent (\(\sigma^+\)) values of -1.33, -0.44 and -0.13 for the 2- pyrrolyl, 2- thienyl and 2- furyl groups respectively were found to be much smaller than those derived from previous data in accord with the reduced electron demand. It was thus suggested that resonance electron-donation by the furyl and thiényl groups
depends upon the particular reaction, and that donation by a furyl group will be less than for thienyl in reactions in which the conjugative electron-release by the heterocyclic substituent is small.

In the most recent determination of $\sigma^+$ constants for the above heterocycles Bruce et al.\textsuperscript{45} have studied the solvolysis rates of 1-heteroarylethyl chlorides (XXXII; $X = O, S$) in 95% acetone at 45° and the rates of sodium borohydride reduction of heteroaryl methyl ketones (XXXIII; $X = O, S, N-H$) in propan-2-ol at 30°. The $\sigma^+$ constants derived (-0.85, -0.76 and -1.61 for the 2-furyl, 2-thienyl and 2-pyrrolyl groups respectively) are in good accord with those derived from earlier solvolytic, pyrolytic\textsuperscript{42} and substitution\textsuperscript{46} reactions.

\begin{align*}
\text{(XXXII)} & \quad \text{(XXXIII)} \\
\begin{array}{c}
\text{CH}_3 \\
\text{CHCl}
\end{array} & \quad \begin{array}{c}
\text{O} \\
\text{C} - \text{CH}_3
\end{array}
\end{align*}

A study of $\text{H} B n.m.r.$ data for a series of compounds $R^1_{3-n} B X_n$ ($R^1 = \text{phenyl, 2- and 3- thienyl, 1- methylpyrrolo- 2-yl and 2-furyl}; X = \text{alkyl, NMe}_2, \text{Cl, Br}; n = 0, 1, 2$) by Wrackmeyer et al.\textsuperscript{47} showed that the extent of $\text{P} \rightarrow \text{P}$ conjugation between the
(hetero) aromatic π system and the vacant 2p orbital of boron increased in the order phenyl ≈ 3-thienyl ≈ 2-thienyl ≈ 1-methylpyrrol-2-yl ≈ 2-furyl, which is in accord with the decreasing aromaticity of the cyclic systems.

In addition to their ability to function as "electron-rich" species, furyl and thiienyl groups are capable of acting as electron-withdrawing substituents, due to the effect of the electronegative heteroatom withdrawing electrons by an inductive mechanism. Thus, although nucleophilic substitution of a ring proton in pyrrole, furan and thiophen is unknown, Manly et al. observed the rate of nucleophilic displacement of halogen in halofurans to be some ten times faster than those for the corresponding phenyl compounds. For substituted heterocyclic halogen compounds the effect is increased, and displacement of halogen in N\(_{5}\)-chloro-2-furoyl)piperidine (XXXIV) by piperidine is 500 times faster than for the corresponding phenyl analogues, whilst in substitutions activated by nitro groups the relative rates of piperidine-debromination are 1-bromo-4-nitrobenzene, 1; 2-bromo-5-nitrothiophen, 4.7 \(\times 10^2\); 2-bromo-5-nitrofuran, 8.9 \(\times 10^4\).
The slightly increased reactivity of the unsubstituted halofurans compared to the unsubstituted halobenzene was attributed to the increase in positive character of the carbon bearing the halogen, due to the inductive effect of the heteroatom. The overall effect is small because of the opposed $\pi$ movement of the heterocycle. In the substituted compounds the relative activity is increased, since the carboxypiperidide and nitro groups reduce the effect of the $\pi$ electron moment and the $\sigma$ inductive effects of the heteroatom become more important.

Further evidence that the 2-furyl and 2-thienyl substituents are more electron withdrawing than phenyl in their inductive effect is obtained from carboxylic and $pK_a$ data, and the relative rates of alkaline hydrolysis of the corresponding carboxyethyl esters. The $pK_a$ data presented in Table 1 reveals that while the pyrrolecarboxylic acids are weaker, thiophen and furancarboxylic acids are stronger than benzoic acid.

Table 1

<table>
<thead>
<tr>
<th>Acid</th>
<th>$pK_a$</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoic acid</td>
<td>4.21</td>
<td>51</td>
</tr>
<tr>
<td>2- Furoic acid</td>
<td>3.16</td>
<td>52</td>
</tr>
<tr>
<td>3- Furoic acid</td>
<td>3.95</td>
<td>53</td>
</tr>
<tr>
<td>2- Thiophencarboxylic acid</td>
<td>3.53</td>
<td>52</td>
</tr>
<tr>
<td>3- Thiophencarboxylic acid</td>
<td>4.10</td>
<td>54</td>
</tr>
<tr>
<td>2- Pyrrolecarboxylic acid</td>
<td>4.45</td>
<td>52</td>
</tr>
<tr>
<td>3- Pyrrolecarboxylic acid</td>
<td>5.07</td>
<td>55</td>
</tr>
</tbody>
</table>
Hill et al. suggested that the values in Table 1 lead to Hammett $\sigma$ values for the 2-furyl and 2-thienyl groups of +1.02 and +0.65 respectively.

![Chemical structures](image)

The kinetics of alkaline hydrolysis of the corresponding carboxyethyl esters (XXXV; $X = 0, S$) and (XXXVI) have been studied by a number of workers. Oae and Price reported the rates of reaction in 70% dioxan to decrease in the order ethyl 2-furoate $\rightarrow$ ethyl benzoate $\rightarrow$ ethyl 2-thenoate, the relative rates being $4.35 : 1.08 : 1$.

Application of the Hammett equation to this data gave substituent ($\sigma$) values of 0.24 and -0.01 for the 2-furyl and 2-thienyl groups respectively. Subsequent attempts by Imoto et al. to correlate these results and the corresponding data for the 3-heteroarylcarboxylic acid esters (XXXVII $X = 0, S$) with the dissociation constants of the acids proved successful for the 3-carboxylates but not for the 2-
carboxylates. It was suggested that there may be a steric effect by the adjacent heteroatom on reactions of the carboxylate group in the 2-position.

The literature contains conflicting opinions with regard to the direction of the dipole moment of furan, thiophen and pyrrole. It had been generally accepted that the dipoles were directed from the positive heteroatom towards the C(3)~C(4) bond. This belief seems to have arisen by analogy with pyrrole whose dipole moment had been shown to have its positive end at nitrogen. It has been suggested, on the basis of reactivity data, theoretical calculations and dipole moment values of substituted derivatives that whilst the direction of the dipole in pyrrole (XXXVIII) is from the heteroatom to the ring, in furan (XXXIX) and thiophen (XL) it is in the opposite direction i.e., from the ring system to the heteroatom.

\[
\text{\begin{array}{c}
\text{V} \\
\text{O} \\
\text{X}
\end{array}}
\]

This view has been reinforced from n.m.r. solvent shift studies by Barton et al who investigated the orientational influence of the heterocycles as solutes in aromatic solvents to determine the direction of their respective dipoles.
In view of the ability of the heteroaryl systems to either withdraw or release electrons according to the type of reaction considered, Marino et al.\textsuperscript{75-77} devised a series of experiments in which the interaction of substituent heteroaryl groups with the reaction site in transition states of different types was investigated.

The ionisation of heteroaryl substituted benzoic acids (XLI; $X = \text{O, S}$) was chosen as the "standard" reaction in which only weak resonance interactions would be possible between the reaction centre and the substituent, whereas the ionization of phenols (XLII; $X = \text{O, S}$) and the solvolysis of 1-phenylethyl acetates (XLIII; $X = \text{O, S}$) were selected as reactions in which the substituent interacts with a negative and positive charge respectively. A series of substituent constants ($\sigma$, $\sigma^-$ and $\sigma^+$) were calculated from the results, and their sign and magnitude discussed in relation to the electronic properties of the heterocycle and its effect upon the respective reaction.
The ionisation constants of the benzoic acids reveal that both the 2-thienyl and 2-furyl substituents in the meta position of the benzene ring exert a weak inductive electron-withdrawing effect. This is reflected by decreases in the pKa of the meta-2-heteroarylbenzoic acids when compared to unsubstituted benzoic acid; para-heteroarylbenzoic acids were found to be less acidic than meta and the values $\sigma_p - \sigma_m$ were negative for both the 2-furyl and 2-thienyl substituents, thus possibly reflecting the importance of such resonance structures as (XLIV).

![Diagram of a molecule with a heteroaryl substituent and a carboxyl group](image)

(XLIV)

The stability of the phenate anion increases on introduction of the heteroaryl substituent into the benzene ring, possibly due to the ability of the substituent to increase delocalization of the negative charge (Mechanism A). Thus the effect is greater for para-substituted phenols than for meta, where decreases in pKa relative to phenol solely reflect electron-withdrawal by the inductive effect of the substituents. The greater acidity of p-(2-furyl) phenol compared with p-(2-thienyl) phenol indicates an increase in the magnitude of the resonance interaction (Mechanism A)
of the 2-furyl substituent compared with the 2-thienyl substituent and also the greater inductive effect of the 2-furyl substituent.

Mechanism A

The ability of the 2-furyl and 2-thienyl groups to stabilize a positive charge was illustrated by an increase in the rate of solvolysis of suitably substituted 1-phenylethylacetates (XLIII; \(X = 0, S\)). The order of relative reactivity, \(p\)-(2-furyl) phenyl \(> p\)-(2-thienyl) phenyl \(> \) phenyl \(> m\)-(2-furyl) phenyl \(> m\)-(2-thienyl) phenyl, indicates both resonance stabilization of the "electron-deficient centre" by heteroaryl substituents in the para-position and destabilization of the centre by the inductive electron-withdrawal of the substituent in the meta-position.

Marino\(^7\) extended the work to investigate the effect of heteroaryl substituents on the frequency of the infrared stretching vibrations of the carbonyl bond in substituted acetophenones (XLV; \(X = 0, S\)). In
keeping with the results of Deady et al. who observed the 2- and 3-furyl and 2- and 3-thienyl groups to act as electron donors in the infrared probe of the nitrile group in cyanoheteroaryl derivatives, Marino found that 2-furyl and 2-thienyl groups in the para-position in (XLV; X = O, S) act as electron donors and decrease the carbonyl stretching frequency relative to the unsubstituted acetophenone. In contrast, electron-withdrawal by the heterocyclic substituents in the meta-positions in (XLV; X = O, S) results in slight increases in the frequency of the carbonyl infrared stretching relative to acetophenone.

The general conclusions reached from the above work were therefore that:

(i) the 2-furyl and 2-thienyl groups are inductively electron-withdrawing and this is reflected in the positive sign of the $\sigma_m$ constants,

(ii) the electronic effect of the substituent in the meta position is practically constant and thus there are only small differences in the values of $\sigma_m$, $\sigma^+_m$ and $\sigma^-_m$. 

\[
\text{[XLV]}
\]
(iii) the 2-furyl and 2-thienyl groups exhibit strong resonance effects for both the release and withdrawal of electrons, depending on the type of reaction. However, the ability to release electrons is greater than the ability to withdraw electrons.

(iv) the electronic effects of the groups are variable in cases where conjugation is possible and cannot be represented by a single substituent constant valid for all cases.

(v) although fewer comparisons of the substituent effect of pyrrolyl systems have been made it seems that where the ring system interacts with a reaction site bearing a developing positive charge on a carbon atom, pyrrolyl systems are able to stabilize the developing charge to a greater extent than the other related heterocyclic substituents. Thus, the pyrrolyl system appears to be "electron-rich" relative to the furyl and thienyl systems.


The Synthesis of 5-aryl and 5-heteroarylpyrimidines

1:1 Introduction

Two groups of compounds were required for kinetic studies (a) a series of 5-heteroarylpyrimidines (I; X = 0, S, N-Me) and 5-(substituted phenyl)pyrimidines (II) for studies of quaternization at nitrogen, to determine the ability of the substituent to stabilize a positive charge on the pyrimidine ring in the transition state of the quaternization reaction, and (b) a series of 2-chloro-5-heteroaryl pyrimidines (III; X = 0, S, N-Me) and 2-chloro-5-substituted phenylpyrimidines (IV) for studies of the rate of nucleophilic displacement of chlorine, in order to investigate the ability of the substituents to stabilize a negative charge on the pyrimidine ring during the transition state of the reaction.
1:2 5-Monosubstitutedpyrimidines

Simple pyrimidines have been prepared conventionally by the removal of unwanted groups from more complex pyrimidines. This is shown for example in the first synthesis of pyrimidine by the hydrogenation of 2, 4, 6-trichloropyrimidine\(^1\) and also in the preparation of simple pyrimidines by the removal of a thio group by the action of Raney nickel\(^2\) or a sponge nickel catalyst\(^3\).

Recently, the synthesis of pyrimidine and simple alkyl pyrimidines has been achieved from readily available starting materials. Pyrimidine can be prepared in 65\%-70\% yield by the action of formamide on 1-methoxy-1, 3, 3-triethoxypropane\(^4\). Alkylpyrimidines have been synthesised by the action of formamide on 1-alkyl-2-N, N-dimethylaminoacroleins\(^5\) (V; R= alkyl) which are readily prepared from ethylalkylacetates and a Vilsmeier reagent (phosphoryl chloride + N, N-dimethylformamide).

\[
\begin{align*}
R & \\
\text{OHC-} & \text{C=CH-NMe}_z
\end{align*}
\]

(V)

At the commencement of this research, few 5-heteroaryl-pyrimidines

\[X\]
were recorded in the literature. 4- Amino- 5 (2- furyl) pyrimidine (VI; R= 2- furyl) and 4- amino- 5 (3- pyridyl) pyrimidine (VI; R= 3- pyridyl) were known, both of which were prepared by the action of s- triazine on the appropriate heteroarylacetonitrile. The only other relevant compound reported was 5 (2- furyl)- 2- phenylpyrimidine (VII), which was prepared by a Comberg-Hey type reaction between 5- amino- 2- phenylpyrimidine- 4- carboxylic acid (VIII) and furan, using n- amyl nitrite in dioxan. Only a 13.5% yield of product was isolated.

\[
\begin{align*}
&\text{(VI)} \\
&\text{(VII)} \\
&\text{(VIII)}
\end{align*}
\]
In order to prepare the required 5-(2- heteroaryl) pyrimidines (I; X = S, O, N-Me) the following route was investigated (Scheme A). The first three stages of the synthesis have been investigated by Davies et al.\(^8\) in the preparation of 4- chloro-5- phenylpyrimidine (XII; X = -CH = CH-). The first stage of the sequence to give I (X = S) involved heating the acetonitrile (IX; X = S) and formamide under distillation conditions while ammonia was passed through the solution, heating being continued until no further water was evolved from the reaction. The hydrolysis of the aminopyrimidine (X; X = S) required vigorous conditions viz. boiling concentrated hydrochloric acid with passage of hydrogen chloride. Providing that the keto derivative (XI; X = S) was thoroughly dried, no difficulty was experienced during the preparation of XII (X = S). The hydrazino derivative (XIII; X = S) was prepared in very good yield simply by heating, under reflux, a mixture of XII (X = S) and hydrazine hydrate in absolute ethanol. The removal of the hydrazino group was based on work by Brown et al.\(^9\) and involved oxidative removal of the hydrazino function with silver oxide.

In the case of the 2- furyl compound, the hydrolysis of the amino derivative (X; X = O) using concentrated hydrochloric acid resulted in extensive decomposition and none of the required keto derivative (XI; X = O) could be obtained. Hydrolysis of X (X = O) with sodium hydroxide solution and also nitrous acid was attempted but only unchanged starting material could be isolated. In view of the well known instability of pyrrole derivatives in the presence of acids, the sequence was not attempted with the 1- methylpyrrolo-2-yl analogue.
Since the completion of this work, Bourguigon et al. have reported the above sequence to XII (X = S) and the subsequent removal of the chlorine group by reduction with hydrogen using a palladium on carbon catalyst.

The next approach to the 5-heteroarylpyrimidines was the condensation of diethylheteroarylmalonates (XIV; \(X = 2\)-furyl, 2-thienyl) with formamidine to give the hydroxypyrimidone, followed by the sequence hydroxyoxo (XV) → dichloro (XVI) → dihydrazino.
(XVII) $\rightarrow$ 5-substituted pyrimidine (I), (Scheme B). This route was satisfactory for both the 2-furyl- and 2-thienyl-derivatives. 4, 6-Dichloro-5(2-furyl) pyrimidine (XVI; $X = 2$-furyl) could not be isolated pure, but by removal of the excess phosphorylchloride from XV $\rightarrow$ XVI followed by the addition of a large excess of hydrazine in ethanol, the dihydrazino compound (XVII; $X = 2$-furyl) could be prepared. The oxidative removal of the hydrazino groups with silver oxide was investigated and it was found that contrary to literature reports higher yields were obtained by carrying out the reaction in primary rather than in secondary or tertiary alcohols.

\[
\begin{align*}
X-\text{CH}(\text{CO}_2\text{Et})_2 & \rightarrow X-\text{CH}(\text{CO}_2\text{Et})_2 \\
& \overset{\text{POCl}_3 \text{DMA}}{\longrightarrow} X-\text{CH}(\text{CO}_2\text{Et})_2 \\
& \overset{\text{Ag}_2\text{O}}{\longrightarrow} X-\text{CH}(\text{CO}_2\text{Et})_2 \\
& \overset{\text{NH}_2\text{NH}_2}{\longrightarrow} X-\text{CH}(\text{CO}_2\text{Et})_2
\end{align*}
\]

(Scheme B)
The synthesis of 5-(1-methylpyrrol-2-yl) pyrimidine (XX) was similarly achieved from 2-chloro-5-(1-methylpyrrol-2-yl) pyrimidine (XVIII) (Scheme C). The chloro derivative (XVIII) was prepared by the photolysis of 2-chloro-5-iodopyrimidine in 1-methylpyrrole using acetonitrile as a diluent (see section 1:4).

![Chemical structure](attachment:structure.png)

**Scheme C**

5-Phenylpyrimidine (XXIII), previously prepared by treatment of 4-mercapto-5-phenylpyrimidine with Raney nickel, was synthesised by application of the method of Bredereck et al (Scheme D). The first stage of this synthesis represents an example of the use of a Vilsmeier reagent; in this instance an acetic acid ester (XXI) is treated with a phosphoryl chloride/dimethylformamide complex to give the N,N-dimethylaminoacrolein (XXII). This compound was ring closed using formamidine to give 5-phenylpyrimidine (XXIII). The purification of the product required two fractionations through a Nester-Faust spinning-band column.
The use of substituted malonaldehydes, especially halomalonaldehydes, in the synthesis of pyrimidine derivatives is of prime importance and many examples exist in the literature. In the preparation of the required 5-substituted pyrimidines (XXVI; $R = \text{substituted aryl}$) use was made of the reaction of the substituted arylmalonaldehydes (XXV) (prepared in situ by the alkaline hydrolysis of the trimethium perchlorate (XXIV)) with formamidine (Scheme E).

\[
\begin{align*}
\text{(XXI)} & \quad \text{(XXII)} & \quad \text{(XXIII)} \\
\text{PhCH}_2\text{CO}_2\text{Et} & \rightarrow \text{Ph-}^\text{C=CHNMe}_2 & \rightarrow \text{Ph}^\text{N} \\
\end{align*}
\]

Scheme D

Scheme E

\[
\begin{align*}
\text{R}^\text{C CH=NMMe}_2 & \quad ,\text{ClO}_4^- & \rightarrow \text{R}^\text{C CH=CHOH} \\
\text{(XXIV)} & \quad \text{(XXV)} \\
\text{R}^\text{N} \quad \text{N} & \\
\text{(XXVI)} \\
\end{align*}
\]
2-Chloro-5-substituted pyrimidines

The required 2-chloro-5-substituted arylpyrimidines (XXIX) were prepared by condensation of substituted arylmalonaldehydes (XXV) with urea in ethanol saturated with hydrogen chloride. The resulting 2-pyrimidinones (XXVII) were treated with phosphoryl chloride using N,N-dimethylaniline as a catalyst (Scheme F).

\[
\text{R-C} = \text{CHOH} \rightarrow \text{R-} = \text{NH} = \text{N} \rightarrow \text{R-} = \text{N} - \text{Cl}
\]

Scheme F

The preparation of the arylmalonaldehydes requires the use of a phosphoryl chloride/dimethylformamide reagent (Scheme G) and therefore this method could not be used for the preparation of heteroarylmalonaldehydes since the heterocyclic ring is very susceptible to formylation with this reagent. \(^{18}\)
In view of this limitation, an alternative synthetic route to the required 2-chloro-5-(heteroaryl) pyrimidines was sought and this was achieved by the photolysis of 2-chloro-5-iodopyrimidine in the appropriate heteroarene using acetonitrile as a diluent (see Section 1:4).

1:4 The Photolysis of Iodopyrimidines

The photolysis of iodoarenes\(^{19-21}\) and the free radical nature of the reaction\(^ {22,23}\) have been known for some time. A great deal of work has been carried out on the preparation of substituted biphenyls\(^ {24}\), phenanthrenes\(^ {25}\) (from o-iodostilbenes) and benzyne in solution\(^ {26}\) (from 1, 2 di-iodobenzenes).

The mechanism of the photolysis of iodoarenes in benzene is well substantiated and involves the intermediate formation of a cyclohexadienyl radical, followed by the loss of a hydrogen radical to yield a biaryl thus:

\[
\begin{align*}
(1) & \quad \text{ArI} \xrightarrow{h\nu} \text{Ar}^* + \text{I}^- \\
(2) & \quad \text{Ar}^* + \text{I}^- \rightarrow \text{ArI} \\
(3) & \quad \text{C}_6\text{H}_6 + \text{Ar}^* \rightarrow \text{ArH} \\
(4) & \quad \text{ArH} \rightarrow \text{ArPh} + \text{H}^-
\end{align*}
\]
The quantum yield of this process in the neat liquid phase or in solution in solvent is less than unity; this has been ascribed to the back reaction (2). The principle evidence for the homolytic nature of the process is as follows:— (i) if the photolysis is carried out in the presence of radical scavengers, e.g. oxygen or nitric oxide, which inhibit the back reaction (2), the quantum yield of the reaction increases; (ii) when the photolysis is conducted in aromatic solvents, the isomer distribution in the arylation product is in good agreement with that obtained with thermally generated aryl radicals; (iii) free radicals are known to participate in abstraction reactions; when aryl radicals are generated photochemically they can also abstract hydrogen, chlorine and bromine from cyclohexane, carbon tetrachloride and bromoform respectively; (iv) the photolysis of iodobenzene in fluorocarbon and hydrocarbon solvents at 77K has been studied by electron spin resonance techniques and the results suggest the formation of "free" phenyl radicals on photolysis.

