A PILOT STUDY OF SYNTHESES
AND
SUBSTITUENT EFFECTS IN SOME
α-CARBOXY AND α-BROMO-ALKYLPYRIMIDINES

a thesis
submitted for the
Degree of Doctor of Philosophy
in the
Australian National University
by
Paul Waring

Medical Chemistry Group
John Curtin School of Medical Research
Australian National University
Canberra
September, 1977
The work described in this thesis was carried out by the candidate at the Australian National University. Where the work of others was employed, appropriate references have been given.
ACKNOWLEDGEMENTS

The author wishes to express his gratitude to Dr D.J. Brown for his very helpful advice, encouragement, supervision, and patience during the course of this work. Thanks also go to Drs W.L.F. Armarego, G.B. Barlin, J.H. Lister and Mr E.P. Serjeant for useful advice on various problems encountered, and to all members of the Medical Chemistry Group for help and support.

Thanks are also offered to the Australian National University for the award of a research scholarship.

Finally, the author wishes to thank Mrs S.M. Schenk for typing this thesis.
For my Parents
and
Jacquie
CONTENTS

Certificate of originality
Acknowledgements
Summary

CHAPTER 1 SURVEY OF RELEVANT LITERATURE
(a) Introduction 1
(b) Substituent effects in organic chemistry 1
(c) Quantitative expressions of substituent effects 4
(d) Applications to the heterocyclic field 9
(e) Synthetic aspects of analogous systems 18

CHAPTER 2 SYNTHESIS
SECTION I
Simple 2- (Pyrimidin-2'-yl)acetic Acids 20
SECTION II
2- (1'-Bromo-1'-methylethyl)pyrimidines 29

CHAPTER 3 SPECTRA AND IONIZATION CONSTANTS
ULTRAVIOLET SPECTRA AND IONIZATION CONSTANTS 33
INFRARED SPECTRA 38
(a) Sodium pyrimidinylacetates 38
(b) Methyl 2- (1',6'-dihydro-6'-oxopyrimidin-2'-yl)acetate 39
NUCLEAR MAGNETIC RESONANCE SPECTRA 40
SUMMARY

In order to examine substituent effects on reactivities of groups attached by a side chain to the pyrimidine ring, two classes of appropriate compound have been synthesized and examined.

A series of 4'-mono- and 4',6'-di-substituted (pyrimidin-2'-yl)acetic acids and their esters have been prepared for measurement of both acidic and basic pK_a values in water. The esters were prepared from the corresponding nitriles via the imino ethers. Simple alkaline hydrolysis of the esters gave the acids which were isolated and characterized as the sodium salts because of the facile decarboxylation of the free acids.

In comparing the acidic pK_a values with those of the dideaza-analogues, phenylacetic acids, it was found that substituent constants derived from the latter were not applicable to the heterocycle when the substituents were considered as formally meta to the side chain bearing the acid group. In some instances, electronic effects were 'reversed', e.g. 4-methoxy was acid-weakening.
A number of 4-substituted-2-(1'-bromo-1'-methylethyl)pyrimidines was made by bromination of each corresponding 2-isopropyl compound with N-bromosuccinimide. Substituent effects on the rates of solvolysis of these tertiary-bromides in 50% aqueous methanol were found not to parallel those in the benzene system: e.g. a 4-phenyl group slightly increased the rate of solvolysis.

In both instances, the results were rationalized in terms of a mesomeric donation of electrons to N-1 which affected the reaction site, either by a secondary inductive effect, or by the formation of intramolecular hydrogen bonds (in the case of the carboxylic acids). Attempts were made to correlate quantitatively the observations along the lines of current views on substituent effects.

The products of methanolysis of the tertiary bromopyrimidines were characterized in some instances as were the olefins formed by base catalysed elimination of hydrogen bromide.

The nuclear magnetic resonance, infrared and mass spectra of the synthesized compounds showed several interesting aspects which are discussed.
CHAPTER 1

SURVEY OF THE RELEVANT LITERATURE

(a) Introduction

The aim of the work to be described was to examine the transmission of substituent effects to groups attached to the pyrimidine ring through an alkyl group. This problem was to be approached in three ways: (a) by $pK_a$ measurements of pyrimidin-2-ylacetic acids (1-1); (b) by examination of the rates for alkaline hydrolysis of the corresponding esters (1-2); and (c) by a study of the rates for solvolysis of the pyrimidine analogues (1-3) of t-cumyl bromides. Although a series of esters was synthesized, hydrolysis rates were not measured for lack of time; thus only methods (a) and (c) were utilized.

This chapter comprises a review of previous work in the field. It begins with a general summary of substituent effects and their origins, followed by a discussion of the various quantitative approaches which have been adopted. Finally, the application of such correlative analysis to simple heterocyclic systems is summarized.