In spite of the great deal of synthetic and mechanistic work carried out on the photolysis of iodoarenes, comparatively little attention has been paid to the synthetic utility of the photolysis of iodoheteroarenes. Only since the completion of this aspect of the research has the photolysis of an iodopyrimidine been reported as a synthetic technique. This communication was concerned with the photolysis of 5, 6-di-iodo -1, 3-dimethyluracil (XXX) in benzene and furan. It was found that, in contrast to 1, 2-di-iodobenzene, the photolysis of the pyrimidine gives products derived from a radical intermediate and none derived from the corresponding pyrimidyne. The
5-iodo-1,3-dimethyluracil radical (XXXI) was believed to be the precursor of all identified products.

\[
\begin{array}{c}
\text{(XXX)} \\
0
\end{array}
\quad
\begin{array}{c}
\text{(XXXI)} \\
\text{I}
\end{array}
\]

The photolysis of 3-iodopyridine (XXXII) in a variety of heteroarenes has been reported, reasonable yields of the products (XXXIII a-d) being obtained (Scheme H).

\[
\begin{array}{c}
\text{(XXXII)} \\
\text{(XXX III)}
\end{array}
\]

Scheme H

A great deal of work has been carried out on isomer distribution in homolytic aromatic substitution, using phenyl radicals, of a variety of heteroaromatic compounds. In these studies the radical has been generated by a variety of methods e.g., in the homolytic phenylation of thiophen, the Gomberg reaction, and the thermal decomposition...
of N-nitrosoacetanilide and dibenzoylperoxide have been used. Only rarely has the photolysis of an iodoarene been used to generate the radical. In the present work, the required 2-chloro-5-(2-heteroaryl)pyrimidines were prepared in good yield by photolysis of 2-chloro-5-iodopyrimidine (XXXIV) in a 257, V vsolution of the heteroarene in acetonitrile (Scheme J). The use of both a low and medium pressure mercury lamp was investigated, the former giving a slightly cleaner product.

\[
\text{(XXXIV)} \quad \text{(XXXV)} \quad \text{(XXXVI)}
\]

(a) X = S (b) X = O (a) X = S
(c) X = N-H
d) X = N-Me
e) X = CH=CH-

Scheme J

T.L.C. examination (157v vchloroform in petroleum ether (b.pt. 40-60°) on alumina) showed that only in the case of thiophen is a trace of the 3- isomer (XXXVIa) formed.

When 2-chloro-5-(2-thienyl) pyrimidine (XXXVa) was photolysed in acetonitrile, no trace of the 3- isomer could be detected even after 48 hours. This is in contrast with the work of Wynberg et al on the photolysis of 2-phenylthiophen (XXXVII); who found that the 3- isomer (XXXVIII) was produced in 40% yield. From later work they deduced that this rearrangement proceeded via a Dewar intermediate (Scheme K).
The photolysis of some other 5-iodopyrimidines in the presence of (hetero) arenes has also been investigated. With 5-iodopyrimidine (XXXIX) it was found that the expected range of products (XLa-d) were obtained in reasonable yields. Less than 5% of 5-(3-thienyl) pyrimidine (XLla) was obtained.

On photolysis of 2,4-dichloro-5-iodopyrimidine (XLII) the expected products (XLIIIa-d) were obtained in the presence of benzene, thiophen and furan (Scheme M) with thiophene, 1 of the 3-isomer (XLIV) was isolated. However, in the case of 1-methylpyrrole, five other products could be detected by T.L.C. besides the expected 2, 4 dichloro-5(1-methylpyrrol-2-yl) pyrimidine (XLIIIId).
<table>
<thead>
<tr>
<th>IXIIl)</th>
<th>(YII1)</th>
<th>(XUV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) ( X = S )</td>
<td>(c) ( X = \text{QH=CH} )</td>
<td>(a) ( X = S )</td>
</tr>
<tr>
<td>(b) ( X = 0 )</td>
<td>(d) ( X = \text{N-Me} )</td>
<td></td>
</tr>
</tbody>
</table>

Scheme M

An attempt was made to characterize the other products of this photolysis by means of a combined G.L.C.-M.S. technique. Apparent resolution of the products could be achieved by the use of a column packed with 10% Apiezon L on Celite at 80°, and the chromatogram obtained showed six rather broad peaks. Using a combined G.L.C.-M.S. technique apparent mass spectra of the components were obtained, but difficulty was experienced in interpreting the spectra. It was then found that if a sample of pure 2,4-dichloro-4-(1-methylpyrrol-2-yl)pyrimidine (IXIIlId) was subjected to G.L.C.-M.S. examination using the above conditions the mass spectrum obtained was not consistent with that obtained from a directly induced sample of IXIIlId, suggesting that decomposition was taking place in the chromatographic column.

By means of column chromatography of the reaction mixture on alumina, pure IXIIlId could be isolated together with a small amount of an unstable compound which was thought to be either XLV.a or b. The \(^1\text{H n.m.r. spectrum of this compound (in CDCl^3) showed the presence of 1 pyrimidine proton (\(f^8.7\)), 6 pyrrole protons (\(^7.3-6.1\)) and 2 methyl groups (\(f^3.8 \text{ and } 3.4\)), and the mass spectrum showed an apparent M of 272 and indicated the presence of 1 chlorine atom. Those facts are consistent with both structures. Because of the instability of the
compound, microanalytical results could not be obtained.

Although there is little significant photochemical cleavage of a carbon-chlorine bond in arylchlorides, Obrycki and Griffin\textsuperscript{41} have reported that photolysis of p-chloroiodobenzene in the presence of trimethylphosphite gives an appreciable amount of the p-phenylenebis phosphonate (XLVII) as well as the expected p-chlorophenylphosphonate (XLVI) (Scheme N).

This unexpected lability of the carbon-chlorine bond has been ascribed to the activating influence of the dimethoxyphosphono group in the para position.

In the case of the formation of XLVa or b, it must be assumed that the 1-methylpyrrolyl-2-yl substituent labilises a C-Cl bond,
in the 2- or 4- position of the pyrimidine ring, although it is
difficult to envisage a reasonable mechanistic rational for this
phenomenum.

The photolysis of 4- chloro- 5- iodopyrimidine (XLVIII) in the
presence of a (hetero) arene resulted in only low yields (ca 10%)
of the expected products (XLIX a-d) (Scheme 0). When the photolysis
was carried out in the presence of thiophene two products could be
detected by T.L.C., one was identified as the 2- isomer (XLIXa), the
second compound was thought to be the 3- isomer (La) but insufficient
could be isolated to allow characterisation. Once again when the
photolysis was carried out in the presence of 1- methylpyrrole a
number of products were detected by means of T.L.C., but none of those
products apart from 4- chloro- 5(1- methylpyrrol- 2- yl) pyrimidine
(XLIXd) could be identified.

\[
\begin{array}{c}
\text{(XLVIII)} \\
\text{(XLIX)} \\
\text{(L)}
\end{array}
\]

\[
\begin{array}{cccc}
X = S & X = CH = CH & X = N-Me \\
(a) & (b) & (c) & (d)
\end{array}
\]

\text{Scheme 0}

The low yields obtained in these photolyses were thought to be
due to the instability of 4- chloro- 5- iodopyrimidine (XLVIII) which
was found to decompose on standing. The instability of 4- chloropyrimidines
is well known, and is illustrated by the ready decomposition of 4-
chloropyrimidine\textsuperscript{12} (L1) and 5-benzyloxy-4-chloropyrimidine\textsuperscript{42} (L11).
EXPERIMENTAL

Melting points were determined on a Koffler hot-stage apparatus and are uncorrected.

'H Nuclear magnetic resonance spectra were determined at room temperature in the stated solvent containing tetramethylsilane as an internal standard, using a JEOL C-60 HL high-resolution 60 MHz instrument.

Mass spectra were recorded at 70eV using an AEI MS-30 spectrometer by Miss M. March of the Polytechnic Chemistry Department.
Microanalyses were carried out by Dr F. B. Strauss, Microanalytical Laboratory, 10, Carlton Road, Oxford and B.M.A.C. Ltd., 41 High Street, Teddington, Middlesex.

Abbreviations used in the experimental section :-
m.p.t. = melting point
d. = decomposed
4- amino- 5(2- furyl) pyrimidine (X; X = 0)

A mixture of 2- furylacetonitrile (0.17 mol) and formamide (0.66 mol) was heated at 180° in a stream of ammonia under distillation conditions for 18 hours.

The mixture was allowed to cool to room temperature and was filtered. The precipitate was extracted with dilute hydrochloric acid, the solution was filtered and then made alkaline with dilute sodium hydroxide solution. The precipitate was isolated by filtration, dried and purified by vacuum sublimation (0.1 mm Hg, 100°) to give 4- amino-5(2- furyl) pyrimidine. Yield 15.9 g (59%); m.pt. 177° (lit. 6 176°); (Found: C, 59·1; H, 4·8; N, 25·9. Calc. for C₈H₇N₃O: C, 59·6; H, 4·4; N, 26·1%). £ (TFA/D₂O), 8.54 (IH,s); 8.47 (IH, s); 7.8 (IH, s); 6.9 (IH, m); 6·7 (IH, m) p.p.m. m/e 161, M⁺.

4- amino- 5(2- thienyl) pyrimidine (X; X = 0)

The above preparation was repeated using 2- thienylacetonitrile (0·1 mol). The crude product was purified by recrystallisation from aqueous methanol to give 4- amino- 5(2- thienyl) pyrimidine. Yield 8 g (45%); m.pt. 184° (lit. 10 180°); (Found : C, 54·0; H, 4·25; N, 23·7. Calc. for C₈H₇N₃S : C, 54·2; H, 4·0; N, 23·7%). £(TFA/D₂O), 87 (IH, s); 8·25 (IH, s); 7·7 (IH, d); 7·4 (2H, m) p.p.m. m/e 177. M⁺.

5(2- thienyl)- 4(3-H) pyrimidone (XI; X = S)

A solution of 4- amino- 5(2- thienyl) pyrimidine (0.014 mol) in hydrochloric acid (7.5cm³, 10M) was heated under reflux for 4 hours whilst hydrogen chloride was passed through the solution. The white precipitate was filtered and dissolved in dilute sodium hydroxide solution (200 cm³, 0.25M). Carbon dioxide was passed through the
solution and the precipitated product was isolated by filtration. Concentration of the filtrate to 50cm³ and resaturation with carbon dioxide resulted in a further crop of product. The combined crops were purified by recrystallisation from boiling water to give 5(2-thienyl)-4(3-H) pyrimidone. Yield 1.4g (56%); m.pt. 230° (lit. 230°); (Found: C 56.2; H, 3.4; N; 16.0. Calc. for C₈H₆N₂O₅: C, 56.1; H, 3.4; N, 15.8%). δ (CDCl₃/TFA), 9.45 (IH, s); 8.5 (IH, s); 7.75 (2H, m); 7.3 (IH, m) p.p.m. m/e 178, M⁺.

4-chloro-5-(2-thienyl) pyrimidine (XII; X = S)

A mixture of 5(2-thienyl)-4(3-H) pyrimidone (0.01 mol), phosphoryl chloride (10cm³) and N, N-dimethylaniline (0.5cm³) was heated under reflux for 1 hour. The excess phosphoryl chloride was removed under reduced pressure, the solid remaining was added to ice and the mixture was stirred for 5 mins. and was then extracted with 5 x 20cm³ portions of diethyl ether. The ethereal fractions were combined and washed with dilute sodium carbonate solution, followed by water. The extract was dried with magnesium sulphate, filtered and evaporated to dryness. The remaining solid was purified by vacuum sublimation (0.1 mm Hg, 80°) to give 4-chloro-5-(2-thienyl) pyrimidine. Yield 1.35g (69%); m.pt. 56° (lit. 55°); (Found: C, 48.9; H, 2.6; N, 14.05. Calc. for C₈H₅Cl₂S: C, 48.85; H, 2.55; N, 14.25%). δ (CDCl₃), 9.17 (IH, s); 8.27 (1H, s); 7.9 (1H, d); 7.65 (1H, m); 7.42 (1H, m) p.p.m. m/e 196, M⁺.

4-hydrazino-5-(2-thienyl) pyrimidine (XIII; X = S)

A solution of 4-chloro-5(2-thienyl) pyrimidine (0.01 mol) in ethanol (20cm³) was heated under reflux whilst hydrazine hydrate (0.02 mol) was added over 5 mins. The mixture was boiled for a further 90 mins. and was then cooled in an ice bath. The crystalline product was isolated and was recrystallised from ethanol to give 4-hydrazino-
5-(2-thienyl) pyrimidine. Yield 1.5g (78%); m.pt. 170°(d); (Found: C, 50.1; H, 4.3; N, 28.85. C\(_8\)H\(_6\)N\(_2\)S requires C, 50.0; H, 4.2; N, 28.8%); \(\delta\) (D\(_6\)-DMSO), 8.30 (1H, s); 7.85 (1H, s); 7.40 (1H, m); 7.0 (2H, m); 4.5 (2H, b.s.); 3.3 (1H, b.s.) p.p.m.; the signals at \(\delta\) 4.5 and 3.3 were removed on addition of D\(_2\)O. m/e 192, M\(^+\).

5-(2-thienyl) pyrimidine (I; X = S)

To a solution of 4-hydrazino-5-(2-thienyl) pyrimidine (0.01 mol) in hot absolute ethanol (30cm\(^3\)) was added silver oxide (0.05 mol). The solution was heated under reflux for 90 mins., Hyflo Supercel (1g) was added and the mixture was filtered. The solution was evaporated to dryness under reduced pressure and the product was purified by vacuum sublimation (0.01 mm. Hg, 50°) to give 5-(2-thienyl) pyrimidine. Yield 0.66g (40%); m.pt. 74° (lit. 1076°); (Found: C, 58.75; H, 3.85; N, 17.4. Calc. for C\(_8\)H\(_6\)N\(_2\)S: C, 59.2; H, 3.7; N, 17.3%). \(\delta\) (CDCl\(_3\)), 8.90 (1H, s); 8.7 (2H, s); 7.3 (2H, m); 7.0 (1H, m) p.p.m. m/e 162, M\(^+\).

6-hydroxy-5-(2-thienyl)-4(3-H) pyrimidone (XV; X = 2-thienyl)

Formamidine acetate (0.145 mol) was added to a solution of sodium ethoxide prepared from sodium (0.375 mol) and absolute ethanol (250cm\(^3\)). Diethyl-2-thienylmalonate (XIV; X=2-thienyl) (0.128 mol) was added and the mixture was stirred at room temperature for 16 hours. The orange precipitate which had formed was isolated by filtration and was dissolved in water (50cm\(^3\)) and the solution was made acid to Congo Red with dilute hydrochloric acid. The white precipitate produced was isolated and dried in a vacuum oven. A sample of the product was purified by recrystallisation from boiling water to give 6-hydroxy-5(2-thienyl)-4(3-H) pyrimidone. Yield 13.8g (58%); m.pt. 300°; (Found: C, 49.85; H, 3.15; N, 14.75. C\(_8\)H\(_6\)N\(_2\)O\(_2\)S requires C, 49.5; H, 3.1; N, 14.45%). \(\delta\) (D\(_6\)-DMSO), 8.4 (1H, s); 8.1 (1H, m); 7.2 (2H, m) p.p.m.;
a v. broad signal corresponding to 2H in the region 8 8.4-7.2 was
removed on shaking with D$_2$O.

4,6-dichloro- 5(2-thienyl) pyrimidine (XVI; X = 2-thienyl)

To a mixture of phosphoryl chloride (30cm$^3$) and N,N-dimethylaniline
(5cm$^3$) was added 6-hydroxy- 5(2-thienyl)-4(3-H) pyrimidone (0.1 mol),
the mixture was heated under reflux for 1 hour and then the excess
phosphoryl chloride was removed under reduced pressure. The residue was
poured onto ice and was stirred for 10 mins and the mixture was then
extracted with diethyl ether (5 x 50cm$^3$). The combined extracts
were washed with dilute sodium carbonate solution followed by water and
were then dried with magnesium sulphate. The ether was removed under
reduced pressure and a portion of the product was recrystallised from
petroleum spirit (b.pt. 40-60°) to give 4,6-dichloro- 5(2-thienyl)
pyrimidine. Yield 14.6g (64%); m.pt. 71°; (Found : C, 41.7; H, 1.95;
N, 11.95. C$_8$H$_4$Cl$_2$N$_2$S requires C,41.6; H,1.75; N,12.1%). $\delta$ (CDCl$_3$),
9.1 (1H,s); 7.9 (1H,m); 7.2 (2H,m) p.p.m. m/e 230, M$^+$. 

4,6-dihydrazino- 5(2-thienyl) pyrimidine (XVII; X=2-thienyl)

To a solution of 4,6-dichloro- 5(2-thienyl) pyrimidine (0.01 mol)
in boiling ethanol (40cm$^3$) was added hydrazine hydrate (0.03 mol) and
the mixture was heated under reflux for 1 hour. On cooling in an ice
bath a crystalline product was obtained which was recrystallised from
ethanol to give 4,6-dihydrazino- 5(2-thienyl) pyrimidine. Yield 2.05g
(92%); m.pt 174°; (Found : C,43.4; H,4.15; N,37.95. C$_8$H$_7$N$_2$S requires
C,43.45; H,4.1; N,38.0%). $\delta$ (D$_6$-DMSO), 8.40(1H,s); 7.6 (1H,m); 7.2 (2H,m);
5.9 (2H,b.s.); 3.9 (4H,b.s.) p.p.m. the signals at $\delta$ 5.9 and 3.9 were
removed on addition of D$_2$O. m/e 222, M$^+$. 

51
M 2-thienyl) pyrimidine (I; X=S)

A solution of 4,6-dihydrazino-5-(2-thienyl) pyrimidine (0.01 mol) in hot absolute methanol (100 cm³) containing silver oxide (0.1 mol) was heated under reflux for 1 hour. Hyflo-Supercel (lg) was added and the mixture was filtered. The methanol was removed under reduced pressure and pure 5(2-thienyl) pyrimidine was isolated by vacuum sublimation (0.01 mm Hg, 45°). Yield 0.61g (37%). The above preparation was repeated using absolute ethanol, propan-2-ol and 2-methylpropan-2-ol, giving yields of 4670, 27% and 20% respectively.

5(2-furyl)-6-hydroxy-4-(3-H) pyrimidine (XV; X=2-furyl)

The method for the preparation of 6-hydroxy-5'(2-thienyl)-4(3-H) pyrimidone was repeated using diethyl-2-furylmalonate (XIV; X = 2-furyl) to give 5~(2-furyl)-6-hydroxy-4*(3-H) pyrimidine. Yield 12.6g (557%); m.pt. 270° (Found : C,54.0; H,3.55; N,15.6. C requires 0, 53.95; H, 3.4; N,15.75%). £ (D^DMSO), 10.2 (2H, b. s.); 7.60 (1H<s); 7.42 (1H,s); 6.74 (1H,d); 6.40 (1H,m); p.p.m. the signal at £ 10.2 was removed on addition of m^e 178, m^m.

4,6 dihydrazino-5-(2-furyl) pyrimidine (XVII; X = 2-furyl)

6-Hydroxy-5'(2 furyl) -4-(3-H) pyrimidene (0.01 mol) was added in small portions to a mixture of phosphoryl chloride (8 cm³) and N, N-dimethylaniline (1 cm³) held at 0°. On completion of the addition, the mixture was allowed to warm slowly to room temperature and was stirred for a further 24 hours. The excess phosphoryl chloride was removed under reduced pressure, keeping the temperature at less than 30°. To the residue was added hydrazine hydrate (0.15 mol) contained in absolute ethanol (25 cm³), the solution was then heated under reflux for 1 hour filtered and then cooled in an ice bath. The crystalline product was isolated and recrystallised from ethanol to give 4,6 dihydrazino-- 5-(2-furyl)
pyrimidine. Yield 1.24g (60%); m.pt. 170-1°; (Found : C, 46.55; H, 4.85; N, 40.6. C₈H₁₀N₆O requires C, 46.6; H, 4.9; N, 40.75%).

δ (D₂-DMSO), 8.3 (1H,s); 7.8 (1H,m); 6.7 (2H,m); 6.0 (6H,b.s.) p.p.m. the signal at δ 6.0 was removed on addition of D₂O. m/e, 206, M⁺.

5(2-furyl) pyrimidine (I; X = 0)

The method for the preparation of 5(2-thienyl) pyrimidine was repeated using 4,6-dihydrazino-5-(2-furyl) pyrimidine (0.01 mol) in absolute ethanol. The product was isolated by vacuum sublimation (1.0-1.5mm Hg, 50°) to give 5(2-furyl) pyrimidine which was found to decompose slowly on standing. Yield 0.43g (29%); m.pt. 57°; (Found : C, 65.45; H, 4.05; N, 19.35. C₈H₆N₂O requires C, 65.75; H, 4.15; N, 19.15%).

δ (CDCl₃) 8.95 (1H,s); 8.9 (2H,s); 7.5 (1H,s); 6.7 (1H,m); 6.5 (1H,m) p.p.m. m/e 146, M⁺.

2-hydrazino-5(1-methylpyrrol-2-yl) pyrimidine (XIX)

A mixture of 2-chloro-5(1-methylpyrrol-2-yl) pyrimidine (0.01 mol) and hydrazine hydrate (0.02 mol) was heated under reflux in ethanol (30 cm³) for 1 hour. On cooling in an ice bath, white crystals were formed which were isolated and recrystallised from ethanol to give 2-hydrazino-5-(1-methylpyrrol-2-yl) pyrimidine. Yield 1.5g (79%); m.pt. 151°;

δ (CDCl₃); 8.15 (2H,s); 6.50 (1H,m); 6.0 (2H,m); 3.85 (3H,b.s.); 3.50 (3H,s) p.p.m. the signal at δ 3.85 was removed on addition of D₂O. m/e 189, M⁺.

5(1-methylpyrrol-2-yl) pyrimidine (XX)

A mixture of 2-hydrazino-5(1-methylpyrrol-2-yl) pyrimidine (0.01 mol) and silver oxide (0.04 mol) was heated under reflux in ethanol (50 cm³) for 1 hour. The mixture was filtered and the ethanol was removed under
reduced pressure. The product was isolated by vacuum sublimation (0.6 mm Hg, 50°) to give 5-(1-methylpyrrol-2-yl) pyrimidine which was found to decompose slowly on standing. Yield 0.73 g (46%), m.p.t. 143-4° (d); (Found: C, 67.55; H, 5.6; N, 26.85. requires C, 67.9; H, 5.7; N, 26.40%) S (CDCl3), 8.94 (1H, s); 8.64 (2H, s); 6.68 (1H, m); 6.2 (2H, m); 3.6 (3H, s) p.p.m. m/e 159, M+.

5-phenylpyrimidine (XXIII)

2-Dimethylamino-1-phenylacrolein (0.05 mol) was added over 5 hours to formamide (20 cm³) held at 180° and after the addition was complete the temperature was held constant for a further hour. The mixture was then allowed to cool to ambient temperature and then shaken with a saturated solution of potassium carbonate (5 cm³). The resultant mixture was extracted with chloroform (100 cm³), the extract dried over potassium carbonate and the excess chloroform was removed under reduced pressure. The product was isolated by two fractionations through a 40 cm. Nester-Faust spinning-band column under reduced pressure to give 5-phenylpyrimidine. Yield 3.6 g (46%); b.p.t. 78° at 0.1 mm Hg; m.p.t. 38° (lit. 120-140° at 0.01 mm Hg); (Found: C, 76.8; H, 5.15; N, 18.05. Calc. for C14H10O2N: C, 76.9; H, 5.15; N, 17.95%) S (CDCl3) 8.98 (1H, s); 8.70 (2H, s); 7.30 (5H, s) p.p.m. m/e 156, M+.

42-substituted trimethinium salts (XXIV)

Phosphoryl chloride (0.3 mol) was added dropwise to dimethylformamide (1.5 mol) contained in a 250 ml flask fitted with a stirrer and a condenser. During the addition, the flask was cooled externally in an ice bath. On completion of the addition, the cooling was removed and the reaction mixture was allowed to come to room temperature. The substituted phenyl acetic acid (XXIX) (0.1 mol) was added in small portions and the reaction mixture was heated to 70° and was held at this temperature.
for 5 hours. The excess dimethylformamide was removed under reduced pressure and the residue was decomposed with ice. Sodium perchlorate (0.11m) dissolved in a minimum volume of water was added, the solution was cooled in an ice bath and the precipitate was isolated and was recrystallised from ethanol to give:–

(XXIVa; R = p-chlorophenyl) Yield 30.6g (917,); m.pt. 146° (lit.43 146°); £ (D-DMSO), 7.5 (6H,m), 3.2 (6H,s), 2.6 (6H,s) p.p.m.

(XXIVb; R = m-chlorophenyl) Yield 27.6g (827,); m.pt. 180°; (Found: C, 46.4; H, 5.3; N, 8.25. £ (D6-DMSO), 7.8 (2H,s); 7.5 (4H,m); 3.3 (6H,s); 2.6 (6H,s) p.p.m.

(XXIVc; R = p-bromophenyl) Yield 34.2g (907,); m.pt. 160°; (Found: C, 41.1; H, 4.8; N, 7.35. £ (D6-DMSO), 7.7 (2H,s); 7.3 (4H,m); 3.25 (6H,s); 2.45 (6H,s) p.p.m.

(XXIVd; R = p-fluorophenyl) Yield 25.3g (797,); m.pt. 133°; (Found: C, 49.2; H, 5.65; N, 8.75. £ (D6-DMSO), 7.75 (2H,s); 7.25 (4H,m); 3.3 (6H,s); 2.50 (6H,s) p.p.m.

(XXIVe; R = 1-naphthyl) Yield 15g (42.57,); m.pt. 203° (lit.44 203-4°); £ (D6-DMSO), 8.1-7.3 (9H,m); 3.3 (6H,s); 2.2 (6H,s) p.p.m.

(XXIVf; R = 2-naphthyl) Yield 30g (857,); m.pt. 210-11°; (Found: C, 58.05; H, 6.1; N, 7.8. £ (D6-DMSO), 8.1-7.4 (9H,m); 3.25 (6H,s); 2.4 (6H,s) p.p.m.

(XXIVg; R = p-tolyl) Yield 28.6g (907,); m.pt. 162° (lit.43 162°) (Found: C, 53.2; H. 6.7; N, 8.65. Calc, for C ^ ^ C I N ^ : C, 53.1; H, 6.7; N, 8.857,) £ (Dg-DMSO), 7.5 (2H,s), 6.9 (4H,s), 3.25 (6H,s); 2.4 (6H,s) p.p.m.
(XXIVh; R = p-anisyl) Yield 28.4g (85.7%); m.pt. 131°;

(Found : C, 50.9; H, 6.1; N, 8.45; Calc, for C_{14}H_{21}ClNO : C, 50.65;
H, 6.35; N, 8.47) S (D^DMSO) 7.5 (2H,s), 6.7 (4H,q); 3.2 (6H,s);
2.4 (6H,s) p.p.m.

(XXIVj; R = p-nitrophenyl) Yield 21.6g (62.7%); m.pt. 225° (lit. 225-6°).

Substituted arylmalonaldehydes (XXV)

A mixture of the perchlorate (XXIV) (0.01 mol), potassium
hydroxide (0.03 mol) in aqueous methanol (507, v, 40 cm) was heated
under reflux for 30 minutes and then the excess methanol was removed
by distillation. The solution was cooled in an ice bath and the
precipitated potassium perchlorate was removed by filtration. The
filtrate was acidified with dilute hydrochloric acid and the precipitated
product was isolated and dried. The product (where possible) was
purified by vacuum sublimation (0.1 mm of Hg, 50°). In one case, the
product could not be purified and was characterised by conversion,
with hydrazine, to a 4-substituted aryl pyrazole.

p-chlorophenylmalonaldehyde, (XXV,a; R = p-chlorophenyl). Yield 1.75g
(96.7%); m.pt. 141-2°; (Found : C, 59.2; H, 3.8. C_{8}H_{7}ClO requires
C, 59.2; H, 3.85) S (D^DMSO), 9.3 (1H,b.s); 8.46 (1H,s); 7.35 (5H,m)
p.p.m. e 182, M+.

m-chlorophenylmalonaldehyde, (XXV,b; R = m-chlorophenyl). Yield 1.68g
(91.7%); m.pt. 105°; (Found : C, 59.05; H, 3.75. C_{8}H_{7}ClO requires
C, 59.2; H, 3.85). & (D^DMSO), 9.5 (1H, b.s); 8.14 (1H,s); 7.25
(5H,m). p.p.m. e 182, M+.

p-bromophenylmalonaldehyde, (XXV,c; R = p-bromophenyl). Yield 2.06g
(91.7%); m.pt. 119°; (Found : C, 47.4; H, 2.9. C_{7}H_{7}BrO requires
C, 47.6; H, 3.1%) S (D^DMSO) 9.65 (1H,b.s); 8.10 (1H,s);
7.05 (5H,m) p.p.m. m^e 226, M+c
p-fluorophenylmalonaldehyde, (XXVd; R = p-fluorophenyl). Yield 1.52g (92%); m.pt. 158-9° (Found: C, 65.0; H, 4.25. C_{9}H_{7}F_{2}O_{2} requires C, 65.05; H, 4.25%). δ (D_{6}-DMSO), 9.8 (1H, b.s.); 9.05 (1H, s); 7.9-7.1 (5H, m) p.p.m. m/e 166, M⁺.

1-naphthylmalonaldehyde, (XXVe; R = 1-naphthyl). Yield 1.65g (83%); m.pt. 185° (Found: C, 78.65; H, 5.0. C_{13}H_{10}O requires C, 78.55; H, 5.05%). δ (CDCl₃), 8.45 (2H, s); 7.8-7.1 (8H, m) p.p.m. m/e 198, M⁺.

2-naphthylmalonaldehyde, (XXVf; R = 2-naphthyl). Yield, not purified, m.pt. 261° (Found: C, 80.15; H, 5.25; N, 14.75. C_{13}H_{10}N₂ requires C, 80.4; H, 5.2; N, 14.4%). δ (D_{6}-DMSO), 8.3-7.3 (9H, m); 3.35 (1H, b.s.) p.p.m., signal at δ 3.35 removed on addition of D₂O. m/e 194, M⁺.

p-tolylmalonaldehyde, (XXVg; R = p-tolyl). Yield 1.50g (93%); m.pt. 128° (lit. 128°).

p-anisylmalonaldehyde, (XXVh; R = p-anisyl). Yield 1.43 (80%); m.pt. 149° (lit. 146-8°).

p-nitrophenylmalonaldehyde, (XXVj; R = p-nitrophenyl). Yield 1.85g (96%); m.pt. 218° (lit. 218°).

Figures quoted for 4(2-naphthyl) pyrazole, prepared from unpurified 2-naphthyl-malonaldehyde and hydrazine.

5-substituted pyrimidines (XXVI)

A mixture of the perchlorate (XXIV) (0.02 mol) and formamidine acetate (0.022 mol) was dissolved in boiling ethanol (70 cm³), sodium ethoxide (0.048 mol) was added and the mixture was heated under reflux for 3 hours. The solution was filtered hot, the filtrate was evaporated to dryness under reduced pressure and the product was isolated by vacuum sublimation (0.1 mm of Hg, 60°) to give:-
(XXVIa; 5-(4-chlorophenyl)pyrimidine) Yield 2.40g (647); m.pt. 152°;
(Found : C, 62.9; H, 3.62; N, 14.75. C^H^CIN^ requires: C, 63.0;
H, 3.70; N, 14.7) S (CDCl3), 9.2 (1H,s); 8.9 (2H,s); 7.48 (5H,s)
p.p.m. e 190, M+.

(XXVIb; 5-13-chlorophenylpyrimidine) Yield 2.35g (61.570); m.pt. 72-3°;
(Found : C, 63.2; H, 3.80; N, 14.55. C^q_H_,CIN2 requires :C, 63.0;
H, 3.7; N, 14.7%). S (CDCl3), 9.1 (1H,s); 8.8 (2H,s); 7.4 (4H,m)
p.p.m. m/e 190, M+.

(XXVIc; 5-(4-bromophenyl)pyrimidine). Yield 1.45g (317); m.pt. 144-6°;
(Found : C, 50.9; H, 3.0; N, 12.0. C10H7BrN2 requires :C, 51.1; H, 3.0;
N, 11.9%). S (CDCl3), 9.32 (1H,s); 9.0 (2H,s); 7.6 (4H,q) p.p.m. m/e 234, M+.

(XXVID; 5-(4-fluorophenyl)pyrimidine). Yield 1.69g (487); m.pt. 86-7°;
(Found : C, 68.6; H, 4.1; N, 16.4. C^^H^FN^ requires : C, 68.95;
H, 4.05; N, 16.1%) S (CDCl3), 9.1 (1H,s); 8.82 (2H,s); 7.25 (4H,m)
p.p.m. e 174, M+.

(XXVIe; 5-(1-naphthyl)pyrimidine). Yield 2.15g (527); m.pt. 82°;
(Found : C, 81.2; H, 5.1; N, 13.7. requires C, 81.5; H, 4.9;
N, 13.6%). £ (CDCl3), 9.16 (1H,s); 8.74 (2H,s); 7.9-7.3 (7H,m) p.p.m.
m^e 206, M+.

(XXVIF; 5-(2-naphthyl)pyrimidine). Yield 1.55g (387); m.pt. 142°;
(Found : C, 81.2; H, 5.2; N, 13.4. ^14^10^2 requires 81.55; H, 4.9;
N, 13.6%). S (CDCl3), 9.31 (1H,s); 8.62 (2H,s); 7.9-7.2 (7H,m) p.p.m.
m/e 206, M+.

(XXVIIg; 5-(4-tolyl)pyrimidine). Yield 1.35g (407); m.pt. 74°; (Found :
C, 77.5; H, 6.0; N, 16.5. ^n^io^2 requires » 77.6; H, 5.9; N, 16.457);
O (CDCl3), 9.1 (IH,s); 8.8 (2H,s); 7.3 (4H,q); 2.25 (3H,s) p.p.m.
m/e 170, M+.
(XXVIh; 5-(4-anisyl)pyrimidine). Yield 1.25 g (34%); m.pt. 140°;
(Found: C, 70.8; H, 5.45; N, 14.85. C₁₁H₁₀N₂ requires C, 70.95; H, 5.4; N, 15.05%). δ (CDCl₃), 9.0 (1H, s); 8.8 (2H, s); 3.8 (3H, s) p.p.m. m/e 186, M⁺.

(XXVIj; 5-(4-nitrophenyl)pyrimidine). Yield 1.36 g (34%); m.pt. 127°;
(Found: C, 59.65; H, 3.15; N, 20.9. C₁₀H₇N₃O₂ requires C, 59.8; H, 3.5; N, 20.8%). δ (CDCl₃), 8.9 (1H, s); 8.65 (2H, s); 7.1 (4H, q) p.p.m. m/e 201, M⁺.

5-substituted pyrimidin-2-ones (XXVII)

A mixture of a substituted malonaldehyde (XXV) (0.01 mol) and urea (0.01 mol) was dissolved in ethanol (40 cm³) saturated with hydrogen chloride. The solution was heated under reflux for 3 hours and the precipitate formed was isolated and was recrystallised from ethanol to give:

(XXVIIa; R = p-chlorophenyl). Yield 1.65 g (80%); m.pt. 306°(d) (lit. 304°(d)).

(XXVIIb; R = m-chlorophenyl). Yield 1.83 g (89%); m.pt. 280°(d);
(Found: C, 58.0; H, 3.15; N, 13.35. C₁₀H₇ClN₂O requires C, 58.1; H, 3.4; N, 13.55%). δ (D₆-DMSO), 8.9 (2H, s); 7.4 (4H, m); 6.3 (1H, b.s.); p.p.m., signal at δ 6.3 removed on addition of D₂O.

(XXVIIc; R = p-bromophenyl). Yield 1.75 g (70%); m.pt. 265°(d) (lit. 270°(d)).

(XXVIIId; R = p-fluorophenyl). Yield 1.35 g (71%); m.pt. 230°(d);
(Found: C, 63.0, H, 3.75; N, 14.90. C₁₀H₇ClN₂O requires C, 63.15; H, 3.7; N, 14.75%). δ (D₆-DMSO), 8.75 (2H, s); 7.65 (4H, q); 6.75 (1H, b.s.) p.p.m. signal at δ 6.75 removed on addition of D₂O.
2-chloro-5-substituted pyrimidines (XXVII)

The substituted pyrimidin-2-one (XXVII) (0.01 mol) was heated under reflux in a mixture of phosphoryl chloride (5 cm³) and N, N-dimethylaniline (0.5 cm³) for 1 hour. The excess phosphoryl chloride was removed under reduced pressure and the residue was decomposed with ice. The product was extracted with diethyl ether (3 x 20 cm³), the extract was washed with a sodium carbonate solution and then with water. The extract was dried with magnesium sulphate, the ether was removed from the filtered solution and the product was isolated by vacuum sublimation (60°, 0.1 mm of Hg) to give:

(XXVIIIa; 2-chloro-5-(4-chlorophenyl)pyrimidine). Yield 1.9g (85%); m.pt. 215° (lit. 215-6°).

(XXVIIIb; 2-chloro-5-(3-chlorophenyl)pyrimidine). Yield 1.95g (87%); m.pt. 121-2°; (Found : C, 53.5; H, 2.95; N, 12.45. C_{10}H_{6}Cl_{2}N_{2} requires C, 53.35; H, 2.7; N, 12.45%). δ (CDCl₃), 8.6 (2H,s); 7.4 (4H,q) p.p.m. m/e 224, M⁺.
(XXVIIIci; 4-bromophenyl-2-chloropyrimidine). Yield 2.15g (80%) m.pt. 215° (lit.45 214°).

(XXVIIIId; 2-chloro-5-(5-fluorophenyl)pyrimidine). Yield 1.80g (86%); m.pt. 183°; (Found : C, 57.15; H, 3.15; N, 13.35. C14H10ClF requires C, 57.6; H, 2.9; N, 13.45%). \( \delta \) (CDC13), 8.95 (2H,s); 7.55 (4H, m) p.p.m. m/e 208, M+.

(XXVIIIe; 2-chloro-5-(1-naphthyl)pyrimidine). Yield 1.65g (69%); m.pt. 101°; (Found : C, 69.65; H, 4.05; N, 11.6. CUH9ClN2 requires C, 69.85; H, 3.75; N, 11.65%). \( \delta \) (CDC13) 8.52 (2H,s); 7.8-7.3 (7H,m) p.p.m. m/e 240, M+.

(XXVIIIIf; 2-chloro-5-(2-naphthyl)pyrimidine). Yield 1.35g (57%); m.pt. 156°; (Found : C, 69.6; H, 4.0; N, 11.55. C14H10Cl requires C, 69.85; H, 3.75; N, 11.65%). \( \delta \) (CDC13), 8.78 (2H,s); 7.85-7.3 (7H,m) p.p.m. m/e 240, M+.

(XXVIIIg; 2-chloro-5-(4-tolyljpyrimidine). Yield 1.83g (90%); m.pt. 163° (lit.45 163-4°).

(XXVIIIh; 5-(4”anisylj-2-chloropyrimidine). Yield 1.80g (82%); m.pt. 128° (lit.45 128-9°).

(XXVIIIj; 2-chloro-5-(4-nitrophenyljpyrimidine). Yield 1.40g (59%); m.pt. 123° (lit. 124 °).

Photolysis of 2-chloro-5-iodopyrimidine in heteroarenes

A solution of 2-chloro-5-iodopyrimidine45 (XXXIV) (0.005 mol) in a heteroarene (25 cm³) was diluted with acetonitrile (75 cm³) and was photolysed with a low pressure mercury lamp until no further starting material could be detected by T.L.C. (on alumina, using 1570 V”v chloroform in petroleum spirit b.pt. 40-60°). The solvent was removed under reduced pressure and the product was extracted into and recrystallised from petroleum spirit b.pt. 40-60°. (The mixture of products from the
thiophen photolysis was separated by column chromatography (Alumina
Type H, 7½% v/v chloroform in petroleum spirit b.pt. 40-60°).
Compounds isolated were:-

(XXVa) 2-chloro-5(2-thienyl) pyrimidine. Yield 0.57g (58%); m.pt.
123°; (Found : C, 48.8; H, 2.5; N, 13.7. C₈H₅ClN₂S requires C, 48.85;
H, 2.55; N, 14.25%). δ (CDCl₃), 8.9 (2H,s); 7.5 (3H,m) p.p.m. m/e 196, M⁺.

(XXVIa) 2-chloro-5(3-thienyl) pyrimidine. Yield 0.02g (2%); m.pt. 146°;
(Found : C, 48.7; H, 2.45; N, 13.85. C₈H₅ClN₂S requires C, 48.85;
H, 2.55; N, 14.25%). δ (CDCl₃), 8.6 (2H,s); 7.3 (3H,m) p.p.m. m/e 196, M⁺.

(XXXVb) 2-chloro-5(2-furyl) pyrimidine. Yield 0.68g (75%) m.pt. 135°
(Found : C, 53.0; H, 2.75; N, 15.4. C₈H₅ClN₂O requires C, 53.2; H, 2.8;
N, 15.5%). δ (CDCl₃), 8.7 (2H,s); 7.6 (1H,d); 6.7 (1H,d); 6.4 (1H,m)
p.p.m. m/e 180, M⁺.

(XXXVc) 2-chloro-5(pyrrol-2-yl) pyrimidine. Yield 0.44g (49%); m.pt.
137-8(d); (Found : C, 53.85; H, 3.45; N, 23.45. C₈H₆ClN₃ requires
C, 53.5; H, 3.35; N, 23.4%). δ (CDCl₃), 8.85 (2H,s); 8.75 (1H,s);
6.9 (1H,m); 6.3 (2H,m) p.p.m. m/e 179, M⁺.

(XXXVd) 2-chloro-5(1-methylpyrrol-2-yl) pyrimidine. Yield 0.46g (58%);
m.pt. 125°; (Found : C, 55.8; H, 4.2; N, 21.75. C₉H₈ClN₃ requires
C, 55.85; H, 4.15; N, 21.7%). δ (CDCl₃), 8.7 (2H,s); 7.3 (1H,m); 6.85
(2H,m); 3.3 (3H,s) p.p.m. m/e 193, M⁺.

(XXXVe) 2-chloro-5-phenyl pyrimidine. Yield 0.71g (74%); m.pt. 123°
(lit. 122-4°).