(b) Substituent effects in organic chemistry

Since the proposal of Hammett (1937), that rates and equilibria in organic reactions could be described by a general expression (equation 1)

$$\log(k/k_0) = \rho \sigma$$  equation 1
la

(1-1)

\[
\begin{align*}
\text{X} & \quad \text{N} \\
\text{CH}_2\text{CO}_2\text{H} & \\
\end{align*}
\]

(1-2)

\[
\begin{align*}
\text{X} & \quad \text{N} \\
\text{CH}_2\text{CO}_2\text{CH}_3 & \\
\end{align*}
\]

(1-3)

\[
\begin{align*}
\text{X} & \quad \text{N} \\
\text{C} & \quad \text{Me} \\
\text{Me} & \quad \text{Br} \\
\end{align*}
\]
in which $k$ is the rate or equilibrium constant for a process in the presence of a general substituent, $k_0$ is the equivalent value with H as substituent, $\rho$ is the reaction constant, and $\sigma$ the substituent constant, the natural desire to quantify substituent effects has led to vast collections of data. These have encompassed diverse kinetic and equilibria studies, together with variations on this original equation. Along with the unquestioned and extremely useful empirical correlations, have gone more disputed theories as to the origins of substituent effects, now seen to comprise two major contributions, the inductive and resonance effects.

For many years discussion has centred on whether the inductive effect occurs through sequential bond polarization or operates through space in the manner of a simple dipole. The electrostatic model proposed by Kirkwood and Westheimer (1938) has gained a great deal of support, especially for long range effects (Stock, 1972): evidence from experimental studies of model systems, such as substituted bicyclo(2,2,2)octanes (1-4)(Holtz and Stock, 1964), and theoretical limits on the size of the attenuation factor, $\epsilon$, have given credence to the electrostatic field theory of the inductive effect. It is proposed that a substituent exerts its effect on a reaction centre via the molecular cavity and surrounding medium.

$$F \propto \mu \cos \theta / r^2 \text{Deff}$$

Equation 2 illustrates the parameters affecting the magnitude of this effect. For a dipolar substituent, $\mu$ is the dipole moment, $r$ the distance between substituent and
The mesomeric or resonance effect is the second

The mesomeric or resonance effect is the second

The mesomeric or resonance effect is the second

The mesomeric or resonance effect is the second
reaction centre, $\theta$ the angle between the axis of the dipole and the line adjoining the centre of the dipole to the reaction centre, and $D_{\text{eff}}$ is the effective dielectric constant. Objections to this approach include the often ill-defined nature of $D_{\text{eff}}$ and the fact that the effect should be angular dependent. This last condition seems at variance with the assumption of Taft and Lewis (1958; 1959) who believed that the inductive effect operated equally well from the para- and meta-position of the benzene nucleus. However, Exner (1966) has proposed that the inductive effect operates more powerfully from the para-position and gives $\sigma_m/\sigma_p=1.14$. This has been attributed to special polarization of the $\pi$-electrons (not involving charge transfer, cf. mesomeric effects) termed the $\pi$-inductive effect. First proposed over twenty-five years ago (Everard and Sutton, 1951), it has gained support from ionization studies (Janda et al., 1976) and analysis of $^{13}\text{C}$-spectra (Bromilow et al., 1977).

Short-range inductive effects (i.e. over one bond) almost certainly exist and have been implicated in anomalous behaviour (Charton, 1964). In a discussion of the solvolysis of 3-bromo adamantanes (1-5) (Calder and Burton, 1971), Grob et al. (1976), have suggested that, like mesomeric effects (see later), inductive effects of substituents are not constant and may adjust to electronic requirements of a particular reaction.

The mesomeric or resonance effect is the second dominant cause of the modification of reactivity by a substituent. In substituted benzenes, this occurs when the substituent has outer filled $p$ orbitals of suitable size and
symmetry which may become admixed with $\pi$ molecular orbitals of the ring. This gives rise to the canonical structures, e.g. (1-6), accounting for the acid-weakening effects of a methoxy group para to a carboxyl moiety, as effected in $\sigma_p (OCH_3)$ of -0.27 ($\sigma_f. \sigma_m + 0.12$). Similarly, substituents like CN or NO$_2$ possessing empty $p$ orbitals can mesomerically withdraw electrons.

It has been suggested (Katritzky and Topsom, 1971) that the total resonance effect is the sum of at least four contributions, the dominant being that immediately above. The others refer to disturbances in the $\pi$-system such as repulsive interaction between filled orbitals on the substituent and the $\pi$-electron system, or polarization of the $\pi$-electrons by the substituent dipole (the $\pi$-inductive effect). These contributions would be incorporated into the substituent parameters ($\sigma$) and have generally been neglected by organic chemists because of their relative unimportance. As interpretations and probes for substituent effects reach higher levels of sophistication and accuracy, such minor contributions may assume increasing importance and experimental indications of their existence are indeed now being sought (Bromilow et al., 1977).

(c) Quantitative expressions of substituent effects

Hundreds of papers and numerous reviews have been published in attempts to quantitatively correlate substituent effects with experimentally derived constants. General reviews include those of Jaffé (1953), Taft (1956), Wells (1963), Shorter (1969, 1970), and Chapman and Shorter (1972).
Theoretical treatment of the Hammett equation is discussed by Ehrenson (1964) and Ritchie and Sager (1964). Wells et al. (1968) and Ehrenson et al. (1973) have produced extensive statistical analyses of effects in the naphthalene and benzene series respectively. Reviews pertinent to the heterocyclic field include those of Jaffé and Jones (1964), Tomasik (1973) and Johnson and Tomasik (1976).

The initial application of the Hammett equation to ionizations of meta and para-substituted benzoic acids setting $\rho=1$, generated a variety of substituent constants denoted by $\sigma_m$ and $\sigma_p$ which have been used in correlating reactivities with varying degrees of success. Extensive compilations of these substituent constants are available in the literature (McDaniel and Brown, 1958; Wells, 1963). In contrast to values derived from benzoic acids, Taft (1960) proposed to minimize direct conjugation between probe and substituent, e.g. as indicated in (1-7), by a new scale of $\sigma$ values based on the ionization of substituted phenylacetic acids. In these, the intervening methylene group would minimize effects of type (1-7). Such values were denoted by $\sigma^0$. Generally values of $\sigma$ and $\sigma^0$ are in close agreement but for some groups (e.g. $\text{NH}_2$) there are significant differences.

The values of $\sigma$ so determined, failed to give satisfactory correlations with reactivities involving transition states which were more electron-demanding than the ionization of substituted benzoic acids (e.g. electrophilic substitution or solvolyses involving carbonium ions or carbonium-ion-like transition states). In order to
overcome this, Brøn and Schemes (1956) set up a new scale using the 20-value of 2-cumyl chloride as the standard reaction (i.e., \( \delta_0 \)) to generate new values, \( \delta_p \), which when compared to 'unexcited' values, gave a measure of the added amount of resonance interaction of substituent with reaction centre. A second scale, denoted by \( \alpha_p \), was based on reaction of the simplest substrates and takes the stabilization of anilinium cation as the standard reaction. Connell (1970) has made a compilation of such values for a large range of substituents.

The recognition of two major factors in the origin of substituent effects (i.e., inductive and mesomeric) had led to the realization that the two effects could be substantially separated. Lewis (1954) proposed that the two effects could be separated by the following equations:

\[
\alpha = \frac{\delta_0 - \alpha}{\delta_0}
\]

\[
\beta = \frac{\delta_0 - \beta}{\delta_0}
\]

They made the assumptions that the inductive effect operates equally well from the meta- and para-positions and that the resonance effect can contribute to \( \alpha_p \) indirectly via canonical forms (1-8).

In order to dissect out values of \( \alpha_p \), an independent scale of inductive effects was necessary; thus a scale of inductive substituent constants, \( \sigma_p \), was set up by left (1956) based on the difference between rates of esterification and basic hydrolysis of substituted aliphatic esters. The
overcome this, Brown and Okamoto (1956) set up a new scale using the solvolysis of t-cumyl chlorides as the standard reaction (i.e. \( \rho = 1.00 \)) thus generating new values, \( \sigma_p^+ \), which when compared to 'unexalted' values, gave a measure of the added amount of resonance interaction of substituent with reaction centre. A second scale, denoted by \( \sigma_p^- \), has been derived for reactions in which substituents can be effectively more electron-attracting than the ionization of benzoic acids: this scale takes the ionization of anilinium salts as the standard reaction. Exner (1972) has made a compilation of such values for a large range of substituents.

The recognition of two major factors in the origin of substituent effects (\( \text{viz.} \) inductive and mesomeric) had led to the suggestion that the two might be quantitatively separated. Taft and Lewis (1958; 1959) proposed that the two effects could be separated by the following equations:

\[
\sigma_m = \sigma_I + \alpha \sigma_R \\
\sigma_p = \sigma_I + \sigma_R
\]

They make the assumptions that the inductive effect operates equally well from the meta- and para-position and that the resonance effect can contribute to \( \sigma_m \) indirectly \textit{via} canonical forms (1-8).

In order to dissect out values of \( \sigma_R \), an independent scale of inductive effects was necessary: thus a scale of inductive substituent constants, \( \sigma^* \), was set up by Taft (1956) based on the difference between rates of acidic and basic hydrolysis of substituted aliphatic esters. The
following assumptions were made: (i) each overall effect was the sum of independent contributions from polar, steric, and resonance effects; (ii) in the acidic and basic reactions, the steric and resonance effects were the same; and (iii) the polar effects of substituents were much greater in basic than acidic reactions. Exner (1966) carried out a similar analysis of separation of inductive and resonance effects.