5-Iodopyrimidine (XXXIX)

To a solution of 2-chloro-5-iodopyrimidine⁴⁶ (0.0125 mol) in
ethanol (20 cm³) was added hydrazine hydrate (0.0125 mol) and the
solution was heated under reflux for 1 hour before being cooled in an ice bath. The precipitate formed was isolated and was recrystallised from toluene to give 2-hydrazino-5-iodopyrimidine. Yield 0.28g (95%) m.pt. 196.7° (Found: C, 20.15; H, 2.00; N, 23.7. C₄H₅IN₄ requires C, 20.35; H, 2.15; N, 23.75%). δ (D₆-DMSO), 8.5 (2H, s); 4.2 (2H, b.s.); 3.4 (1H, b.s.) p.p.m. the signals at δ 4.2 and 3.4 were removed on addition of D₂O. m/z 236, M⁺.

A mixture of 2-hydrazino-5-iodopyrimidine (0.01 mol) and silver oxide (0.02 mol) was heated under reflux for 2 hours in absolute ethanol (40 cm³). The solution was filtered hot and the ethanol was removed under reduced pressure. The 5-iodopyrimidine produced was isolated by vacuum sublimation (0.2 mm of Hg, 60°).

Yield 1.13g (55%); m.pt. 126°(s); (Found: C, 23.05; H, 1.1; N, 13.25. C₄H₃IN₂ requires C, 23.3; H, 1.45; N, 13.6%). δ (CDCl₃); 9.25 (1H, s); 9.1 (2H, s) p.p.m. m/z 206, M⁺.

Photolysis of 5-iodopyrimidine in (hetero) arenes.

The procedure used in the photolysis of 2-chloro-5-iodopyrimidine was repeated using 5-iodopyrimidine (XXXIX) (0.005m) to give:-

(XLa) 5-(2-thienyl) pyrimidine. Yield 0.47g (58%); m.pt. 75° (lit.10 76°).
(XLla) 5-(3-thienyl) pyrimidine. Yield 0.05g (6%); m.pt. 61° (lit.10 61°).
(XLb) 5-(2-furyl) pyrimidine. Yield 0.45g (62%); m.pt. 57°; Identical analytical data as that for compound (I; X = 0).
(XLc) 5-(1-methylpyrrol-2-yl) pyrimidine. Yield 0.36g (46%) m.pt. 143-4°; Identical analytical data as that for compound XX.
(XLd) 5-phenyl pyrimidine. Yield 0.58g (74%) m.pt. 38° (lit.13 25°); Identical analytical data as that for compound XXIII.
Photolysis of 2,4-dichloro-5-iodopyrimidine in (hetero)arenes.

The above procedure was repeated using 2,4-dichloro-5-iodopyrimidine (XLII) (0.005 mol) to give:

(XLIIa) 2,4-dichloro-5(2-thienyl) pyrimidine. Yield 0.72 g (62%); m.p.t. 81-2°; (Found: C, 41.4; H, 1.8; N, 12.0. C₈H₄Cl₂N₂S requires C, 41.6; H, 1.75; N, 12.1%). δ (CDCl₃); 8.9 (1H, s); 7.7 (2H, m); 7.4 (1H, m) p.p.m. m/e 230, M⁺.

(XLIIb) 2,4-dichloro-5(3-thienyl)pyrimidine. Yield 0.08 g (7%); m.p.t. 73°; (Found: C, 41.35; H, 1.85; N, 11.95. C₈H₄Cl₂N₂S requires C, 41.6; H, 1.75; N, 12.1%). δ (CDCl₃); 8.65 (1H, s); 7.6-7.1 (3H, m) p.p.m. m/e 230, M⁺.

(XLIIc) 2,4-dichloro-5(2-furyl) pyrimidine. Yield 0.60 g (56%) m.p.t. 66° (Found: C, 44.45; H, 1.75; N, 11.90. C₉H₇Cl₂N₂O requires C, 44.7; H, 1.9; N, 13.0%). δ (CDCl₃); 9.25 (1H, s); 7.8 (1H, m); 7.4 (1H, m); 6.7 (1H, m) p.p.m. m/e 214, M⁺.

(XLIIId) 2,4-dichloro-5(1-methylpyrrol-2-yl) pyrimidine. Yield 0.45 g (39%); m.p.t. 59-60°; (Found: C, 47.2; H, 2.85; N, 18.20. C₉H₇Cl₂N₃ requires C, 47.4; H, 3.10; N, 18.4%). δ (CDCl₃); 8.4 (1H, s); 6.8 (1H, m); 6.2 (2H, m); 3.55 (3H, s) p.p.m. m/e 227, M⁺.

4-chloro-5-iodopyrimidine (XLVIII)

Vacuum dried 5-iodopyrimidin-4-one (0.01 mol) was added to a mixture of phosphoryl chloride (5 cm³) and N, N-dimethylaniline (0.5 cm³), and the mixture was heated under reflux for 1 hour. The excess phosphoryl chloride was removed under reduced pressure and the residue was added to ice. The aqueous phase was extracted with diethyl ether (4 x 10 cm³).
and the ethereal extract was washed with sodium metabisulphite solution followed by water and then dried over magnesium sulphate.

The ether from the filtered extract was removed under reduced pressure and the product was isolated by vacuum sublimation (1 mm Hg, 40°) to give 4-chloro-5-iodopyrimidine. Yield 1.18g (49%); m.pt. 61-2°;

(Found : C, 20.1; H, 1.15; N, 11.4. C₅H₅ClIN₂ requires C, 20.0; H, 0.85; N, 11.65%). δ (CDCl₃), 9.25 (1H,s); 8.9 (1H,s) p.p.m. m/e 240, M⁺.

Photolysis of 4-chloro-5-iodopyrimidine in (hetero)arenes.

The procedure used in the photolysis of 2, 4 dichloro-5-iodopyrimidine was repeated using 4-chloro-5-iodopyrimidine (XLVII) (0.005m).

(XLIXa) 4-chloro-5(2-thienyl) pyrimidine. Yield 0.1g (10%); m.pt. 56° (lit.¹⁰ 55°).

(XLIXb) 4-chloro-5(2-furyl) pyrimidine. Yield 0.13g (14%) m.pt. 83°.

(XLIXc) 4-chloro-5-phenylpyrimidine. Yield 0.15g (16%) m.pt. 72° (lit.⁸ 71-72°).

(XLIXd) 4-chloro-5(1-methylpyrrol-2-yl)pyrimidine. Yield 0.08g (8%) m.pt. 93° (Found : C, 55.6; H, 4.25; N, 21.85. C₇H₇ClN₂ requires 
C, 55.85; H, 4.15; N, 21.7%). δ (CDCl₃); 8.6 (1H,s); 8.4 (1H,s); 6.7 (1H,m); 6.1 (2H,m); 3.8 (3H,s) p.p.m. m/e 193, M⁺.

44. Z. Arnold, **Ibid.**, 1961, **26**, 3051.


47. M. Prystas and F. Sorm, **Coll. Czech. Chem. Comm.** 1964, **29**, 121.


2:1 Aromatic Nucleophilic Substitution

(a) Introduction

Nucleophilic substitution at an aromatic carbon resembles other nucleophilic substitution reactions at carbon in that a bond to the carbon at the reaction site is formed by a reagent Y and a group X is correspondingly displaced with its bonding electrons (Scheme A).

\[ Y^- + Ar - X \rightarrow Y - Ar + X^- \]

Scheme A

In simple compounds such as halobenzenes, nucleophilic substitution requires very vigorous conditions, whereas the nucleophilic substitution reactions of haloalkanes are relatively facile. Nevertheless aromatic nucleophilic substitution reactions are of prime importance in the chemical industry. For example, both phenol and aniline are prepared industrially by nucleophilic substitution reactions. In the laboratory much use is made of aromatic nucleophilic substitution; for example the nucleophilic displacement reactions of aromatic diazonium salts is a well established process for the introduction of a range groups into an aromatic nucleus.

Several mechanisms are known to exist for aromatic nucleophilic reactions. Among these are the unimolecular mechanism \( (S_{N1}) \), the bimolecular mechanism \( (S_{N2}) \), the benzyne (or elimination - addition)
mechanism and the nucleophilic addition - ring opening - ring closing
(ANROC) mechanism.

(b) **Unimolecular Mechanism**

A large number of mechanisms have been proposed to account for
experimental findings obtained from studies of the nucleophilic replacement
of aromatic diazonium groups but even now the situation has not been
completely resolved.

Early results were interpreted as showing the involvement of an
aryl cation (Scheme B). This belief was based on kinetic studies which
showed independence of reaction rate with various anions\(^1\), independence
on acidity over a wide range\(^2\), and a low solvent sensitivity\(^3\). The
effect of substituents on the rate of displacement was also consistent
with a unimolecular nitrogen loss mechanism\(^4\).

\[
\begin{align*}
\text{(Scheme B)}
\end{align*}
\]

Lewis and co-workers showed that this simple explanation did not
fit all the available experimental results\(^5-7\), but were unable to produce
a plausible alternative mechanism. More recently Swain et al\(^8,9\), have
shown that under special conditions (the absence of a strong base or
reducing agent or light) nucleophilic displacements on benzene diazonium
ions proceed by the rate determining product of aryl cations.

(c) **Bimolecular Mechanism**

The majority of aromatic nucleophilic substitutions proceed via
a bimolecular mechanism. The general belief is that the reaction proceeds
via a negatively charged intermediate. This is represented as shown (Scheme C):

\[
Y^- + \text{[Scheme C]}
\]

\[
\text{Scheme C}
\]

Theoretically two possible reaction profiles could exist for this process (Figure 1a and 1b). If the bond formation step is rate determining \( G_A \geq G_B \) Fig. 1a, whilst if the bond breaking step is rate determining \( G_B \geq G_A \) Fig. 1b.

**Figure 1a**

**Figure 1b**
If the bond formation step is rate determining it would be expected that the presence of electron-withdrawing substituents in the aromatic ring would facilitate this step by stabilisation of the developing negative charge and lead to an increase in the rate of reaction compared to that of the unsubstituted compound. If, on the other hand, the bond breaking step is rate determining it would be expected that the presence of electron-withdrawing substituents would retard the rate of reaction by making the ejection of the leaving group less favoured.

In practice it is found that electron-withdrawing substituents enhance the rate of nucleophilic substitution. It is therefore accepted that the bond formation step is rate determining.

The effect of substituents on the rate of aromatic nucleophilic substitution is illustrated in Table 1 which shows the relative rates of reaction of a series of 1-chloro-2-nitro-4-X-benzenes with methoxide ion in methanol at 50°C. These results clearly show that electron-withdrawing substituents enhance the rate of reaction whilst electron-donating substituents retard the rate of reaction. The apparently anomalous result for fluorine (compared with the other halogens) is due to its high mesomeric electron-donating ability which just offsets its high inductive electron-withdrawing powers. The overall result is that fluorine acts as a weak electron-donating substituent in the above reaction.
In aromatic nucleophilic substitutions reactions the formation of stable intermediates has been postulated for over 70 years i.e., the formation of covalent adducts of alkoxides with trinitroalkoxy benzenes (Meisenheimer complexes)\textsuperscript{11,12}. More recent work on such compounds\textsuperscript{13-16} and on Meisenheimer complexes of dinitro-aromatic ethers\textsuperscript{17} has confirmed the existence of stable complexes of the type shown in Figure 2.

![Figure 2](image_url)
The majority of nucleophilic substitution reactions of pyrimidine derivatives appear to take place by a bimolecular mechanism.

Pyrimidine contains two nitrogen atoms which are more electronegative than carbon and this results in a greater electron density on the nitrogen atoms and a corresponding reduction on the remaining carbon atoms in contrast to the symmetrical electron distribution found in benzene. This effect is shown in quantum mechanical calculations of charge distribution in the pyrimidine system (Figure 3). Since these calculations are for the ground state these results must be used with caution in the prediction of activation or deactivation compared to benzene and orders of positional reactivity. These results, however, suggest that pyrimidine should be more reactive than benzene towards nucleophilic reagents and this is confirmed by experimental results.

Figure 3 (electron deficiency shown with a positive sign)

Nucleophilic replacement in pyrimidine derivatives is the most used metathesis of complex pyrimidines. The groups which can be replaced include alkoxyl, alkylthio, alkylsulphinyl, halides. The latter are still the most widely used leaving groups although alkylsulphinyl- and alkylsulphonyl pyrimidines are more reactive towards nucleophiles. A very wide range of nucleophilic reagents have been used in the pyrimidine field e.g., amines, mercaptans, alkoxide and hydroxyl ions, thiocyanate and related ions, halide and cyanide ions.
A number of kinetic studies have been carried out on the reaction of chloropyrimidines with amines. Although the majority of these investigations have been carried out under pseudo first order conditions by the use of an excess of amine the results are nevertheless very useful in the determination of optimum synthetic conditions. Chapman et al. determined Arrhenius parameters for the reaction in ethanol of piperidine and morpholine with 2-chloro-, 2-chloro-4-methyl-, 2-chloro-4,6-dimethyl-, 4-chloro-6-methyl- and 4-chloro-2-methylpyrimidine. It was found that nucleophilic displacement of chlorine from the 4-position is associated with an activation energy of approximately 8KJ less than that for the 2-position. Qualitative and semi-quantitative results from preparative organic chemistry support this reactivity relationship.

Shein et al. measured the reaction rates of 4(6)- and 5-substituted 2-chloropyrimidines with piperidine in various solvents. In benzene the order of reactivity was found to be 4-CNH$_2$ > 5-Cl > 5-C$_6$H$_5$ > H,4-C$_6$H$_5$, 4-MeO > 4,6-diC$_6$H$_5$ > 4-CH$_3$-6-CH$_3$O > 4,6-diCH$_3$ > 5-CH$_3$ > 5-CH$_3$. The order of reactivity of the 5-substituents are in the order that would be predicted from the relative rate factors determined by Greizerstein et al. in the reaction of piperidine with 1-chloro-2-nitro-4-substituted benzenes in benzene, but there is not a linear relationship between log k and Hammett $\sigma$ or $\sigma^-$ functions.

(d) **Elimination - Addition Mechanisms**

Another main class of aromatic nucleophilic substitution mechanisms is the aryne or elimination-addition mechanism. This occurs when a haloarene, which is relatively inert to nucleophilies, is treated with a strong base (Scheme D).
This mechanism is readily recognised by the production of rearranged as well as unrearranged products when a second ring substituent is present. Alternatively it may be revealed by isotopic labelling of ring atoms. Thus, Roberts et al.\textsuperscript{35} showed that chlorobenzene 1-\textsuperscript{14}C(I) reacts with amide ions in liquid ammonia to give almost equal amounts of aniline 1-\textsuperscript{14}C(II) and aniline-2-\textsuperscript{14}(III) (Scheme E).

A pyrimidyne intermediate has been inferred in the reaction of a halopyrimidine with amide ions in liquid ammonia. The reaction of 5-chloro-2-methylpyrimidine (IV) and sodium amide in liquid ammonia gives 4-amino-2-methylpyrimidine (VI) and what was believed to be 5-amino-2-methylpyrimidine (VII), a result consistent with the involvement of a pyrimidyne intermediate\textsuperscript{36} (V) (Scheme F).
A pyrimidyne intermediate has been used to explain the observation of Van der Plas et al. that 5-bromo-4-substituted pyrimidines (VIII; \( R = \text{Ph, OMe, OH} \)) react with potassium amide in ammonia to give exclusively the 6-amino derivative (XI). They suggest that structure (X) contributes to the resonance hybrid of the reaction intermediate and consequently the addition of amide ions to this is very specific resulting in entirely 6-addition. (Scheme G). However, this does not appear to be a very plausible explanation and the involvement of an ANROC mechanism would seem more likely.
ANROC Mechanism

Ring transformations are sometimes found to occur in the reactions of halopyrimidines with nucleophiles. When 4-chloro-2-phenyl pyrimidine (XII) is treated with potassium amide in ammonia, 2-methyl-4-phenyl-1,3,5-triazine (XV) is formed together with a little 4-amino-2-phenyl pyrimidine \(^{38}\) (XVI). If a \(^{14}\)C label is incorporated in the substrate (XII) the label appears at the 2-position of the triazine ring. This observation has been rationalised by initial attack of the amide ion at the 6-position (XIII) followed by ring fission at the 5,6-bond of the pyrimidine ring to give an intermediate such as (XIV) which recyclises to give the triazine \(^{39}\) (XV) (Scheme H).

\[ \text{Scheme H} \]
The Kinetics of the Reaction of Piperidine with 2-chloro-5-substituted pyrimidines

The rate of the reaction between piperidine and 2-chloro-5-substituted pyrimidines (Scheme J) in 50%, aqueous dioxan was investigated at 30° and 40° by stop-start methods. Linear second order kinetic plots were obtained throughout the reaction range examined (up to approximately 70% completion).

No evidence could be found for autocatalysis during the reaction, probably due to the very weak basicity of the substrates compared with that of the nucleophile. The kinetic data is summarised in Table 2.

Scheme J

The results show that the reactions are enthalpy controlled as is usually found in aromatic nucleophilic substitution. The rates can be explained as a consequence of the electron-withdrawing or donating ability of the 5-substituent. Thus, the reaction is facilitated by an electron-withdrawing substituent (e.g. p-bromophenyl) and retarded by an electron donating substituent (e.g. p-anisyl). The range of rate constants is, however, quite narrow.

That electron-withdrawing substituents cause overall rate increases is consistent with the reaction being dominated by the bond formation stage as previously suggested. The narrow range of rates covering the
The kinetics and thermodynamics for the reaction of piperidine with 2-chloro-5-substituted pyrimidines in 50% aqueous dioxan

<table>
<thead>
<tr>
<th>R</th>
<th>$10^3 k_{303}$ (1 mol$^{-1}$ s$^{-1}$)</th>
<th>$10^3 k_{313}$ (1 mol$^{-1}$ s$^{-1}$)</th>
<th>Relative Rate (303)</th>
<th>$\Delta H^\ddagger$ (kJ mol$^{-1}$)</th>
<th>$\Delta S^\ddagger$ (J K$^{-1}$ mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-methylpyrrol-2-yl</td>
<td>2.78</td>
<td>6.28</td>
<td>0.72</td>
<td>65.24</td>
<td>-79</td>
</tr>
<tr>
<td>p-anisyl</td>
<td>3.34</td>
<td>6.98</td>
<td>0.86</td>
<td>58.66</td>
<td>-99</td>
</tr>
<tr>
<td>p-tolyl</td>
<td>3.54</td>
<td>7.18</td>
<td>0.91</td>
<td>56.18</td>
<td>-106</td>
</tr>
<tr>
<td>phenyl</td>
<td>3.89</td>
<td>7.74</td>
<td>1.00</td>
<td>54.58</td>
<td>-111</td>
</tr>
<tr>
<td>2-naphthyl</td>
<td>5.83</td>
<td>11.40</td>
<td>1.50</td>
<td>53.13</td>
<td>-112</td>
</tr>
<tr>
<td>p-fluorophenyl</td>
<td>6.11</td>
<td>11.81</td>
<td>1.57</td>
<td>52.27</td>
<td>-115</td>
</tr>
<tr>
<td>1-naphthyl</td>
<td>6.67</td>
<td>12.73</td>
<td>1.72</td>
<td>51.22</td>
<td>-117</td>
</tr>
<tr>
<td>2-thienyl</td>
<td>7.22</td>
<td>13.61</td>
<td>1.86</td>
<td>50.19</td>
<td>-120</td>
</tr>
<tr>
<td>2-furyl</td>
<td>9.16</td>
<td>17.02</td>
<td>2.36</td>
<td>48.99</td>
<td>-122</td>
</tr>
<tr>
<td>m-chlorophenyl</td>
<td>10.00</td>
<td>18.71</td>
<td>2.57</td>
<td>49.52</td>
<td>-120</td>
</tr>
<tr>
<td>p-bromophenyl</td>
<td>14.90</td>
<td>26.30</td>
<td>3.83</td>
<td>44.72</td>
<td>-132</td>
</tr>
</tbody>
</table>

Table 2

Notes (a) Rate results are the mean of two or more determinations. The results for each determination agreed to within 0.03 of the quoted value.
electron-withdrawing and donating substituents possibly results from a lack of co-planarity between the substituent and the pyrimidine ring thereby decreasing the ability of the substituent to affect the rate of the reaction. In an analogous study of the rates of hydrolysis of 4'-substituted biphenyl-4-carboxylic esters it was calculated that lack of co-planarity between the two ring systems resulted in a 60% decrease in substituent effects. This decrease in substituent effect was also found by Brown et al in a study of the kinetics of rearrangement of 2-methoxy-5-substituted aryl pyrimidines (XVII) to the N-methyl derivatives (XVIII).

For the phenyl and 5-membered heterocyclic substituents the electron-withdrawing ability was found to be in the order 1-methyl - pyrrol-2-yl < phenyl < 2-thienyl < 2-furyl. This conclusion is consistent with pKₐ data for benzoic acid, pyrrole-2-carboxylic acid, 2-furoic acid and 2-thiophen-carboxylic acid as discussed in the Introduction to the thesis.

The difference in electronic character between the 2-furyl- and 2-thienyl- substituents and the 1-methylpyrrol-2-yl substituent is of considerable interest. The differences cannot be simply attributed to the different electronegativities of the heteroatoms since oxygen and nitrogen have similar electronegativities and both are more electronegative than sulphur. It is of interest that the direction of the dipole moment
in 1-methylpyrrole is from the heteroatom to the ring system whereas the opposite is true for furan and thiophen\textsuperscript{42,43}. In discussing the relative inductive effects of the above heteroaryl substituents one should bear in mind that what is being considered is the overall inductive effect of the ring system, which is related to the direction of the dipole moment in the parent heterocycle and includes a contribution from both the $\sigma$ and $\pi$ electron systems. The 1-methylpyrrol-2-yl substituent appears to be a weaker electron-withdrawing system than the 2-furyl or 2-thienyl groups because of a significant contribution to the overall inductive effect by electron-donation from the nitrogen atom to the system of the ring.