From these suggestions, a variety of equations have been proposed, all of them involving a dual substituent parameter (DSP) treatment of one form or another. Yukawa and Tsuno (1959) suggested use of the relationship

\[ \log(\frac{k}{k_0}) = \rho [\sigma + r(\sigma^+ - \sigma)] \]

which provides a scale of enhanced resonance effects and implies multiple correlation of \( \log(\frac{k}{k_0}) \) with \( \sigma \) and \( (\sigma^+ - \sigma) \). The value of \( r \) gives a measure of enhanced resonance effects: when \( r=0 \), the expression reduces to the normal Hammett equation, but if \( r=1 \), correlation is with \( \sigma^+ \) alone.

Dewar and Grisdale (1962) divided the substituent constant into field and resonance effects and calculated the latter by a quantum-mechanical method. This approach has had some success in predicting values of \( \sigma \) (Butler, 1970) but has been criticized because the angular dependence of the substituent dipole was not taken into account. It failed when applied to systems involving an organic side-chain conjugated with benzene (Eaborn et al., 1971).

Swain and Lupton (1968) have suggested one form of separation in which \( \sigma_1 \) and a single universal scale of resonance (R) parameters were adopted. They formulated
their equation as
\[ \sigma = ff + rR \]  \hspace{1cm} \text{equation 6}
and claimed that R was generally applicable to diverse reaction types. This work has been criticized by Ehrenson et al. (1973) whose main objection centred on the adoption of the scale of resonance. Since resonance effects do not respond rectilinearly to electron-demand, i.e. \( \sigma^+_p \) is not proportional to \( \sigma_p \) (Katritzky and Topsom, 1971), it seems unreasonable to expect satisfactory correlations between one resonance parameter and reactions of different electron-demand. Ehrenson and co-workers formulated their dual substituent parameter equation as
\[ \log(k/k_o) = \rho_I\sigma_I + \rho_R\sigma_R \]  \hspace{1cm} \text{equation 7.}

The values of \( \rho_I \) and \( \rho_R \) reflected the relative importance of inductive and resonance effects, as measured by \( \sigma_I \) and \( \sigma_R \) respectively. The values of \( \sigma_I \) were determined by taking the ionization of 4-substituted bicyclo(2,2,2)octane-1-carboxylic acids (1-4) and related systems as the standard reaction (Baker et al., 1967). The salient feature of this approach was the use of four scales for \( \sigma_R: \sigma^0_R, \sigma_R (BA), \sigma^-_R \) and \( \sigma^+_R \). Values of \( \sigma^0_R \) were derived from ionization of phenylacetic acids or like insulated systems. In contrast, \( \sigma_R (BA) \) values were derived directly from ionization of benzoic acids. The values of \( \sigma^+_R \) were not the same as Brown's values but were derived from the rates of cleavage of \textit{para}-substituted phenyltrimethylsilanes (Eaborn, 1956; Dean and Eaborn, 1959). Finally, \( \sigma^-_R \) values were derived from ionization of anilinium salts in water.
Each of these sets of parameters are said to have "limited
generality" and discrimination between sets depends on the
type of interaction between substituent and \( \pi \) systems,
\( i.e. \) weak, moderate, or strong electron-donation or
-withdrawal. The choice of constant used may be apparent
from the type of reaction \( (e.g. \sigma_R^+ \) for electrophilic
substitution) or it may be determined by applying equation 7
and determining which scale of \( \sigma_R \) gives the best fit, using
the usual statistical criteria \( (e.g. \) multiple correlation
coefficient).