From table 2 the rates of reaction of 2-chloro-5(1-methyl pyrrol-2-yl) pyrimidine and 5-p-anisyl-2-chloropyrimidine with piperidine can be seen to be fairly similar. The methoxy group has an electron-withdrawing inductive effect (which because of the distance over which it is operating would be expected to be fairly small) but an electron-donating mesomeric effect which in this case predominates. This results in a decrease in the reaction rate relative to 2-chloro-5-phenyl pyrimidine due to a destabilising effect on the reaction transition state (Fig. 4).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure4.png}
\caption{Figure 4}
\end{figure}
The transition state for bond formation will receive a degree of resonance stabilisation from the 5-substituent as shown in Fig. 5. This effect will be reduced due to the lack of co-planarity between the ring systems which is an essential prerequisite for maximum mutual conjugation between the substituent and reaction centre through an intervening conjugated system.

![Figure 5](image)

**Figure 5**

The similarity between the substituent effect of the 1-methyl-pyrrol-2-yl and p-anisyl groups is further illustrated by the pK\(a\) of 1-methylpyrrole-2-carboxylic acid\(^{45}\) (4.45) and p-methoxy-benzoic acid\(^{46}\) (4.47). Both of these compounds are weaker acids than benzoic acid\(^{46}\) (4.20) showing the electron donating character of these substituents.

The substituent effect of the naphthyl group has been relatively little studied prior to this work, the results of which show that the naphthyl system can stabilise negatively charged transition states, the order of electron-withdrawing ability being 2-naphthyl ≪ 1-naphthyl. The gradation in electron-withdrawing ability is also shown in the p\(K_a\)'s of the naphthoic acids which are 3.69 and 4.17 for the 1- and 2- isomers respectively\(^ {46}\).

The rates of reaction of 2-chloro-5-(1-naphthyl) pyrimidine and 2-chloro-5-(2-thienyl) pyrimidine with piperidine were found to be fairly similar, both the 1-naphthyl and 2-thienyl groups being electron
withdrawing substituents. This similarity in electron withdrawing ability is reflected in the pKa of 2-thenoic acid<sup>45</sup> (3.50) and 1-naphthoic acid<sup>46</sup> (3.69).

The results for the m-chlorophenyl and p-bromophenyl substituents are rather surprising, rather lower reaction rates being expected for these groups. The bromo and chloro substituents are accepted as having an -I/+M effect, with the inductive influence usually being dominant. Since the chloro group is situated meta to the carbon-carbon bond connecting the two ring systems mesomeric effects should not be possible whereas for the bromo group a +M effect would be expected (Fig. 6).

![Figure 6](image)

It would therefore be expected that the m-chlorophenyl substituted pyrimidine would react faster than the p-bromophenyl analogue. Table 2 shows this was not found to be the case.

In the above discussion attention has been drawn to the correlation between the rate of nucleophilic substitution of the substituted chloropyrimidine and the pKa of the appropriate (hetero) arylcarboxylic acid (from which the Hammett substituent constant,<sup>5</sup> is obtained from the equation log (k<sub>o</sub>) = $\delta p$ - where $p$ is defined as 1 for pka data of benzoic acids). In a somewhat similar study of the pipefido-debromination of 4<sup>1</sup>-substituted-3-nitro-4-bromobiphenyls, Dell et al<sup>47</sup> found a rectilinear relationship between the rate of reaction and Hammett $p$ values (except for very strongly electron-withdrawing substituents for which the value $\delta p + 0.32$ (C=\text{-}) was necessary).
In the study by Dell'Erba the $\sigma$ values used were derived from pKa data of benzoic acids with the whole of the substituted phenyl group being treated as the substituent and the carboxylic acid group being treated as the reaction centre. The correlation between reaction rate and $\sigma$ (rather than $\sigma^-$) suggests a lower contribution of a structure such as Fig. 7 to the intermediate complex than happens in the same reaction on para-substituted benzene derivatives.

![Figure 7](image)

If the same approach is applied to the piperidino-dechlorination of the 2-chloropyrimidines a straight line relationship between log k and Hammett functions is found for 8 of the 11 compounds investigated (Fig. 8).

No correlation can be found between the rate of reaction and Hammett $\sigma^-$ functions (from the pKa of substituted phenols) suggesting that resonance stabilisation of the type shown in Fig. 5, has little or no effect on the stabilisation of the reaction transition state.

As can be seen the results for the three halophenylpyrimidines do not satisfactorily fit the above graph. The reason for this failure is not clear, the apparently most likely possibility, that side reactions were occurring during the course of the kinetic determinations can be ruled out since careful thin layer chromatographic examination of the
reaction mixtures failed to reveal the presence of any unexpected products. It is possible that the observed inconsistencies result from a solvent effect but it is difficult to envisage a reason for this occurring.

Three main conclusions can be drawn from this work:

(i) The reaction between piperidine and 2-chloropyrimidines in aqueous dioxan is enthalpy controlled and the rate of reaction appears to be dominated by the bond formation step.
(ii) The order of electron-withdrawing ability of phenyl and the 5-membered heteroaryl substituents studied was found to be 1-methylpyrrol-2-yl 😳 phenyl 😳 2-thienyl 😳 2-furyl, a result consistent with present knowledge of the electronic character of these substituents.

(iii) A linear relationship was found between the rate of piperidino-debromination of 5-substituted-2-chloropyrimidines and the Hammett σ function. It was further found that electron-donating substituents reduce the rate of reaction whilst electron-withdrawing substituents enhance the reaction rate.
Experimental

The 2-chloro-5-substituted pyrimidines were prepared as described in Chapter 1.

**Kinetic Determinations**

The chloropyrimidine solution (0.01M; 10cm$^3$) and piperidine solution (0.02M, 10cm$^3$), both in 50% v/v aqueous dioxan, were equilibrated at 30° or 40° (± 0.01°). The solutions were mixed and conductance readings were taken over a period of several hours using a Wayne-Kerr bridge. The determinations were then repeated using freshly prepared solutions.

If the reaction is first order with respect to each reagent the rate equation is:

\[-\frac{d (\text{chloropyrimidine})}{dt} = k (\text{chloropyrimidine}) (\text{piperidine})\]

If the initial molar concentration of the chloropyrimidine in the reaction mixture is 'a' then, under the conditions used, the initial concentration of the piperidine is '2a'. If 'x' is the fall in the concentration of chloropyrimidine after time 't', then the remaining chloropyrimidine concentration is (a-x) and that of the piperidine is (2a - 2x). Therefore the rate equation becomes:

\[-\frac{d (a-x)}{dt} = k (a-x) (2a-2x)\]

i.e. \[\frac{dx}{dt} = 2k (a-x)^2\] since \[\frac{da}{dt}\] is zero.

Inversion and integration gives

\[2kt = \frac{1}{a-x} - \frac{1}{a}\]

i.e. \[\frac{1}{a-x} = 2kt - \frac{1}{a}\]

Therefore, if the reaction is second order, a plot of \[\frac{1}{a-x}\] against 't'
will be a straight line and from this plot the rate constant for the reaction can be calculated.

Since piperidine is a much stronger base than both the chloropyrimidine and the piperidinylpyrimidine produced during the reaction it can be assumed that the conductance reading is due only to piperidinium chloride. From a standard plot of conductance, the piperidinium chloride concentration at time 't' during the reaction can be determined. This concentration is equal to the value 'x' in the above equations.

For the kinetic determinations the dioxan was purified by the method recommended by Vogel, whilst the water was de-ionized and then distilled from potassium permanganate. The piperidine was dried over potassium hydroxide and then distilled through a spinning band column, the middle fraction boiling at 106° being collected (Lit. 106°).

The following compounds were isolated from the kinetic reaction mixtures:

5-(l-methylpyrrol-2-yl)-2-[l-piperidinyl]pyrimidine. m.p. 103°(d).
(Found: C, 69.55; H, 7.4; N, 23.05. C_{14}H_{18}N_{4} requires C, 69.4; H, 7.5; N, 23.1%). δ (CDCl₃) 8.5(s, 2H), 7.3(m, 3H), 4.3(s, 3H), 2.7(b.s., 4H), 1.6(b.s., 6H). m/e 242, K⁺

5-(4-anisyl)-2-[l-piperidinyl]pyrimidine. m.p. 91°. (Found: C, 71.4; H, 7.10; N, 15.45. C_{16}H_{19}N_{3}O requires C, 71.35, H, 7.1; N, 15.6%). δ (CDCl₃) 8.45(s, 2H), 7.3(s, 4H), 3.75(s, 3H), 3.6(b.s., 4H), 1.75 (b.s., 6H). m/e 269, K⁺
5-(2-furyl)-2-[l-piperidinyl]pyrimidine. m.p.t. 71°. (Found: C, 68.3; H, 6.75; N, 18.4. \( \text{C}_13\text{H}_{15}\text{N}_3 \) requires C, 68.1; H, 6.60; N, 18.3%. 8.6(s,2H), 7.5(m,3H), 4.1(b.s.,4H), 1.9(b.s.,6H) m/e 229, M+.

2-[l-piperidinyl]-5(2-thienyl)pyrimidine. m.p.t. 85°. (Found: C, 63.6; H, 6.2; N, 17.2. \( \text{C}_13\text{H}_{15}\text{N}_3 \) requires C, 63.65; H, 6.15; N, 17.1%. 8.6(s,2H), 7.2(m,3H), 3.9(b.s.,4H), 1.6(b.s.,6H) m/e 245, M+.

5-(4-fluorophenyl)-2-[l-piperidinyl]pyrimidine. m.p.t. 106°. (Found: C, 70.15; H, 6.15; N, 16.15. \( \text{C}_15\text{H}_{16}\text{FN}_3 \) requires C, 70.0; H, 6.30; N, 16.35%). 8.4(s,2H), 7.1(m,4H), 3.8(b.s.,4H), 1.85(b.s.,6H) m/e 257, M+.

5-(4-bromo phenyl)-2-[l-piperidinyl]pyrimidine. m.p.t. 169° (Found: C, 56.8; H, 5.3; N, 13.1. \( \text{C}_15\text{H}_{16}\text{BrN}_3 \) requires C, 56.6; H, 5.10; N, 13.2%). 8.5(s,2H), 7.3(m,4H), 3.95(b.s.,4H), 2.0 (b.s.,6H) m/e 317, M+.

5-(3-chlorophenyl)-2-[l-piperidinyl]pyrimidine. m.p.t. 91° (Found: C, 65.8; H, 5.9; N, 15.4. \( \text{C}_15\text{H}_{16}\text{BrN}_3 \) requires C, 65.8; H, 5.9; N, 15.35%). 8.6(s,2H), 7.5(m,7H), 4.0(b.s.,4H), 1.9(b.s.,6H) m/e 273, M+.

5-(1-naphthyl)-2-[l-piperidinyl]pyrimidine. m.p.t. 97° (Found: C, 78.7; H, 6.75; N, 14.3. \( \text{C}_19\text{H}_{19}\text{N}_3 \) requires C, 78.85; H, 6.6; N, 14.5%). 8.6(s,2H), 7.5(m,7H), 4.0(b.s.,4H), 1.9(b.s.,6H) m/e 289, M+.

5-(2-naphthyl)-2-[l-piperidinyl]pyrimidine. m.p.t. 146-7° (Found: C, 78.7; H, 6.5; N, 14.6. \( \text{C}_19\text{H}_{19}\text{N}_3 \) requires 78.85; H, 6.6; N, 14.5%. 8.6(s,2H), 7.4(m,7H), 3.8(b.s.,4H), 1.8(b.s.,6H) m/e 289, M+.

2-[l-piperidinyl]-5-(4-tolyl)pyrimidine. m.p.t. 127° (Found: C, 76.1; H, 7.7; N, 16.2. \( \text{C}_16\text{H}_{19}\text{N}_3 \) requires 75.85; H, 7.55; N, 16.6%. 8.6(s,2H), 7.4(m,4H), 4.1(b.s.,4H), 2.7(s,3H), 1.8(b.s.,6H) m/e 253, M+.

5-phenyl-2-[l-piperidinyl]pyrimidine. m.p.t. 91° (lit. 93°-95°)
REFERENCES

1. J.C. Cain, Ber., 1905, _38, 2511.
5. E. S. Lewis and J. E. Cooper, Ibid., 1962, 84, 3847.
6. E. S. Lewis and J. M. Insole, Ibid., 1964, _86_, 34.
15. R. C. Farmer; Ibid., 1959, 3425 and 3430.
Chapter 3

The Quaternization of 5-substituted pyrimidines

3.1 Introduction

If a nitrogen atom in a heterocyclic system possesses a lone pair of electrons which are not involved in $\sigma$ or $\pi$ bonding orbitals, the electron pair is able to form a bond between the nitrogen atom and a carbon of suitable polarisability, the nitrogen becoming quaternary. The attacking molecule must be able to lose an anion during the quaternizing reaction and hence alkyl or acyl halides are the most used quaternizing agents.

The reaction can be regarded as a nucleophilic replacement of the leaving group of the quaternizing agent by attack of the lone pair of the nitrogen atom (Scheme A).

$$\text{N}:+\text{R-X} \rightarrow \text{N-R}^{+} + \text{X}^{-}$$

Scheme A

It would therefore be expected that the availability of the electron pair, as influenced by the ring containing the nitrogen atom, the substituents present in the ring, and the steric environment should affect the rate of quaternization.
The influence of substituents in the heterocyclic system

The most thoroughly investigated compounds are the alkylpyridines, the results being rather difficult to assess due to the variation of inductive and steric effects as well as the possibility of hyperconjugation with some of the substituents.

If the effect of delocalization of the developing positive charge during the quaternization of pyridine derivatives is considered it is apparent that electron-donating groups in the 2- and 4-positions should facilitate the reaction (Figure 1). The presence of electron-donating groups in the 3-position should also increase the rate of reaction but to a lesser extent.

![Figure 1](image)

In practice it is found to be very difficult to differentiate between steric and electronic effects in the 2-position of the pyridine ring.

Coleman et al. determined the rate of reaction of pyridine, 4-methylpyridine and 4-isopropylpyridine with n-butyl bromide and found a steady increase in the rates in the order given. The activation energies were found to be 66.9, 66.5 and 65.2 KJmol\(^{-1}\) respectively.
Since the order of the inductive effects of the substituents is H < Me < i-Pr the rates appear to comply with the simple delocalization explanation.

Brown et al.² investigated the reaction of 2-, 3- and 4-alkyl-pyridines with methyl, ethyl and isopropyl iodide (Table 1). The results show higher activation energies with 2-substituted pyridines and a sharp increase with the bulk of the substituent or the entering group. An activating effect is apparent for a 3- or 4-alkyl group. The greater reactivity of 4-methyl compared with 4-t-butylpyridine can be explained by hyperconjugation of the methyl group which is not possible with the t-butyl substituent.

<table>
<thead>
<tr>
<th>Pyridine substituent</th>
<th>MeI</th>
<th>EtI</th>
<th>i-PrI</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>58.1</td>
<td>66.9</td>
<td>74.0</td>
</tr>
<tr>
<td>2-methyl</td>
<td>58.5</td>
<td>69.0</td>
<td>80.3</td>
</tr>
<tr>
<td>2-ethyl</td>
<td>59.4</td>
<td>69.4</td>
<td>-</td>
</tr>
<tr>
<td>2-isopropyl</td>
<td>61.9</td>
<td>71.5</td>
<td>-</td>
</tr>
<tr>
<td>2-t-butyl</td>
<td>73.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3-methyl</td>
<td>56.9</td>
<td>64.8</td>
<td>72.7</td>
</tr>
<tr>
<td>4-methyl</td>
<td>56.9</td>
<td>66.1</td>
<td>72.3</td>
</tr>
<tr>
<td>4-t-butyl</td>
<td>57.3</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 1
(Energies of activation (KJmol⁻¹) for the reaction of alkyl iodides with pyridines).

Other data from the same investigation show that as the 3-alkyl
group increases in size, with therefore a decrease in inductive effect, there is a steady increase in the rate of quaternization in the order 3-methyl < 3-ethyl < 3-isopropyl < 3-t-butyl.

The definitive study of substituent effects on the rate of quaternization of pyridine derivatives was carried out by Fischer et al.3 who found that the rates of reaction of 4- (+M) substituted pyridines correlated well with Taft $\sigma^0$ constants whereas the rate of reaction of 4-(-M) substituted pyridines correlated with $\sigma_I$ rather than $\sigma^0$. These results were explained in terms of the effect of the nuclear nitrogen atom in withdrawing $\pi$ electrons from the 4-position, thereby causing $+M$ effects to be enhanced and $-M$ effects to be inhibited.

3.3 Quaternization of pyrimidine derivatives

In spite of much interest in the chemistry of pyrimidine few of its simple derivatives have been studied in detail and only a small number of simple quaternary pyrimidinium salts have been reported. Only one of the nitrogen atoms of pyrimidine is alkylated by agents such as methyl iodide5 but triethyloxonium fluoroborate will give rise to a diquaternary salt6 (I).

Note: $\sigma^0$ is the Taft substituent constant4 derived from reactions where an aromatic ring is shielded from the reaction centre (e.g. phenyl acetic acids) or where substituents are in the meta position. It is proposed that these values are more representative of non-conjugative effects than the Hammett $\sigma$ substituent constant derived from ionization of substituted benzoic acids. $\sigma_I$ is a measure of polar effects exclusive of resonance.
The majority of early work on the quaternization of pyrimidines was centred on the amino- and hydroxypyrimidines and some of the conclusions of this work appear to be suspect e.g. methyl iodide was reported to react with 4-amino-2-methoxypyrimidine to give the N-1 salt (II). This proposed structure has been shown to be incorrect, the alkylidihydro-iminopyrimidine (III; R = OMe) being the actual product of the reaction.

The treatment of a 2- or 4-aminopyrimidine with an alkyl halide almost invariably leads to alkylation at a ring nitrogen and the formation of an alkylidihydro-iminopyrimidine. Thus, 4-amino-2-methylthio-
pyrimidine on treatment with methyl iodide yields III (R = MeS)\(^{10}\) whilst 2-aminopyrimidine reacts with methyl iodide in ethanol to give 1,2-dihydro-2-imino-1-methyl pyrimidine hydroiodide\(^{11}\) (IV)

\[
\text{N} \quad \text{Me} \quad \text{NH} \\
\text{HI}
\]

(IV)

Despite the overwhelming evidence regarding the reaction of alkyl halides with aminopyrimidines to give iminopyrimidines some confusion still appears to remain. Two recent patents\(^{12}\) concerning the synthesis of central nervous system stimulating compounds claim that 2-aminopyrimidines react with \(o\)-bromophenalkylene bromides to form the quaternary salts (V). It would seem more probable that the product of the reaction would in fact be the imino salts (VI).

\[
\begin{align*}
\text{(V)} & \quad \text{(VI)}
\end{align*}
\]
Some synthetic applications of quaternary pyrimidinium salts have been reported recently. For example, Kasuga et al.\(^{13}\) have shown that pyrazolo (1,5-\(c\)) pyrimidines (IX) were obtained by 1,3-dipolar cyclo addition of \(N\)-aminopyridinium mesitylene sulphonates (VIII) with methylacetylene carboxylate.

\[
\begin{align*}
\text{(VIII)} & \\
\text{(IX)} & 
\end{align*}
\]

Van der Plas et al.\(^{14}\) have demonstrated ring conversion reactions of pyrimidinium salts e.g. 1-methylpyrimidinium methosulphate (X) gives isoxazole (XI) in good yield when treated with hydroxylamine hydrochloride.

\[
\begin{align*}
\text{(X)} & \\
\text{(XI)} & \\
\text{(XII)} & 
\end{align*}
\]
It has also been shown\(^*\) that (X) when treated with the carbanion of diethylmalonate gives, after saponification, 1,2-dihydro-2-oxonicotinic acid (XII).

3.4 The kinetics of quaternization of 5-rconosubstituted -pyrimidines

It would be expected that the electronic character of substituents in the 5-\(\text{position}\) of the pyrimidine ring could be determined by studies of the rates of quaternization of 5-monomosubstituted pyrimidines since (i) the pyrimidine derivatives are symmetrical and hence only one product is possible (ii) the substituent is sufficiently remote from the ring nitrogens so that steric effects should be non-existent and (iii) resonance interactions are not possible between the reaction site and the substituents.

Despite these favourable points no systematic studies of the rate of quaternization of 5-substituted pyrimidines have been carried out.

In order to determine the electronic effects of substituents in the course of a reaction in which a positive charge is developing on the transition state, the kinetics of the reaction of 5-substituted pyrimidines with phenacyl bromide (Scheme B) in methylcyanoide was investigated at 30\(^\circ\) and 40\(^\circ\) by con auclimetrie methods (see experimental section).

\[
\text{R} + \text{PhCOCH}_2\text{Br} \rightarrow \text{NCH}_2\text{COBr} \quad \text{(XIII) XIV}
\]

Scheme B
After approximately 15% completion of the reaction, catalysis was found to be occurring (probably due to a salt effect) so kinetic and thermodynamic data was calculated from the results for the first 10% of the reaction. In this range second order kinetic plots were obtained as is usually found for quaternization reactions. The experimental findings are summarized in Table 2.

The thermodynamic data show that the reaction is enthalpy controlled as is usually found in quaternization processes. The relative rates of reaction can be explained as a consequence of the electron-donating or withdrawing ability of the 5-substituent.

For example, 5-p-anisylpyrimidine (XIII; R = p-anisyl) is found to react faster with phenacyl bromide than does 5-p-bromo phenylpyrimidine (XIII; R = p-bromophenyl). The anisyl group is accepted as being an electron-donating substituent and hence will tend to stabilize the positive charge developing during the course of the quaternization process and thus enhance the rate of reaction. On the other hand, the p-bromophenyl group (an electron-withdrawing substituent) will tend to destabilize the developing positive charge and hence retard the rate of reaction.

The effect of the 5-membered heterocyclic substituents on the rate of the quaternization reaction is of considerable interest; for this reaction, the electron-donating ability of these substituents is 1-methylpyrro-2-yl > 2-furyl > 2-thienyl, all of which are more electron donating than the phenyl group.

It is interesting at this stage to recall the electron-withdrawing ability of the substituents determined from the nucleophilic displace-
The kinetics and thermodynamics for the reaction of phenacyl bromide with 5-substituted pyrimidines in acetonitrile

<table>
<thead>
<tr>
<th>Substituted Pyrimidine</th>
<th>$10^5k_{303}$ (l mol$^{-1}$ s$^{-1}$)</th>
<th>$10^5k_{313}$ (l mol$^{-1}$ s$^{-1}$)</th>
<th>Relative Rate</th>
<th>$\Delta H^\ddagger$ (kJ mol$^{-1}$)</th>
<th>$\Delta S^\ddagger$ (J K$^{-1}$ mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-methylpyrrol</td>
<td>11.21</td>
<td>22.94</td>
<td>1.94</td>
<td>57.02</td>
<td>-132</td>
</tr>
<tr>
<td>2-yl</td>
<td>10.88</td>
<td>22.73</td>
<td>1.88</td>
<td>58.73</td>
<td>-127</td>
</tr>
<tr>
<td>p-anisyl</td>
<td>9.16</td>
<td>19.29</td>
<td>1.58</td>
<td>59.40</td>
<td>-126</td>
</tr>
<tr>
<td>2-furyl</td>
<td>8.51</td>
<td>18.38</td>
<td>1.47</td>
<td>61.50</td>
<td>-120</td>
</tr>
<tr>
<td>p-tolyl</td>
<td>7.75</td>
<td>17.10</td>
<td>1.34</td>
<td>63.23</td>
<td>-115</td>
</tr>
<tr>
<td>2-thienyl</td>
<td>6.72</td>
<td>14.95</td>
<td>1.16</td>
<td>63.96</td>
<td>-114</td>
</tr>
<tr>
<td>1-naphthyl</td>
<td>6.03</td>
<td>13.83</td>
<td>1.04</td>
<td>66.49</td>
<td>-106</td>
</tr>
<tr>
<td>2-naphthyl</td>
<td>5.79</td>
<td>13.52</td>
<td>1.00</td>
<td>67.99</td>
<td>-102</td>
</tr>
<tr>
<td>phenyl</td>
<td>5.00</td>
<td>12.07</td>
<td>0.86</td>
<td>70.75</td>
<td>-94</td>
</tr>
<tr>
<td>p-fluorophenyl</td>
<td>4.52</td>
<td>11.10</td>
<td>0.78</td>
<td>72.17</td>
<td>-90</td>
</tr>
<tr>
<td>m-chlorophenyl</td>
<td>4.02</td>
<td>10.04</td>
<td>0.69</td>
<td>73.58</td>
<td>-86</td>
</tr>
<tr>
<td>p-bromophenyl</td>
<td>3.98</td>
<td>9.87</td>
<td>0.68</td>
<td>72.99</td>
<td>-88</td>
</tr>
</tbody>
</table>

Table 2

(a) Rate results are the mean of two or more determinations. The results for each determination agreed to within 0.05.
ment reaction of piperidine on 2-chloro-5-substituted pyrimidines (Chapter II) which was 1-methylpyrrol-2-yl < phenyl < 2-thienyl < 2-furyl.

It can be seen that in both reactions the 1-methylpyrrol-2-yl group is the best electron-donor whereas the relative orders of the other substituents varies according to the nature of the reaction considered.

In the quaternization reaction if the ability of the heterocyclic substituent in stabilizing the developing positive charge were merely a function of the electronegativity of the heteroatom the expected order of electron-donating ability would be 2-thienyl > l-methylpyrrol-2-yl > 2-furyl. Since, in practice, this order is not found a further factor must be influencing the results, the most obvious explanation being the involvement of the 3d electrons on the sulphur atom in the thienyl group.

Thus, the observed order would appear to be explicable by consideration of the possible canonical forms for the reaction transition state. 1-methylpyrrol-2-yl and 2-furyl are able to 'feed' electrons into the pyrimidine ring by use of the 2p lone pair of electrons on the hetero atom (Figure 2; X = N-Me,0). This situation also arises for thiophen (Figure 2; X = S) but in addition it can use its 3d electrons to inductively withdraw electrons from the pyrimidine ring (Figure 3).

![Figure 2](image-url)
It would appear that withdrawal of electrons by the 3d effect is sufficient to cause the 2-thienyl substituent to be a poorer electron-donor than either the 1-methylpyrrol-2-yl or 2-furyl substituent.

The electronic effect of other substituents on the rate of quaternization of 5-substituted pyrimidines can be clearly seen in Table 2. The 1-naphthyl group is a better electron-donor than the 2-naphthyl group and both of these are better donors than the phenyl group.

The p-fluorophenyl group is a better electron-donor than the other halo substituted phenyl groups. Although the fluorine atom is more electronegative than the other halogen substituents it has a larger +M effect (Figure 4) and this compensates for its higher electronegativity.
The conclusions to be drawn from this work are as follows:

1. During a reaction in which a positive charge is developing the order of electron-donating ability of the 5-membered heterocycles is 1-methylpyrrol-2-yl > 2-furyl > 2-thienyl > phenyl.

2. The electron-donating ability of the 2-thienyl group appears to be associated with the destabilizing effect of the 3d electrons of the sulphur atom.

3. This work clearly demonstrates that the relative electron-donating ability of the 5-membered heterocyclic substituents depends on the nature of the reaction being considered.
Experimental

The 5-substituted pyrimidines were prepared as detailed in Chapter 1 of this thesis.

Kinetics

Equimolar solutions (usually 0.02m) of the 5-substituted pyrimidine and phenacyl bromide in acetonitrile were prepared. 10 ml aliquots of each solution were equilibrated at 30°C (±0.05), the solutions were mixed and conductance readings were taken at 15 minute intervals over approximately 8 hours. After leaving the reaction mixture for ca. 7 days the pyrimidinium salt was isolated and characterized. The conductance of standard solutions of the salt in acetonitrile were measured and the value for a 0.01M solution was obtained by extrapolation, this value was used in the kinetic calculations as detailed later. Each kinetic run was carried out at least twice. The whole procedure was then repeated at 40°C (±0.05).

For the reaction

\[ A + B \rightarrow C + D \]

\[ \frac{dx}{dt} = k(a-x)(b-x) \]

if the reaction is first order with respect to both A and B

where \( a \) = initial concentration of A

\( b \) = initial concentration of B and

\( x \) = amount of A reacted after time \( t \)

If equimolar solutions of A and B are used

\[ \frac{dx}{dt} = k(a - x)^2 \]
Integration gives
\[ \frac{1}{a-x} - \frac{1}{a} = kt \]

... a plot of \( \frac{1}{a-x} \) against 't' will be a straight line of slope 'k' and intercept \( \frac{1}{a} \)

For the conductrimetric method used in this determination \( a = 0.01 \) and \( x = 0.01 \times y \) where

\( y \) = conductance reading after time 't' and

\( y \) = conductance of a 0.01M solution of the pyrimidinium salt

For the kinetic determinations the acetonitrile was dried over Molecular Sieve 4A and then distilled through a spinning band column, the middle fraction boiling at 81.6° was collected (Lit. 81.6°). The phenacylbromide was twice recrystallized from petroleum spirit to give a product of m.pt. 50.9° (Lit. 51°).

The following compounds were isolated from the kinetic mixtures:

**XIVa** 5-phenyl-N-phenacylpyrimidinium bromide (XIV; \( R = \) phenyl)

m.pt. 146°. Found C: 60.65; H, 4.2; N, 8.05. \( \text{C}_{16}H_{15}BrN_{2}O \) requires C, 60.85; H, 4.25; N, 7.9%. \( \delta (D_{6}-DMSO) \) 10.2(s,1H), 9.9(s,1H), 9.3(s,1H), 8.6(m,10H), 2.3(s,2H).

**XIVb** 5-(2-furyl)-N-phenacylpyrimidinium bromide (XIV; \( R = \) 2-furyl)

m.pt. 156°. Found C: 55.80; H, 4.05; N, 8.0. \( \text{C}_{16}H_{15}BrN_{2}O_{2} \) requires C, 55.65; H, 3.80; N, 8.1%. \( \delta (D_{6}-DMSO) \) 10.6(s,1H), 9.7(s,1H), 9.5(s,1H), 8.6 - 7.1 (m,8H), 2.8(s,2H).

**XIVc** 5-(1-naphthyl)-N-phenacylpyrimidinium bromide (XIV; \( R = \) 1-naphthyl) m.pt. 142°. Found: C, 64.95; H, 4.40; N, 6.95. \( \text{C}_{22}H_{17}BrN_{2}O \)
requires $C_{65.20}$; $H_{4.25}$; $N_{6.90}$. $\delta (D_6 - DMSO)$ $10.4(s,1H)$, $10.2$
(b.s.,2H) $8.4 - 6.8(m,12H)$, $2.3(s,2H)$.

XIVd  $5-(2$-naphthyl$)-N$-phenacylpyrimidinium bromide (XIV; $R = 2$-

naphthyl) m.pt. $241^\circ$. Found: $C_{65.4}$; $H_{4.3}$; $N_{7.1}$. $C_{22}H_{17}Br_2O$ requires
$C_{65.20}$; $H_{4.25}; N_{6.90}$. $\delta (D_6 - DMSO)$ $10.3(s,1H)$, $10.1(s,1H)$, $9.9$
(s,1H), $8.5 - 6.8(m,12H)$, $2.0(s,2H)$.

XIVe  $5-(1$-methylpyrrrol-2-yl$)-N$-phenacylpyrimidinium bromide (XIV; $R = 1$-
methylpyrrrol-2-yl) m.pt. $240^\circ(d)$. Found: $C_{59.70}$; $H_{3.75}$; $N_{7.75}$. $C_{19}H_{16}Br_3O$ requires
$C_{59.7}$; $H_{4.2}$; $N_{11.0}$. $\delta (D_6 - DMSO)$ $9.9$
(s,1H), $9.7(s,1H)$, $9.4(s,1H)$, $8.3 - 7.6(m,8H)$, $2.9(s,3H)$, $2.2(s,2H)$.

XIVf  $5-(2$-thienyl$)-N$-phenacylpyrimidinium bromide (XIV; $R = 2$-
thienyl) m.pt. $214^\circ(d)$. Found: $C_{52.85}$; $H_{3.75}$; $N_{7.75}$. $C_{16}H_{13}Br_3OS$
requires $C_{53.2}; H_{3.65}; N_{7.75}$. $\delta (D_6 - DMSO)$ $9.9(s,1H), 9.7(s,1H)$,
$9.4(s,1H)$, $8.2 - 6.8(m,8H)$, $2.2(s,2H)$.

XIVg  $5-(4$-chlorophenyl$)-N$-phenacylpyrimidinium bromide (XIV; $R =$
p-chlorophenyl) m.pt. $161^\circ$. Found: $C_{55.75}$; $H_{3.8}$; $N_{7.3}$. $C_{16}H_{14}BrCl_2N_2O$
requires $C_{55.5}; H_{3.6}; N_{7.2}$. $\delta (D_6 - DMSO)$ $9.9(s,1H)$, $9.8(s,1H)$, $9.0$
(s,1H), $8.2 - 6.6(m,9H)$, $2.5(?,2H)$ *peak under DMSO, integration

carried out by comparison with a $D_6 - DMSO'$ blank'.

XIVh  $5-(3$-chlorophenyl$)-N$-phenacylpyrimidinium bromide (XIV; $R =$
m-chlorophenyl) m.pt. $174^\circ(d)$. Found: $C_{55.7}; H_{3.75}; N_{7.4}$. $C_{16}H_{14}BrClN_2O$
requires $C_{55.5}; H_{3.6}; N_{7.2}$. $\delta (D_6 - DMSO)$ $9.0(s,1H)$,
$8.9(s,1H)$, $8.7(s,1H)$, $8.2 - 6.6(m,9H)$, $2.0(s,2H)$.

109
XIVj 5-(4-bromophenyl)-N-phenacylpyrimidinium bromide (XIV; R = p-bromophenyl) m.p. 171°. Found: C, 50.05; H, 2.5; N, 6.5. C₁₈H₁₄Br₂N₂O requires C, 49.80; H, 2.30; N, 6.45%. δ (D₆ - DMSO) 9.2(s,1H), 8.9(2,1H), 8.8(s,1H), 8.1 - 6.8(m,9H), 2.1(s,2H).

XIVk 5-(4-fluorophenyl)-N-phenacylpyrimidinium bromide (XIV; R = p-fluorophenyl) m.p. 141°. Found: C, 58.05; H, 3.6; N, 7.35. C₁₈H₁₄Br₂N₂O requires C, 57.9; H, 3.8; N, 7.5%. δ (D₆ - DMSO) 9.4(s,1H), 9.3(s,1H), 8.9(s,1H), 8.2 - 6.6 (m,9H), 2.3(s,2H).

XIVl 5-(4-anisyl)-N-phenacylpyrimidinium bromide (XIV; R = p-anisyl) m.p. 203°(d). Found: C, 59.5; H, 4.6; N, 7.35. C₁₉H₁₇BrN₂O₂ requires C, 59.25; H, 4.45; N, 7.3%. δ (D₆ - DMSO) 9.9(s,1H), 9.8(s,1H), 9.6(s,1H), 8.2 - 6.6 (m,9H), 3.8(s,3H), 2.3(s,2H).

XIVm 5-(4-tolyl)-N-phenacylpyrimidinium bromide (XIV; R = p-tolyl) m.p. 177°(d) Found: C, 62.05; H, 4.75; N, 7.3. C₁₉H₁₇BrN₂O requires C, 61.8; H, 4.65; N, 7.6%. δ (D₆ - DMSO), 10.1(s,1H), 10.0(s,1H), 9.3(s,1H), 8.3 - 6.7(m,9H), 2.4(s,3H), 2.1(s,2H).
References

Chapter 4

The molecular structure of 2,4-diazido-5-iodopyrimidine and 2,4-diazido-6-methylpyrimidine

4:1 Introduction

Some confusion exists as to the preferred tautomeric form of the diazidopyrimidines. It has been suggested\(^1\) that, contrary to general belief, 2,3,4,5 2,4-diazidopyrimidines exist predominantly in the 5-azido-tetrazolo (1, 5-a) pyrimidine form (1\(_c\)) with the isomeric 5-azido-tetrazolo (1, 5-c) pyrimidine form (1\(_b\)) as a likely minor constituent, rather than in the diazido form (1a).

The 2,4-diazido-6-methylpyrimidine/5-azido-7-methyl tetrazolo (1,5-a) pyrimidine tautomerism (1\(_a\) ↔ 1\(_c\); R = Me, R\(^1\) = H) has been investigated\(^1\) and on the evidence of \(^1\)H n.m.r. data it was concluded that (1\(_c\)) was the predominant form with approximately 10% of the 5-azido-8-methyltetrazolo - (1, 5-c) pyrimidine tautomer (1\(_b\); R = Me, R\(^1\) = H) also present. Earlier work\(^2\) on the same system, based on chemical and u.v. data indicated that the diazido form (1a) was preferred.
The reaction of sodium azide with 2,4-dichloro-5-iodopyrimidine in aqueous ethanol was carried out and a product was isolated in which both of the chlorine atoms had been replaced by azide groups. This compound can potentially exist in five tautomeric forms (I a-e; R = H, R¹ = I). The i.r. spectrum (KBr disc) showed a strong azide absorption at 2130 cm⁻¹ and only weak absorption at 1000 - 1100 cm⁻¹ where a tetrazolo system would be expected to absorb.

2,4-Diazido-6-methylpyrimidine (I; R = Me, R¹ = H) was prepared by the action of sodium azide on 2,4-dichloro-6-methylpyrimidine. The i.r. spectrum (KBr disc) showed a strong azide absorption at 2150 cm⁻¹ and once again only weak absorption at 1000 - 1100 cm⁻¹.

In order to resolve the forms in which the above compounds exist, single crystal X-ray studies were undertaken.

4:2 Crystal Data
(a) 2,4-diazido-5-iodopyrimidine

The colourless crystals were rectangular in shape and extinguished polarised light in directions coincident with the external crystal axes. Consequently crystals were mounted on glass fibres along their long axes and preliminary rotation and Weissenberg photographs indicated that the crystals were monoclinic. The rotation axis was chosen as c and accurate
unit cell dimensions were measured from precession photographs taken with Zr filtered Mo Kα radiation. The unit cell dimensions were found to be:

\[ a = 11.08 \ (1), \ b = 4.823(5), \ c = 15.86(1) \ \text{fbc} \]
\[ \beta = 92.10(1)^\circ. \]

The h0l reflections with (h+1) odd were absent, indicating the presence of a n-glide plane normal to the b axis with a translation of (a+c)/2. A screw axis parallel with the b axis was also present since 0k0 reflections with k odd were absent. These systematic absences place the crystals unambiguously in the space group P2₁/n.

The theoretical density for occupation of the 4 general positions \((X, Y, Z; \% + X, k - Y, b + Z)\) by C^HNgl molecules is 2.26 gcm\(^{-3}\). The density measured by floatation of the crystals in a bromomethane/petroleum spirit mixture, (2.19 gcm\(^{-3}\)), was in good agreement with this calculated figure.

(b) 2,4-diazido-6-methylpyrimidine

The very pale green crystals were rectangular in shape and extinguished polarised light in directions coincident with the external crystal axes. The crystals were mounted on glass fibres along their long axes and preliminary rotation and Weissenberg photographs indicated that the crystals were monoclinic. The rotation axis was chosen as b and accurate unit cell dimensions were measured from precession photographs taken with Zr filtered Mo radiation. The unit cell dimensions were found to be:

\[ a = 14.99, \ b = 6.60, \ c = 15.10 \ \text{fbc} \]
\[ \beta = 90.83^\circ. \]

From systematic absences the space group was determined as P2₁/c#.
The theoretical density for occupation of the four general positions — 

\((X, Y, Z; X, Y, Z - 2)\) by \(\text{CH}_2\text{N}_2\) molecules is 0.79 \(\text{g} \cdot \text{cm}^{-3}\). The density by floatation of the crystals in a bromomethane/petroleum spirit mixture, 

\((0.80 \text{ g} \cdot \text{cm}^{-3})\), was in good agreement with the calculated figure.

On the precession photographs there was a suspicion of twinning in the crystal. After the collection of two layers of data it was apparent that the crystal was twinned so the structure determination was abandoned.

4.3 Collection of data

This was achieved using a Stoe, computer controlled 2 circle diffractometer with Mo radiation produced by a graphite monochromator. This instrument is essentially a Weissenberg camera but with a scintillation counter replacing the film. A background—scan—background technique was used for each reflection and also a variable \(\omega\) range was used on upper levels which allows a wider scan of low 20 reflections. The output data is processed and only reflections with \(I/\sigma(I)\) values greater than or equal to 3 were used in the refinement process.

\[
I = A \left( \frac{I_m - B_1 + B_9}{\sqrt{2}} \right) ts
\]

where

\[
\begin{align*}
I_m &= \text{peak count} \\
B^\omega, B^b &= \text{background counts} \\
t^\omega &= \text{peak scan time} \\
t^b &= \text{background scan time} \\
I &= \text{corrected intensity} \\
A &= \text{attenuator factor} (=1 \text{ for this data collection}) \\
\sigma(I) &= \text{standard deviation of intensity}
\end{align*}
\]
Solution of the structure

(a) Patterson Synthesis

The phase problem can be overcome by using either direct or indirect methods. The most common approach, and that used in this determination, is an indirect method where a 'heavy' atom is located by means of the Patterson function. This function enables atom positions to be determined directly from the structure amplitudes without any knowledge of the phases of the reflections. It is defined by the equation:-

\[ P(U, V, W) = \sum \frac{E(hkli)}{Vc} |F_{hkl}|^2 \cos 2\pi \frac{(hU + kV + lW)}{Vc} \]

Where

- \( P(U, V, W) \) = Patterson function at position \((U, V, W)\) in the unit cell.
- \( Vc \) = volume of cell and \(|F_{hkl}| = \) structure amplitude.

A three-dimensional Patterson synthesis provides a vector map of the contents of the unit cell of the crystal. The value of \( P(U, V, W) \) will be low except where the values of \( U, V, W \) represent a vector between two atoms. If a Patterson synthesis is calculated for a crystal containing a heavy atom, then maxima on the vector map which represent heavy atom - heavy atom vectors will appear as much larger peaks than any of the others since the peak height is proportional to the atomic number of the atoms. Due to the space group symmetry, the iodine atom in 2, 4-diazido-5-iodopyrimidine occurs at four positions in the unit cell and from these positions the I-I vectors can be calculated (Fig. 1).
The vectors due to the interaction of an atom with itself occur at the origin. The other twelve vectors can be reduced, by symmetry considerations, to three unique vectors.

(a) \(2X_j + 2Y_j + 2Z\)

(b) \(\frac{1}{2} - 2X_j \frac{1}{2} \frac{1}{2} - 2Z\)

(c) \(\frac{1}{2} \frac{1}{2} 2Y_j \frac{1}{2}\)

Examination of the 3-D Patterson map allowed the location of the iodine atom in the unit cell to be determined as \(X = 0.77, Y = 0.80\) and \(Z = 0.85\).

(b) Fourier Refinement.

The electron density at any point \((x, y, z)\) in the unit cell is given by a three-dimensional Fourier summation:

\[
p(x, y, z) = \frac{1}{V_c} \sum_{h} \sum_{k} \sum_{l} |F_{hkl}| \cos \left(2\pi \left(hx + ky + kz - \phi_{hkl}\right)\right)
\]

where

- \(p\) = electron density at \((x, y, z)\) in the unit cell
- \(\phi_{hkl}\) = phase of reflection.