(d) Applications to the heterocyclic field

In connection with substituent effects, the presence
of a heteroatom in a formally aromatic ring has been
approached generally in one of three ways: (i) The hetero-
cyclic ring can be treated in the same way as the original
benzene system and new values of \( \sigma \) generated from a standard
reaction \( (i.e. \) by setting \( p=1 \)); the new values can then be
compared to those derived from the benzene system.
(ii) Values of \( \sigma \), derived from ionizations of benzoic acids,
can be used for correlation with side-chain reactivity in
heterocycles; deviations which do occur may give insight
into the effect of replacing \( =\text{CH}^- \) by \( =\text{X}^- \). (iii) The
heterocycle can be treated as a substituted benzene nucleus
and substituent constants for the heteroatom are then
calculated from interpolation with data from the same type
of reaction in the benzene series.
The first approach was used by Butler (1970). In his treatment of the dissociation of ring substituted thiophene-2-carboxylic acids he used Dewar and Grisdale's method and calculated values of $\sigma$ which were compared to experimental values derived from $pK_a$ values for the acids by using equation 1 with $\rho=1.00$. The agreement was excellent and furthermore, the values were very close to those derived from benzoic acids, indicating that the sulphur played no unusual role in transmitting substituent effects. The results indicated predominantly inductive transmission. Relevant to this was the claim by Kemula and Krygowski (1968) that substituent effects are transmitted through the hydrocarbon portion of the molecule rather than sulphur. This is at variance with the "through space" field effect. Janda et al. (1976) have examined inductive effects in thiophene by measuring $pK_a$ values for 4-methyl-2-thiophene- (1-9), 5-methyl-3-thiophene- (1-11) and 5-methyl-2-thiophene-carboxylic acids (1-10), each substituted in the methyl groups. The insulating methyl group prevented direct mesomeric interaction with the ring. The $\sigma_I$ values of Exner (1966) were used in this correlation with ionization constants. Although the number of bonds between substituent and probe were kept constant, differences in the sensitivity to changes of substituent were apparent: this was attributed to participation of the $\pi$-electrons in transmission of the inductive effect (the $\pi$-inductive effect - see Bromilow et al., 1977; Brownlee et al., 1976; and Reynolds, 1973). The thiophene ring also appears to transmit effects better than benzene.
Faner and Simon (1964) showed that the reaction constant \( k \) for the reaction of thiophene-carboxylic acids with benzene, acetic anhydride, and ethyl acetate for systems having the same sensitivity to substituent effects have the same values at units (i.e., the same values for systems having the same sensitivity to substituent effects). Conversely, Fringuelli (1964), in studies of ionization of pyrrole-2-carboxylic acids, found a rectilinear relationship between \( \alpha \) and \( \log K \), a value for \( \alpha \) different from that for the benzyol system, that for the benzene ring (as for the pyrrole ring) is a variable interaction between probe and electron and it was suggested that hydrogen bonding in both neutral and anionic species (1-12) was stabilizing the \( \alpha \) values. In order to obtain substituent constants for the heterocyclic ring (as for the benzyol ring) and the heterocyclic substituent effects (1-13) and (1-14) synthesized (Katsufuchio et al., 1970). The substitution produces shifts and the values of \( \alpha \) for the heterocyclic moiety (Spinelli et al., 1972; 1976) have obtained good correlations in the thiophene system with rates of nucleophilic displacement of groups sensitive to substituents. This rationalization is being due to the much lower steric requirements of thiophene than of benzene. Other work in this field supports this view (Clementi et al., 1972).

Fischer et al. (1964) has measured \( \psi \) values for a number of 3- and 4-substituted pyridines and have shown that the reaction constant of 6.0, which was to be expected since the reaction...
Exner and Simon (1964) showed that the reaction constant ($\rho$) for ionization of thiophene-2-carboxylic acids in 80% ethoxyethanol was the same as that for the corresponding benzoic acids, the difference between corresponding log $k$ values being ~0.5 units (i.e. they showed the two systems have the same sensitivity to substituent effects). Conversely, Fringuelli (1969), in studies of ionization of pyrrole-2-carboxylic acids, found a rectilinear relationship between $\sigma$ and log $k$, but a value for $\rho$ very different from that for the benzoic acid series. This was indicative of a variable interaction between probe and heteroatom and it was suggested that hydrogen bonding in both neutral and anionic species (1-12) was modifying the $pK_a$ values. In order to obtain substituent constants for the heterocyclic ring (as distinct from the heterocyclic atoms as a substituent) compounds such as (1-13) and (1-14) were synthesized (Matyushecheva et al., 1976). The $^{19}$F substituent-induced shifts and $pK_a$ values allowed determination of $\sigma$ for the heteroaryl moiety. Spinelli et al. (1972; 1976) have obtained good correlations in the thiophene system with rates of nucleophilic displacement of groups ortho to substituents. This was rationalized as being due to the much lower steric requirements of thiophene than of benzene; other work in the field supports this view (Clementi et al., 1971).

Fischer et al. (1964) has measured $pK_a$ values for a number of 3- and 4-substituted pyridines and have correlated such values with $\sigma^0$. They found a high reaction constant of 6.01 which was to be expected since the reaction
site was in the ring. In their analysis, groups such as OMe and NH$_2$, showed an enhancement of basic strength, attributed to extra resonance interaction with the ring (1-15). Ellam and Johnson (1971) carried out a similar correlation of pK$_a$ values with 3- and 4-substituted vinylpyridines using $\sigma_m$ and $\sigma_p$ values. Brownlee and Topsom (1972) criticized these approaches on the basis that correlation would reasonably be expected with $\sigma_R^+$ not $\sigma^0$. They treated the data using the dual substituent parameter approach and concluded that values were best fitted by the equation

$$pK_a = 5.15 \sigma_I + 2.69 \sigma_R^+ \quad \text{equation 8.}$$

As a model for inductive effects in pyridine, Grob and Taft (1974) examined the ionization of 4-substituted quinuclidinium salts (1-16) in which resonance effects were absent and the substituent had the same orientation towards nitrogen as in 4-substituted pyridines. They correlated the pK$_a$ values of these compounds with $\sigma_I$ values and a least-squares treatment of the data gave equation 9

$$\log(k/k_0) = 4.81 \sigma_I + 0.20 \quad \text{equation 9.}$$

The difference between the ratio $\log(k/k_0)$ in each series, should give the resonance contribution in the pyridine series. This difference was found to fit equation 10

$$\log(k/k_0)_{\text{pyrid.}} - \log(k/k_0)_{\text{quinuc.}} = 2.87 \sigma_R^+ - 0.09 \quad \text{equation 10.}$$