A map of the electron density will show the positions of the other atoms in the structure as well as showing the iodine atom. Using the estimated iodine position, a Fourier map was drawn up and from it the location of the nitrogen and carbon atoms in the molecule was determined. The structure was refined by full-matrix least-squares methods, finally with all atoms being given anisotropic thermal parameters. The scattering factors of reference 9 were used, those of iodine being corrected for real and imaginary components of the anomalous dispersion. The function minimised was \(\sum W (F_o - F_c)^2\), with \(W\) being adjusted to give best constancy of average values of \(W (F_o - F_c)^2\), the final scheme being

\[
W = \begin{cases} 45 & \text{when } |F_o| \leq 45 \\ \frac{|F_o|}{45} & \text{when } |F_o| > 45 \\
\end{cases}
\]

The final \(R = \frac{\sum |F_o - F_c|}{\sum |F_o|}\)
for the 1170 observed reflections was 0.046. Final observed and
calculated structure factors are given in Appendix 1. Positional
and thermal parameters are given in Table 1, and bond lengths and
valency angles are given in Table 2.

4.5 Discussion of Structure

The preferred tautomer was found (Fig. 2) to be the diazido form
(la). The pyrimidine ring is effectively planar (Table 3) and the
average C-C and C-N bond lengths of 1.41(1) and 1.34(1) Å respectively
are as expected for a nitrogen heteroaromatic system. The ring
bond angles are similar to those found in 5- bromo- 4,6-diaminopyrimidine.
The C-I bond length is in agreement with that for other aromatic iodo
compounds. The ring substituents lie slightly out of the best
pyrimidine mean plane, the deviations being given in Table 3. Both
azide chains are non-linear and the N-N-N angles of 174(1) and 172(1)°
are significantly different from 180° but lie within the range of
values found for other azides. The average C-N-N angle of 113.5° is
similar to that found in 1-azido-4-nitrobenzene. As expected from
bonding considerations, the two N-N distances within each azide group
differ significantly (av. 1.26 and 1.12Å).

Since a tetrazolo ring is electron-withdrawing and an azido group
electron rich, it has been suggested that the tetrazolo forms are
destabilised by electron-withdrawing substituents in the ring, the
tautomeric azido form being favoured. In 2,4-diazido-5-iodopyrimidine
it seems likely that it is the electron withdrawing effect of the iodo
substituent which destabilises the possible tetrazolo forms I₉ and I₄,
respectively.
Figure 2
<table>
<thead>
<tr>
<th>( (s) )</th>
<th>( \frac{(s) 8}{(s) 6} )</th>
<th>( \frac{(s) 3}{(s) 2} )</th>
<th>( \frac{(s) 2}{(s) 3} )</th>
<th>( \frac{(s) 3}{(s) 4} )</th>
<th>( \frac{(s) 5}{(s) 6} )</th>
<th>( \frac{(s) 7}{(s) 8} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( (s) )</td>
<td>( \frac{(s) 8}{(s) 6} )</td>
<td>( \frac{(s) 3}{(s) 2} )</td>
<td>( \frac{(s) 2}{(s) 3} )</td>
<td>( \frac{(s) 3}{(s) 4} )</td>
<td>( \frac{(s) 5}{(s) 6} )</td>
<td>( \frac{(s) 7}{(s) 8} )</td>
</tr>
<tr>
<td>( (s) )</td>
<td>( \frac{(s) 8}{(s) 6} )</td>
<td>( \frac{(s) 3}{(s) 2} )</td>
<td>( \frac{(s) 2}{(s) 3} )</td>
<td>( \frac{(s) 3}{(s) 4} )</td>
<td>( \frac{(s) 5}{(s) 6} )</td>
<td>( \frac{(s) 7}{(s) 8} )</td>
</tr>
<tr>
<td>( (s) )</td>
<td>( \frac{(s) 8}{(s) 6} )</td>
<td>( \frac{(s) 3}{(s) 2} )</td>
<td>( \frac{(s) 2}{(s) 3} )</td>
<td>( \frac{(s) 3}{(s) 4} )</td>
<td>( \frac{(s) 5}{(s) 6} )</td>
<td>( \frac{(s) 7}{(s) 8} )</td>
</tr>
<tr>
<td>( (s) )</td>
<td>( \frac{(s) 8}{(s) 6} )</td>
<td>( \frac{(s) 3}{(s) 2} )</td>
<td>( \frac{(s) 2}{(s) 3} )</td>
<td>( \frac{(s) 3}{(s) 4} )</td>
<td>( \frac{(s) 5}{(s) 6} )</td>
<td>( \frac{(s) 7}{(s) 8} )</td>
</tr>
<tr>
<td>( (s) )</td>
<td>( \frac{(s) 8}{(s) 6} )</td>
<td>( \frac{(s) 3}{(s) 2} )</td>
<td>( \frac{(s) 2}{(s) 3} )</td>
<td>( \frac{(s) 3}{(s) 4} )</td>
<td>( \frac{(s) 5}{(s) 6} )</td>
<td>( \frac{(s) 7}{(s) 8} )</td>
</tr>
<tr>
<td>( (s) )</td>
<td>( \frac{(s) 8}{(s) 6} )</td>
<td>( \frac{(s) 3}{(s) 2} )</td>
<td>( \frac{(s) 2}{(s) 3} )</td>
<td>( \frac{(s) 3}{(s) 4} )</td>
<td>( \frac{(s) 5}{(s) 6} )</td>
<td>( \frac{(s) 7}{(s) 8} )</td>
</tr>
<tr>
<td>( (s) )</td>
<td>( \frac{(s) 8}{(s) 6} )</td>
<td>( \frac{(s) 3}{(s) 2} )</td>
<td>( \frac{(s) 2}{(s) 3} )</td>
<td>( \frac{(s) 3}{(s) 4} )</td>
<td>( \frac{(s) 5}{(s) 6} )</td>
<td>( \frac{(s) 7}{(s) 8} )</td>
</tr>
</tbody>
</table>

*Standard deviations are in parentheses.*
Table 2

Bond distances (Å) and angles (degrees), with standard deviations in parentheses.

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C(1)</td>
<td>C(2)</td>
<td>C(3)</td>
<td>C(4)</td>
<td>N(6)</td>
</tr>
<tr>
<td>I</td>
<td>2.08(1)</td>
<td>1.40(1)</td>
<td>1.35(1)</td>
<td>1.35(1)</td>
<td>1.41(1)</td>
</tr>
<tr>
<td>C(1)</td>
<td>2.08(1)</td>
<td>1.40(1)</td>
<td>1.35(1)</td>
<td>1.35(1)</td>
<td>1.41(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>2.08(1)</td>
<td>1.40(1)</td>
<td>1.35(1)</td>
<td>1.35(1)</td>
<td>1.41(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>2.08(1)</td>
<td>1.40(1)</td>
<td>1.35(1)</td>
<td>1.35(1)</td>
<td>1.41(1)</td>
</tr>
<tr>
<td>N(1)</td>
<td>2.08(1)</td>
<td>1.40(1)</td>
<td>1.35(1)</td>
<td>1.35(1)</td>
<td>1.41(1)</td>
</tr>
<tr>
<td>N(2)</td>
<td>2.08(1)</td>
<td>1.40(1)</td>
<td>1.35(1)</td>
<td>1.35(1)</td>
<td>1.41(1)</td>
</tr>
<tr>
<td>N(3)</td>
<td>2.08(1)</td>
<td>1.40(1)</td>
<td>1.35(1)</td>
<td>1.35(1)</td>
<td>1.41(1)</td>
</tr>
<tr>
<td>N(4)</td>
<td>2.08(1)</td>
<td>1.40(1)</td>
<td>1.35(1)</td>
<td>1.35(1)</td>
<td>1.41(1)</td>
</tr>
<tr>
<td>N(5)</td>
<td>2.08(1)</td>
<td>1.40(1)</td>
<td>1.35(1)</td>
<td>1.35(1)</td>
<td>1.41(1)</td>
</tr>
<tr>
<td>N(6)</td>
<td>2.08(1)</td>
<td>1.40(1)</td>
<td>1.35(1)</td>
<td>1.35(1)</td>
<td>1.41(1)</td>
</tr>
<tr>
<td>N(7)</td>
<td>2.08(1)</td>
<td>1.40(1)</td>
<td>1.35(1)</td>
<td>1.35(1)</td>
<td>1.41(1)</td>
</tr>
<tr>
<td>N(8)</td>
<td>2.08(1)</td>
<td>1.40(1)</td>
<td>1.35(1)</td>
<td>1.35(1)</td>
<td>1.41(1)</td>
</tr>
</tbody>
</table>

122
\[ \begin{align*}
&\text{(a)} -0.001, \quad \text{(b)} -0.001, \quad \text{(c)} -0.001, \quad \text{(d)} -0.001, \quad \text{(e)} 0.001, \\
&\text{(f)} 0.001, \quad \text{(g)} 0.001, \quad \text{(h)} 0.001, \quad \text{(i)} 0.001, \quad \text{(j)} 0.001, \\
&0.5857x - 0.7082x - 0.7899 < 0.171
\end{align*} \]

In this case, the quaternion of the least-squares plane through the primitive ring is referred to an orthogonal axis system and the distances of the ring arrays and the ring substituents from the plane are given.
Experimental

2,4-Diazido-5-iodopyrimidine

A mixture of 2,4-dichloro-5-iodopyrimidine (5 x 10^{-3} mol) and sodium azide (1.08 x 10^{-2} mol) was heated under reflux for 45 mins. in aqueous ethanol (1:1 v/v; 50 cm³). On cooling in an ice-bath, colourless crystals were obtained. These were isolated and recrystallised from petroleum (b.p.t. 40-60°) to give 2,4-diazido-5-iodopyrimidine (72%), m.p.t. 86° (decomp). (Found : C, 16.65; H, 0.35; N, 39.35. C₄H₅IN₄ requires C, 16.70; H, 0.35; N, 38.90%). m/e = 288, M^+.

2,4-Diazido-6-methylpyrimidine was prepared by the method of Reynolds et al.⁴
References

Appendix 1

Measured and calculated structure factors for 2,4-diazido-5-iodopyrimidine.
<table>
<thead>
<tr>
<th>V</th>
<th>A</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>G</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>k</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>-17</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>-15</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>-13</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>-11</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>-9</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>-7</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>-5</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>-3</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>-16</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>-14</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>-12</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>-10</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>-8</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>-6</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>-4</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>-2</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>G</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>O</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>1C</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>C</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>-10</td>
</tr>
<tr>
<td>k</td>
<td>0</td>
<td>-16</td>
</tr>
<tr>
<td>k</td>
<td>0</td>
<td>-16</td>
</tr>
<tr>
<td>k</td>
<td>G</td>
<td>-12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>2</td>
<td>291.71</td>
<td>283.92</td>
</tr>
<tr>
<td>2</td>
<td>291.71</td>
<td>283.92</td>
</tr>
<tr>
<td>2</td>
<td>32.58</td>
<td>35.3A</td>
</tr>
<tr>
<td>2</td>
<td>5.70</td>
<td>5.59</td>
</tr>
<tr>
<td>2</td>
<td>9.20</td>
<td>9.76</td>
</tr>
<tr>
<td>2</td>
<td>60.99</td>
<td>62.0A</td>
</tr>
<tr>
<td>2</td>
<td>66.22</td>
<td>72.20</td>
</tr>
<tr>
<td>2</td>
<td>11.88</td>
<td>13.71</td>
</tr>
<tr>
<td>2</td>
<td>21.71</td>
<td>23.39</td>
</tr>
<tr>
<td>2</td>
<td>60.32</td>
<td>63.2A</td>
</tr>
<tr>
<td>2</td>
<td>16.06</td>
<td>15.73</td>
</tr>
<tr>
<td>2</td>
<td>21.93</td>
<td>22.21</td>
</tr>
<tr>
<td>2</td>
<td>8.91</td>
<td>9.27</td>
</tr>
<tr>
<td>2</td>
<td>3A.15</td>
<td>3A.39</td>
</tr>
<tr>
<td>2</td>
<td>17.18</td>
<td>17.75</td>
</tr>
<tr>
<td>2</td>
<td>32.1B</td>
<td>30.12</td>
</tr>
<tr>
<td>2A-8</td>
<td>3.3</td>
<td>9.0A</td>
</tr>
<tr>
<td>2A-16</td>
<td>20.21</td>
<td>20.17</td>
</tr>
<tr>
<td>2A-16</td>
<td>17.05</td>
<td>18.25</td>
</tr>
<tr>
<td>2A-16</td>
<td>65.9A</td>
<td>67.56</td>
</tr>
<tr>
<td>2A-16</td>
<td>11.9A</td>
<td>11.69</td>
</tr>
<tr>
<td>2A-16</td>
<td>2A.93</td>
<td>25.23</td>
</tr>
<tr>
<td>2A-16</td>
<td>2A.22</td>
<td>25.37</td>
</tr>
<tr>
<td>2A-9</td>
<td>1CA.6C</td>
<td>105.39</td>
</tr>
<tr>
<td>2A-8</td>
<td>52.10</td>
<td>50.83</td>
</tr>
<tr>
<td>2A-7</td>
<td>85.99</td>
<td>85.75</td>
</tr>
<tr>
<td>2A-6</td>
<td>9.08</td>
<td>9.08</td>
</tr>
<tr>
<td>2A-5</td>
<td>35.99</td>
<td>36.97</td>
</tr>
<tr>
<td>2A-4</td>
<td>1A.69</td>
<td>39.6A</td>
</tr>
<tr>
<td>2A-3</td>
<td>105.33</td>
<td>101.08</td>
</tr>
<tr>
<td>2A-2</td>
<td>3A.93</td>
<td>31.88</td>
</tr>
<tr>
<td>2A-1</td>
<td>10.15</td>
<td>8.8A</td>
</tr>
<tr>
<td>2A-1</td>
<td>29.7A</td>
<td>27.57</td>
</tr>
<tr>
<td>2A-1</td>
<td>11A.36</td>
<td>CA.15</td>
</tr>
<tr>
<td>2A-3</td>
<td>28.26</td>
<td>26.63</td>
</tr>
<tr>
<td>2A-3</td>
<td>96.93</td>
<td>95.07</td>
</tr>
<tr>
<td>2A-3</td>
<td>35.9A</td>
<td>3A.-5</td>
</tr>
<tr>
<td>2A-3</td>
<td>35.07</td>
<td>3A.15</td>
</tr>
<tr>
<td>2A-3</td>
<td>33.76</td>
<td>33.67</td>
</tr>
<tr>
<td>2A-7</td>
<td>121.3C</td>
<td>125.13</td>
</tr>
<tr>
<td>2A-8</td>
<td>26.82</td>
<td>26.3A</td>
</tr>
<tr>
<td>2A-9</td>
<td>39.05</td>
<td>38.56</td>
</tr>
<tr>
<td>2A-8</td>
<td>1A.73</td>
<td>15.62</td>
</tr>
<tr>
<td>2A-8</td>
<td>65.32</td>
<td>66.75</td>
</tr>
<tr>
<td>2A-2</td>
<td>26.82</td>
<td>26.69</td>
</tr>
<tr>
<td>2A-13</td>
<td>63.A3</td>
<td>65.3A</td>
</tr>
<tr>
<td>2A-13</td>
<td>12.6A</td>
<td>12.69</td>
</tr>
<tr>
<td>2A-13</td>
<td>11.70</td>
<td>11.31</td>
</tr>
<tr>
<td>2A-17</td>
<td>36.86</td>
<td>35.76</td>
</tr>
<tr>
<td>2A-18</td>
<td>10.59</td>
<td>9.05</td>
</tr>
<tr>
<td>2A-18</td>
<td>31.36</td>
<td>31.35</td>
</tr>
<tr>
<td>2A-17</td>
<td>7.2A</td>
<td>8.15</td>
</tr>
<tr>
<td>2A-15</td>
<td>1D.97</td>
<td>1CA.3</td>
</tr>
<tr>
<td>2A-1A</td>
<td>60.21</td>
<td>61.38</td>
</tr>
<tr>
<td>2A-12</td>
<td>6.51</td>
<td>6.50</td>
</tr>
<tr>
<td>2A-11</td>
<td>15.15</td>
<td>15.30</td>
</tr>
<tr>
<td>2A-10</td>
<td>36.72</td>
<td>48.A8</td>
</tr>
<tr>
<td>2A-9</td>
<td>31.56</td>
<td>31.AO</td>
</tr>
<tr>
<td>2A-8</td>
<td>88.AA</td>
<td>89.27</td>
</tr>
<tr>
<td>2A-7</td>
<td>5.95</td>
<td>3.95</td>
</tr>
<tr>
<td>2A-6</td>
<td>6.08</td>
<td>A8A</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>61.82</td>
</tr>
<tr>
<td>----</td>
<td>----</td>
<td>-------</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>126.43</td>
</tr>
<tr>
<td>.7</td>
<td>5</td>
<td>39.71</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>13.87</td>
</tr>
<tr>
<td>7</td>
<td>11.16</td>
<td>11.16</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>AC0.2</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>A1.2A</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>A6.C1</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>26.22</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>17.39</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>15.87</td>
</tr>
<tr>
<td>2</td>
<td>1A</td>
<td>33.6A</td>
</tr>
<tr>
<td>2</td>
<td>115</td>
<td>20.5A</td>
</tr>
<tr>
<td>2</td>
<td>116</td>
<td>9.72</td>
</tr>
<tr>
<td>2</td>
<td>116</td>
<td>21.22</td>
</tr>
<tr>
<td>2</td>
<td>115</td>
<td>1A.12</td>
</tr>
<tr>
<td>2</td>
<td>113</td>
<td>14x1C</td>
</tr>
<tr>
<td>2</td>
<td>112</td>
<td>35.11</td>
</tr>
<tr>
<td>2</td>
<td>111</td>
<td>A5.68</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>23.A7</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>27.78</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>29.85</td>
</tr>
<tr>
<td>2</td>
<td>-7</td>
<td>56.CC</td>
</tr>
<tr>
<td>2</td>
<td>-6</td>
<td>A7.85</td>
</tr>
<tr>
<td>2</td>
<td>-5</td>
<td>65.A6</td>
</tr>
<tr>
<td>C</td>
<td>-A</td>
<td>2A.92</td>
</tr>
<tr>
<td>2</td>
<td>-3</td>
<td>2A.53</td>
</tr>
<tr>
<td>2</td>
<td>-2</td>
<td>36.71</td>
</tr>
<tr>
<td>2</td>
<td>-1</td>
<td>7C.AA</td>
</tr>
<tr>
<td>2</td>
<td>C</td>
<td>AA.82</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>7.05</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>53.36</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>29.75</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>56.C9</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>31.52</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>20.CA</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>A3.A6</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>A1+38</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>2A.73</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>13.82</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>16.A9</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>25.92</td>
</tr>
<tr>
<td>2</td>
<td>1A</td>
<td>25.96</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>18.58</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>8.72</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>2A.12</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>11.61</td>
</tr>
<tr>
<td>6</td>
<td>13</td>
<td>12.35</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>17.92</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>15.69</td>
</tr>
<tr>
<td>6&quot;</td>
<td>-9</td>
<td>9.27</td>
</tr>
<tr>
<td>6</td>
<td>-8</td>
<td>21.82</td>
</tr>
<tr>
<td>6</td>
<td>-7</td>
<td>36.09</td>
</tr>
<tr>
<td>6</td>
<td>-6</td>
<td>6A.0A</td>
</tr>
<tr>
<td>6</td>
<td>-5</td>
<td>24.97</td>
</tr>
<tr>
<td>6</td>
<td>-A</td>
<td>7.85</td>
</tr>
<tr>
<td>6</td>
<td>-A</td>
<td>AA.A7</td>
</tr>
<tr>
<td>6</td>
<td>-2</td>
<td>A7.C8</td>
</tr>
<tr>
<td>6</td>
<td>-1</td>
<td>53.61</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>A1.65</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>25.91</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>52.16</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>5A.1A</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>9</td>
<td>17.46</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>A6.A1</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>1A.19</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>20.70</td>
</tr>
<tr>
<td>6</td>
<td>13</td>
<td>13.AA</td>
</tr>
<tr>
<td>6</td>
<td>1A</td>
<td>21.33</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>13.59</td>
</tr>
<tr>
<td>7</td>
<td>-15</td>
<td>13.85</td>
</tr>
<tr>
<td>7</td>
<td>-13</td>
<td>18.63</td>
</tr>
<tr>
<td>7</td>
<td>-12</td>
<td>33.11</td>
</tr>
<tr>
<td>7</td>
<td>-11</td>
<td>35.73</td>
</tr>
<tr>
<td>7</td>
<td>-10</td>
<td>25.76</td>
</tr>
<tr>
<td>7</td>
<td>-9</td>
<td>3A.36</td>
</tr>
<tr>
<td>7</td>
<td>-7</td>
<td>A1.11</td>
</tr>
<tr>
<td>7</td>
<td>-6</td>
<td>22.96</td>
</tr>
<tr>
<td>7</td>
<td>-5</td>
<td>31.7A</td>
</tr>
<tr>
<td>7</td>
<td>-3</td>
<td>A2.77</td>
</tr>
<tr>
<td>7</td>
<td>-2</td>
<td>22.56</td>
</tr>
<tr>
<td>7</td>
<td>-1</td>
<td>56.38</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>17.65</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>22.80</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>53.70</td>
</tr>
<tr>
<td>7</td>
<td>2A</td>
<td>31.AC</td>
</tr>
<tr>
<td>7</td>
<td>B</td>
<td>16.36</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>3A.8C</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>3A.57</td>
</tr>
<tr>
<td>7</td>
<td>9</td>
<td>19.78</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>18.35</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>11.0A</td>
</tr>
<tr>
<td>7</td>
<td>13</td>
<td>2.0.6C</td>
</tr>
<tr>
<td>7</td>
<td>1A</td>
<td>17.7C</td>
</tr>
<tr>
<td>8</td>
<td>-12</td>
<td>31.35</td>
</tr>
<tr>
<td>8</td>
<td>-11</td>
<td>10.56</td>
</tr>
<tr>
<td>8</td>
<td>-10</td>
<td>1A.A6</td>
</tr>
<tr>
<td>8</td>
<td>-8</td>
<td>2A.52</td>
</tr>
<tr>
<td>8</td>
<td>-7</td>
<td>2A.7C</td>
</tr>
<tr>
<td>8</td>
<td>-6</td>
<td>A6.A5</td>
</tr>
<tr>
<td>8</td>
<td>-5</td>
<td>27.59</td>
</tr>
<tr>
<td>8</td>
<td>-A</td>
<td>33.91</td>
</tr>
<tr>
<td>8</td>
<td>-3</td>
<td>37.8A</td>
</tr>
<tr>
<td>8</td>
<td>-2</td>
<td>28.2A</td>
</tr>
<tr>
<td>8</td>
<td>-1</td>
<td>A1.98</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>23.30</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>26.69</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>27.9A</td>
</tr>
<tr>
<td>8</td>
<td>A</td>
<td>38.65</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>1A.68</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>12.62</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>31.03</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>16.56</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>15.0A</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>17.AA</td>
</tr>
<tr>
<td>8</td>
<td>13</td>
<td>13.56</td>
</tr>
<tr>
<td>9</td>
<td>-12</td>
<td>17.35</td>
</tr>
<tr>
<td>9</td>
<td>-11</td>
<td>12.33</td>
</tr>
<tr>
<td>9</td>
<td>-8</td>
<td>13.65</td>
</tr>
<tr>
<td>9</td>
<td>-7</td>
<td>26.06</td>
</tr>
<tr>
<td>9</td>
<td>-5</td>
<td>2A.86</td>
</tr>
<tr>
<td>9</td>
<td>-A</td>
<td>6.97</td>
</tr>
<tr>
<td>9</td>
<td>-3</td>
<td>26.59</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>9 2 -2</td>
<td>19.75</td>
<td>20.47</td>
</tr>
<tr>
<td>9 2 -1</td>
<td>28.68</td>
<td>29.63</td>
</tr>
<tr>
<td>9 2 1</td>
<td>13.65</td>
<td>13.95</td>
</tr>
<tr>
<td>9 2 2</td>
<td>16.7A</td>
<td>17.11</td>
</tr>
<tr>
<td>9 2 3</td>
<td>3A.11</td>
<td>35.21</td>
</tr>
<tr>
<td>9 2 A</td>
<td>29.68</td>
<td>32.AA</td>
</tr>
<tr>
<td>9 2 7</td>
<td>23.A2</td>
<td>23.20</td>
</tr>
<tr>
<td>9 2 8</td>
<td>18.32</td>
<td>18.87</td>
</tr>
<tr>
<td>9 2 9</td>
<td>21.6A</td>
<td>22.75</td>
</tr>
<tr>
<td>9 2 12</td>
<td>8.9A</td>
<td>7.8A</td>
</tr>
<tr>
<td>1C 2 -1</td>
<td>1C.PA</td>
<td>12.00</td>
</tr>
<tr>
<td>10 2 -9</td>
<td>8.88</td>
<td>11.5A</td>
</tr>
<tr>
<td>10 2 -8</td>
<td>26.9E</td>
<td>28.9E</td>
</tr>
<tr>
<td>10 2 -7</td>
<td>22.13</td>
<td>23.82</td>
</tr>
<tr>
<td>10 2 -6</td>
<td>13.65</td>
<td>1A.82</td>
</tr>
<tr>
<td>10 2 -A</td>
<td>19.63</td>
<td>19.82</td>
</tr>
<tr>
<td>10 2 -3</td>
<td>1A.18</td>
<td>16.31</td>
</tr>
<tr>
<td>10 2 -2</td>
<td>2A.A7</td>
<td>26.99</td>
</tr>
<tr>
<td>10 2 -1</td>
<td>15.57</td>
<td>17.5A</td>
</tr>
<tr>
<td>10 2 0</td>
<td>8.03</td>
<td>10.58</td>
</tr>
<tr>
<td>10 2 1</td>
<td>9.77</td>
<td>8.61</td>
</tr>
<tr>
<td>1C 2 2</td>
<td>20.85</td>
<td>22.58</td>
</tr>
<tr>
<td>10 2 3</td>
<td>17.51</td>
<td>19.88</td>
</tr>
<tr>
<td>10 2 A</td>
<td>15.55</td>
<td>16.57</td>
</tr>
<tr>
<td>10 2 6</td>
<td>10.25</td>
<td>1A.A2</td>
</tr>
<tr>
<td>10 2 8</td>
<td>1A.7I</td>
<td>15.10</td>
</tr>
<tr>
<td>10 2 9</td>
<td>13.26</td>
<td>1A.A2</td>
</tr>
<tr>
<td>11 2 -8</td>
<td>10.98</td>
<td>11.53</td>
</tr>
<tr>
<td>11 2 -7</td>
<td>18.90</td>
<td>20.2A</td>
</tr>
<tr>
<td>11 2 1</td>
<td>11.8A</td>
<td>13.77</td>
</tr>
<tr>
<td>11 2 -3</td>
<td>19.AA</td>
<td>20.22</td>
</tr>
<tr>
<td>11 2 -2</td>
<td>18.65</td>
<td>20.A3</td>
</tr>
<tr>
<td>11 2 -1</td>
<td>8.97</td>
<td>9.55</td>
</tr>
<tr>
<td>11 2 1</td>
<td>11.72</td>
<td>12.86</td>
</tr>
<tr>
<td>11 2 2</td>
<td>9.65</td>
<td>12.23</td>
</tr>
<tr>
<td>11 2 3</td>
<td>22.32</td>
<td>23.00</td>
</tr>
<tr>
<td>11 2 A</td>
<td>12.22</td>
<td>1A.07</td>
</tr>
<tr>
<td>11 2 7</td>
<td>10.19</td>
<td>16.69</td>
</tr>
<tr>
<td>11 2 8</td>
<td>10.86</td>
<td>13.46</td>
</tr>
<tr>
<td>12 2 -A</td>
<td>10.23</td>
<td>11.62</td>
</tr>
<tr>
<td>12 2 -3</td>
<td>9.5A</td>
<td>11.A6</td>
</tr>
<tr>
<td>12 2 -2</td>
<td>18.56</td>
<td>19.59</td>
</tr>
<tr>
<td>12 2 2</td>
<td>15.72</td>
<td>17.2A</td>
</tr>
<tr>
<td>12 2 3</td>
<td>12.19</td>
<td>13.67</td>
</tr>
<tr>
<td>5 3 0</td>
<td>39.61</td>
<td>38.10</td>
</tr>
<tr>
<td>0 3 -1A</td>
<td>8.65</td>
<td>6.81</td>
</tr>
<tr>
<td>0 3 13</td>
<td>A3.87</td>
<td>A2.66</td>
</tr>
<tr>
<td>0 3 12</td>
<td>28.53</td>
<td>28.76</td>
</tr>
<tr>
<td>0 3 11</td>
<td>13.75</td>
<td>12.65</td>
</tr>
<tr>
<td>0 3 9</td>
<td>28.3A</td>
<td>28.01</td>
</tr>
<tr>
<td>0 3 8</td>
<td>A2.33</td>
<td>A2.A2</td>
</tr>
<tr>
<td>0 3 7</td>
<td>58.95</td>
<td>61.06</td>
</tr>
<tr>
<td>0 3 6</td>
<td>28.96</td>
<td>3C.C5</td>
</tr>
<tr>
<td>0 3 5</td>
<td>9.53</td>
<td>10.A5</td>
</tr>
<tr>
<td>0 3 4</td>
<td>32.95</td>
<td>3A.AA</td>
</tr>
<tr>
<td>0 3 3</td>
<td>68.53</td>
<td>7A.56</td>
</tr>
<tr>
<td>0 3 2</td>
<td>26.3A</td>
<td>31.A6</td>
</tr>
<tr>
<td>1 3 -1A</td>
<td>30.A7</td>
<td>27.05</td>
</tr>
<tr>
<td>1 3 -13</td>
<td>2A.50</td>
<td>23.82</td>
</tr>
<tr>
<td>1 3 -12</td>
<td>35.77</td>
<td>3A.AA</td>
</tr>
<tr>
<td>1 3 -11</td>
<td>13.7A</td>
<td>10.75</td>
</tr>
<tr>
<td>1 3 -10</td>
<td>8.51</td>
<td>8.35</td>
</tr>
<tr>
<td>1 3 -9</td>
<td>22.91</td>
<td>22.50</td>
</tr>
</tbody>
</table>