The essential identity of the coefficients determining polar and resonance contributions was strong evidence for the existence of independent scales for each.
It has been suggested by Grob and Schlageter (1976) that the quinuclidinium system would offer a better model for inductive effects since, in the ionization of \((1-16)\), the number of charged species is the same and entropy effects should be minimal; this is not the case for carboxylic acids.

An interesting study by Taft et al. (1972) of proton affinities of 4-substituted pyridines in the gas phase showed that in the absence of solvents, pyridine was a base stronger than ammonia and comparable with aliphatic amines. Nevertheless, the values in the gas phase did correlate with those in the condensed phase although the sensitivities were exalted by a constant factor of about 3.5. The attenuation of substituent effects in solution was attributed to a higher effective dielectric constant (cf. equation 2) and differential solvent effects, in particular hydrogen bonding.

The alkaline hydrolysis of substituted pyridine carboxylates has been the subject of a great deal of study by Campbell et al. (1970). They examined rates of hydrolysis in a series of 2-substituted [series (1-17) to (1-19)] and 3- or 4-substituted pyridinecarboxylates [series (1-20) to (1-22)]. In (1-17) and (1-19) the least unsatisfactory correlation was with \(\sigma_p\), especially when the substituent was strongly mesomerically electron donating. There was no correlation in series (1-18). Rates for compounds (1-20) showed good correlation with \(\sigma_p\) as expected but in the (1-21) and (1-22) series,
correlation was with $\eta$. This was surprising since strong conjugation of groups such as alkoxy with the nitrogen was expected in (1-21), particularly in the light of the results of prior studies. The 'abnormal' behaviour of substituents in the heterocyclic nitrogen area has been commented on by a number of workers. Thus Joyce et al. (1973) have also found that substituent effects in the aminolytic and amidolytic of compounds such as (1-20) and (1-21) cannot be treated as if they were simply formally added to the reaction site. Recent studies of aminolytic of compounds of the type (1-21), substituted in the 4 or 5-positions correlated well with the Hammett equation, as reported by Perkin (1974) and others. They have suggested that the distribution of substituent effects in the reaction area is due to the possible operation of an overall electrostatic effect operating over one bond. They also suggested that the total substituent effect could be divided into a component from the direct effect of the substituent and a component due to the resonance effects of the substituent and the aromatic ring. The latter component was found to be large and much larger than the former. Cotton and Slikker (1971) have proposed data as a general expression of the aminolytic effect, i.e. of the effect rather than a steric one, as is usually assumed.
correlation was with $\sigma_m$. This was surprising since strong conjugation of groups such as methoxy with the nitrogen was expected in (1-21), particularly in the light of the anomalous behaviour of the ortho substituents. The 'abnormal' behaviour of substituents $\alpha$ to the heterocyclic nitrogen atom has been commented on by a number of workers. Thus Noyce et al. (1973) have also found that substituent effects in the aqueous solvolysis of compounds such as (1-23) and (1-24) cannot be treated as if they were simply formally meta to the reaction site. Rates of solvolysis of compounds of the type (1-21), substituted in the 4- or 5-positions correlated well with Brown's $\sigma^+$ values. Perrin (1965) and Barlin and Perrin (1966) have also noted the difficulty in predicting basic strengths of heterocycles with substituents adjacent to nitrogen. Charton (1964; 1969) proposed that this apparently anomalous behaviour was due to a short range electrostatic effect operating over one bond. He suggested that the total polar effect could be divided into the sum of a contribution from the field effect and a through-bond process. The latter component becomes effective only over short distances and thus, in general, $\sigma_1$ measures the through-space portion only. Charton (1971) has proposed this as a general explanation of the ortho effect, i.e. that it is predominantly an electronic effect rather than a steric one, as is usually assumed.
Deady and Shanks (1972), using rates of alkaline hydrolysis of pyridine carboxylates, and interpolating these values into the data for substituted benzoates, determined the substituent constants for the three possible orientations of the aza group within the ring. They found values of 0.75 (2-N), 0.65 (3-N) and 0.96 (4-N) (Cf. 0.71 and 0.78 for meta and para NO₂). The values were shown to be solvent-independent except for σ₂N.

Blanch (1966) has determined the substituent constants for the nitrogen in pyridine by measuring the pKₐ value, for the three possible pyridinylacetic acids. These microscopic constants were determined from the macroscopic values and the zwitterionic ratios. The values obtained were 0.08 (2-N), 0.55 (3-N) and 0.94 (4-N). The σ₂N value determined in this way was much smaller than values determined from other reaction series and its low value is ascribed to the presence of intramolecular hydrogen bonding in the neutral molecule reducing the ionization constant (1-25). A similar effect, although in the reverse direction was noted by Jones (1970) in the relatively high value of σ he obtained for N in 2-substituted pyrroles. This was attributed to stabilization of the anion by hydrogen bonding (1-26).

Bruce et al. (1975) have criticized the use of σ values for heteroatoms derived from ionization of carboxylic acids because of the possibility of proximity effects. Their studies of rates for the reduction of heterocyclic ketones (1-27) with sodium borohydride, showed that Hammett plots produced curved lines but that rectilinearity
was achieved by applying the Van't Hoff equation. However, values of \( \delta \) were those derived from hydrolysis of heterocyclic esters. In satisfactory correlation could be obtained with the esters of Butler (1979) and the values of the correlation activity

(1-23)  
(1-24)

(1-25)  
(1-26)

(1-27)  
(1-28)

\( X = \text{NH, S, O.} \)
was achieved by applying the Yukawa-Tsuno equation. However, values of \( \sigma \) used were those derived from hydrolysis of heterocyclic esters. No satisfactory correlation could be obtained with the values of Butler (1970) based on ionization of the corresponding acids.

Brown and Moser (1971) have made a study of the rates for decarboxylation of 6-substituted pyridine-2-carboxylic acids in 3-nitrotoluene. Rates were correlated with \( \sigma_1 \) except when the substituent was \( \text{CH}_3\text{CONH}-, \text{NH}_2 \) or \( \text{OCH}_3 \), a further example of 'anomalous' ortho effects. Such results suggested a transition state involving partial formation of the N-H bond and an ylide intermediate (1-28) although others (Taylor, 1972; Button and Taylor, 1973) have suggested that reaction proceeds through a zwitterion.

Pyridine-N-oxides have been examined by Nelson et al. (1967) who suggested that a self consistent set of \( \sigma \) values should be developed, based on the ionization of these compounds as the standard reaction (1-29). The values so derived were used to correlate successfully other reactions of N-oxides (e.g. 4-substituted pyridine-N-oxides with iodine). Such an approach seems to be necessary in this system because, in the same reaction series, different values of \( \sigma \) (i.e. \( \sigma^+, \sigma^- \)) are required if meaningful correlations are to be obtained: an obviously unsatisfactory situation. This seems to arise from the amphoteric nature of the N-oxide group enabling contributions from canonical structures of type (1-30) or (1-31) to become important, depending on electronic requirements of the reaction or capabilities of the substituent.
Correlations in the diazine series have employed mainly the basic $pK_a$ values of ring nitrogen atoms. Mizukami and Hirai (1966) correlated ionization constants of 5-substituted-4-amino-2-methylpyrimidines and 4,5-disubstituted-2-methylpyrimidines with $\sigma$ values. They found correlations with $\sigma_m$ for 5-substituents and $\sigma_p$ for 4-substituents. They also found correlations with $\Sigma\sigma$, the sum of individual substituent constants in the 4,5-disubstituted compounds. Roth and Strelitz (1969) carried out an extensive study of the $pK_a$ values of seventy 2,4-diaminopyrimidines and analogous systems: they found that values for 5-substituted compounds followed Equation 11, and those for 6-substituted pyrimidines, Equation 12.

$$\log(k/k_0) = 4.69 \sigma_I + 1.82 \sigma_R \quad \text{equation 11}$$

$$\log(k/k_0) = 7.83 \sigma_I + 0.32 \sigma_R \quad \text{equation 12}$$

The size of the coefficient of the inductive contribution of Equation 12 and the lack of any significant resonance component suggests that protonation occurs on the nitrogen adjacent to the substituent. Khromov-Borisov (1968) found a rectilinear relationship between $\sigma_p$ and $pK_a$ values of 4-substituted pyrimidines, and Zagulyaeva et al. (1970) correlated half-neutralization potentials of substituted 2-chloropyrimidines with $\sigma^+$ values.

Cookson and Cheeseman (1972) examined $pK_a$ values of 6-substituted pyridazines. In (1-32) they obtained good correlation with $\sigma_m$ and gave some evidence for protonations of the nitrogen ortho to the dimethylamino group. It was
suggested that (1-29) protonates on oxygen since the best correlation was with $\alpha$. Values of (1-30) also correlated with $\alpha$ and the author claimed that protonation occurs on the nitrogen opposite to the substituent and not on the other as they fail.