133
<table>
<thead>
<tr>
<th>9 3 10</th>
<th>10.73</th>
<th>20.61</th>
<th>2 4 -4</th>
<th>11.52</th>
<th>10.75</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 3 9</td>
<td>15.30</td>
<td>14.57</td>
<td>2 4 -3</td>
<td>6.52</td>
<td>7.86</td>
</tr>
<tr>
<td>9 3 0</td>
<td>17.90</td>
<td>18.94</td>
<td>2 4 -2</td>
<td>8.85</td>
<td>8.17</td>
</tr>
<tr>
<td>9 3 -6</td>
<td>24.77</td>
<td>25.33</td>
<td>2 4 -1</td>
<td>53.48</td>
<td>52.22</td>
</tr>
<tr>
<td>9 3 -5</td>
<td>14.75</td>
<td>15.46</td>
<td>2 4 0</td>
<td>12.17</td>
<td>11.65</td>
</tr>
<tr>
<td>9 3 -4</td>
<td>27.87</td>
<td>27.22</td>
<td>2 4 1</td>
<td>29.71</td>
<td>29.35</td>
</tr>
<tr>
<td>9 3 -1</td>
<td>16.50</td>
<td>15.50</td>
<td>2 4 2</td>
<td>9.34</td>
<td>10.02</td>
</tr>
<tr>
<td>9 3 0</td>
<td>21.65</td>
<td>22.29</td>
<td>2 4 3</td>
<td>20.44</td>
<td>20.82</td>
</tr>
<tr>
<td>9 3 2</td>
<td>22.27</td>
<td>21.62</td>
<td>2 4 5</td>
<td>38.73</td>
<td>40.6U</td>
</tr>
<tr>
<td>9 3 4</td>
<td>19.23</td>
<td>19.93</td>
<td>2 4 6</td>
<td>22.52</td>
<td>23.44</td>
</tr>
<tr>
<td>9 3 6</td>
<td>19.42</td>
<td>19.22</td>
<td>2 4 7</td>
<td>20.09</td>
<td>21.66</td>
</tr>
<tr>
<td>9 3 0</td>
<td>22.69</td>
<td>22.69</td>
<td>2 4 8</td>
<td>14.12</td>
<td>14.34</td>
</tr>
<tr>
<td>9 3 9</td>
<td>8.70</td>
<td>8.75</td>
<td>2 4 9</td>
<td>35.88</td>
<td>36.65</td>
</tr>
<tr>
<td>9 3 -8</td>
<td>9.45</td>
<td>5.80</td>
<td>2 4 10</td>
<td>12.11</td>
<td>13•7</td>
</tr>
<tr>
<td>10 3 -5</td>
<td>19.26</td>
<td>21.32</td>
<td>3 4 -12</td>
<td>27.94</td>
<td>27.22</td>
</tr>
<tr>
<td>10 3 -4</td>
<td>18.17</td>
<td>18.02</td>
<td>3 4 -10</td>
<td>25.69</td>
<td>24.74</td>
</tr>
<tr>
<td>10 3 -3</td>
<td>11.32</td>
<td>11.61</td>
<td>3 4 -9</td>
<td>9.12</td>
<td>9.33</td>
</tr>
<tr>
<td>10 3 -2</td>
<td>9.12</td>
<td>7.71</td>
<td>3 4 -7</td>
<td>8.48</td>
<td>8.64</td>
</tr>
<tr>
<td>10 3 -1</td>
<td>12.02</td>
<td>12.82</td>
<td>3 4 -6</td>
<td>47.37</td>
<td>44.64</td>
</tr>
<tr>
<td>0 3 1</td>
<td>25.39</td>
<td>27.15</td>
<td>3 4 -5</td>
<td>18.14</td>
<td>17.70</td>
</tr>
<tr>
<td>0 3 0</td>
<td>11.56</td>
<td>9.72</td>
<td>3 4 -4</td>
<td>24.32</td>
<td>22.97</td>
</tr>
<tr>
<td>1 3 1</td>
<td>17.40</td>
<td>17.68</td>
<td>3 4 -3</td>
<td>33.69</td>
<td>32.83</td>
</tr>
<tr>
<td>1 3 0</td>
<td>9.92</td>
<td>10.34</td>
<td>3 4 -2</td>
<td>17.74</td>
<td>17.37</td>
</tr>
<tr>
<td>1 2 4</td>
<td>16.14</td>
<td>16.27</td>
<td>3 4 -1</td>
<td>47.19</td>
<td>44.57</td>
</tr>
<tr>
<td>1 2 2</td>
<td>10.24</td>
<td>11.24</td>
<td>3 4 0</td>
<td>10.90</td>
<td>10.73</td>
</tr>
<tr>
<td>1 1 4</td>
<td>35.33</td>
<td>33.43</td>
<td>3 4 3</td>
<td>12.32</td>
<td>12.34</td>
</tr>
<tr>
<td>1 1 2</td>
<td>33.44</td>
<td>33.60</td>
<td>3 4 2</td>
<td>55.97</td>
<td>56.07</td>
</tr>
<tr>
<td>1 1 0</td>
<td>10.03</td>
<td>11.23</td>
<td>3 4 1</td>
<td>14.93</td>
<td>14.93</td>
</tr>
<tr>
<td>0 1 4</td>
<td>34.03</td>
<td>33.46</td>
<td>3 4 0</td>
<td>26.81</td>
<td>26.84</td>
</tr>
<tr>
<td>0 1 8</td>
<td>1.34</td>
<td>11.93</td>
<td>4 4 -11</td>
<td>34.44</td>
<td>33.31</td>
</tr>
<tr>
<td>0 1 7</td>
<td>21.13</td>
<td>22.19</td>
<td>4 4 -1b</td>
<td>16.22</td>
<td>14•CC</td>
</tr>
<tr>
<td>0 1 6</td>
<td>11.90</td>
<td>12.92</td>
<td>4 4 -9</td>
<td>16.41</td>
<td>16.25</td>
</tr>
<tr>
<td>0 1 5</td>
<td>49.59</td>
<td>54.56</td>
<td>4 4 -8</td>
<td>16.51</td>
<td>16.62</td>
</tr>
<tr>
<td>0 1 4</td>
<td>10.44</td>
<td>12.38</td>
<td>4 4 -7</td>
<td>49.53</td>
<td>46.13</td>
</tr>
<tr>
<td>0 1 3</td>
<td>5.65</td>
<td>7.15</td>
<td>4 4 -6</td>
<td>35.17</td>
<td>33.40</td>
</tr>
<tr>
<td>0 1 -1</td>
<td>17.15</td>
<td>16.21</td>
<td>4 4 -5</td>
<td>9.70</td>
<td>8.73</td>
</tr>
<tr>
<td>1 1 -12</td>
<td>14.60</td>
<td>14.15</td>
<td>4 4 0</td>
<td>57.57</td>
<td>53.96</td>
</tr>
<tr>
<td>1 1 -10</td>
<td>34.35</td>
<td>33.08</td>
<td>4 4 1</td>
<td>16.72</td>
<td>15.64</td>
</tr>
<tr>
<td>1 1 -8</td>
<td>9.95</td>
<td>10.44</td>
<td>4 4 3</td>
<td>23.83</td>
<td>22.97</td>
</tr>
<tr>
<td>1 1 -7</td>
<td>8.86</td>
<td>8.79</td>
<td>4 4 2</td>
<td>29.81</td>
<td>28.07</td>
</tr>
<tr>
<td>1 1 -6</td>
<td>9.51</td>
<td>10.66</td>
<td>4 4 4</td>
<td>17.77</td>
<td>17.53</td>
</tr>
<tr>
<td>0 1 -3</td>
<td>38.39</td>
<td>58.65</td>
<td>4 4 5</td>
<td>31.75</td>
<td>31.72</td>
</tr>
<tr>
<td>0 1 -2</td>
<td>11.67</td>
<td>11.82</td>
<td>4 4 4</td>
<td>7.46</td>
<td>6.14</td>
</tr>
<tr>
<td>0 1 -1</td>
<td>39.69</td>
<td>42.05</td>
<td>4 4 3</td>
<td>33.27</td>
<td>33.46</td>
</tr>
<tr>
<td>0 1 0</td>
<td>17.02</td>
<td>17.64</td>
<td>5 4 -12</td>
<td>22.6</td>
<td>21.24</td>
</tr>
<tr>
<td>0 1 -9</td>
<td>8.94</td>
<td>10.16</td>
<td>5 4 -10</td>
<td>15.48</td>
<td>16.61</td>
</tr>
<tr>
<td>0 1 -8</td>
<td>17.64</td>
<td>20.46</td>
<td>5 4 -9</td>
<td>9.66</td>
<td>15.23</td>
</tr>
<tr>
<td>0 1 -7</td>
<td>17.20</td>
<td>19.37</td>
<td>5 4 -8</td>
<td>9.11</td>
<td>7.86</td>
</tr>
<tr>
<td>0 1 -6</td>
<td>9.45</td>
<td>11.42</td>
<td>5 4 -7</td>
<td>34.32</td>
<td>33.39</td>
</tr>
<tr>
<td>0 1 -5</td>
<td>51.61</td>
<td>56.99</td>
<td>5 4 -6</td>
<td>12.49</td>
<td>12.15</td>
</tr>
<tr>
<td>0 1 -4</td>
<td>9.24</td>
<td>11.07</td>
<td>5 4 -5</td>
<td>40.07</td>
<td>37.14</td>
</tr>
<tr>
<td>0 1 -3</td>
<td>24.09</td>
<td>26.07</td>
<td>5 4 -4</td>
<td>17.22</td>
<td>16.40</td>
</tr>
<tr>
<td>0 1 -2</td>
<td>17.05</td>
<td>18.17</td>
<td>5 4 -3</td>
<td>14.76</td>
<td>13.58</td>
</tr>
<tr>
<td>0 1 -1</td>
<td>37.63</td>
<td>38.27</td>
<td>5 4 -2</td>
<td>18.07</td>
<td>17.03</td>
</tr>
<tr>
<td>0 1 0</td>
<td>23.92</td>
<td>22.40</td>
<td>5 4 -1</td>
<td>11.15</td>
<td>1C.07</td>
</tr>
<tr>
<td>0 1 -1</td>
<td>36.32</td>
<td>35.51</td>
<td>5 4 0</td>
<td>42.41</td>
<td>40.65</td>
</tr>
<tr>
<td>0 1 -10</td>
<td>15.64</td>
<td>15.77</td>
<td>5 4 7</td>
<td>19.83</td>
<td>19.9 C</td>
</tr>
<tr>
<td>2 4 -10</td>
<td>21.68</td>
<td>20.57</td>
<td>5 4 6</td>
<td>7.62</td>
<td>4.4</td>
</tr>
<tr>
<td>2 4 -9</td>
<td>12.68</td>
<td>20.85</td>
<td>5 4 5</td>
<td>24.83</td>
<td>24•o6</td>
</tr>
<tr>
<td>2 4 -7</td>
<td>34.06</td>
<td>33.96</td>
<td>5 4 4</td>
<td>26.55</td>
<td>25.24</td>
</tr>
<tr>
<td>2 4 -5</td>
<td>45.91</td>
<td>45.15</td>
<td>6 4 -11</td>
<td>26.13</td>
<td>26.74</td>
</tr>
<tr>
<td>2 4 -3</td>
<td>6 4 -7</td>
<td>34.33</td>
<td>33.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>-6</td>
<td>8.92</td>
<td>9.14</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>----</td>
<td>------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>-5</td>
<td>22.10</td>
<td>22.39</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>-3</td>
<td>9.72</td>
<td>10.31</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>-1</td>
<td>37.67</td>
<td>36.22</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>3</td>
<td>29.38</td>
<td>23.85</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>5</td>
<td>23.58</td>
<td>23.01</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>7</td>
<td>18.99</td>
<td>19.13</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>9</td>
<td>12.25</td>
<td>10.82</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>11</td>
<td>8.69</td>
<td>4.83</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>-10</td>
<td>12.10</td>
<td>12.27</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>-8</td>
<td>25.42</td>
<td>24.47</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>-6</td>
<td>26.12</td>
<td>25.60</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>-2</td>
<td>35.04</td>
<td>33.71</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>-1</td>
<td>16.56</td>
<td>15.70</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>0</td>
<td>20.14</td>
<td>21.12</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>2</td>
<td>20.45</td>
<td>20.27</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>3</td>
<td>13.43</td>
<td>11.21</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>4</td>
<td>26.54</td>
<td>26.99</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>8</td>
<td>17.84</td>
<td>17.99</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>-8</td>
<td>9.64</td>
<td>7.51</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>-7</td>
<td>18.00</td>
<td>17.70</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>-5</td>
<td>15.86</td>
<td>16.22</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>-3</td>
<td>19.08</td>
<td>18.31</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>-2</td>
<td>5.27</td>
<td>5.15</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>-1</td>
<td>23.47</td>
<td>24.58</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>3</td>
<td>22.13</td>
<td>22.41</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>5</td>
<td>15.20</td>
<td>16.51</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>7</td>
<td>20.03</td>
<td>20.79</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>8</td>
<td>11.39</td>
<td>13.12</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>-6</td>
<td>20.11</td>
<td>20.11</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>-4</td>
<td>9.51</td>
<td>8.57</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>-2</td>
<td>22.33</td>
<td>23.57</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>2</td>
<td>14.17</td>
<td>14.57</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>4</td>
<td>17.21</td>
<td>16.58</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 2

Postgraduate courses and lectures attended.
1. Pharmaceutical Chemistry - W.D. Ollis (The University of Sheffield).

2. Vitamins and co-enzymes - G.M. Blackburn (The University of Sheffield).

3. Organo-metallic chemistry - D.H. Jones (The University of Sheffield).

4. Nuclear Magnetic Resonance - D. Mowthorpe (Sheffield Polytechnic)