Only one 2-(pyrimidin-2'-yl)acetic acid has previously been described. Derrow and Hiihonen (1969) made the 6-derivative (1-31) by hydrolysis of the 6-dehydrated (1-32) similarly made 2-(6-chloro-5-hydroxy-2'-pyridyl)acetic acid (1-33) from 2-ethyl-5-(2-chlorophenyl)-1,2,4-triazole-3,5-dione (1-32) by condensation with diazooxalic acid. The latter was also converted to the quaternary intermediate with diazooxalic acid and concentrated hydrochloric acid to yield 2-(5-chloro-2-pyridyl)-5-acetamidopyridine (1-34) along with a variety of $\gamma$- and 4-yl-pyrimidin-2-yl)acetic acids (1-34) (Derrow, 1971).
suggested that (1-34) protonates on oxygen since the best correlation was with $\sigma_p$. Values for (1-33) also, correlated with $\sigma_p$ and the authors claimed that protonation occurs on the nitrogen ortho to the substituent. This was not as surprising as they felt, given the correlation between $\sigma_p$ and $\sigma_o$ indicated by Charton (1972).

(e) Synthetic aspects of analogous systems

Only one 2-(pyrimidin-2'-yl)acetic acid has previously been described. Dornow and Siebrecht (1960) made the 4',5'-derivative (1-36) by hydrogenolysis of 2,3-dimethylpyrazolo[2,3-α]pyrimidin-7(6H)-one followed by hydrolysis of the resulting amide. Imbach et al. (1960) have similarly made 2-(1',6'-dihydro-4'-methyl-6'-oxopyrimidin-2'-yl)acetamide (1-37) from the pyrazolopyrimidine (1-38) with Raney nickel.

A number of 2-(pyrimidin-4'-yl)acetic acids is known. Thus Hepworth and Thomson (1971) made ethyl 2-(2'-p-chlorophenyl-1',6'-dihydro-6'-oxopyrimidin-4'-yl)acetate (1-39) by condensing para chlorobenzamidine hydrochloride with diethyl acetonedicarboxylate. The latter reagent was also condensed with guanidine carbonate to yield 2-(2'-amino-1',6'-dihydro-6'-oxopyrimidin-4'-yl)acetic acid (1-40) (Worrall, 1918; 1943). A variety of 2-(3' and 4'-p-chlorophenylpyrimidin-4'-yl) acetic acids has been described by Fauran et al. (1974).
No 2-(1'-bromo-1'-methylethyl)pyrimidines have previously been described. Brown and Waring (1974) have made some simple 2- and 4-bromomethylpyrimidines by treatment of the corresponding methylpyrimidines with N-bromosuccinimide.

Noyce et al. (1973) have made the chloropyridine analogues by treatment of the corresponding tertiary alcohols with thionyl chloride although the products were not fully characterized.
Simple 8-(Pyrimidinyl)glycine Acids

An important reagent in the synthesis of many of the glycine acids was diethyl glycine hydrochloride (1-39), and the important glycine (1-38). The 8-(Pyrimidinyl)glycine (1-38) was converted (HCl gas and NaOEt, 1951) into the dichloropyrimidinylglycine (1-39) which was then converted.

In this regard, the use of the method in water containing sodium carbonate gave diethyl glycine-8-(pyrimidinyl)glycine (1-39). This procedure resulted in the formation of a (1-39), which resulted in the formation of a (1-40).
SECTION I

Simple 2-(Pyrimidin-2'-yl)acetic Acids

An important precursor in the synthesis of many of the above acids was 2-(1',6'-dihydro-4'-hydroxy-6'-oxopyrimidin-2'-yl)acetamide (2-1) which was prepared by the self condensation of malondiamide (Brown, 1956). This material could also be prepared from condensation of malonic ester with amidinoacetamide hydrochloride (2-2) but the latter method appeared to give an inseparable mixture of (2-1) and the isomeric pyridine (2-3). The pyrimidinylacetamide (2-1) was converted (McElvain and Tate, 1951) into the dichloropyrimidinylacetonitrile (2-4) with phosphoryl chloride. The nitrile was then converted, in the manner used by Winterfeld and Flick (1956) for a pyridine analogue, into the hydrochloride of the corresponding methyl and ethyl acetimidates (2-5). On stirring in water, these smoothly and quantitatively gave the corresponding acetates (2-6; R=Me, Et). Catalytic hydrogenation of the methyl ester in water containing sodium carbonate gave methyl 2-(pyrimidinyl-2'-yl)acetate (2-7). This procedure resulted in some hydrolysis of the ester, but the use of a milder base (e.g. MgO) resulted in the formation of a (1,4,5,6)-tetrahydropyrimidine (2-8),
 isolated as the hydrochloride (2-5). Similar procedures involving the pyridine ring usually yield products containing 4-alkyl groups. When an alcohol was used in place of the base, the 4-alkyl compounds were obtained in a similar manner. The dichloropyridazine [2-4] was similarly prepared from the acetate.

The dichloroester (2-6) was converted into the pyridazine [2-7] with sodium hydroxide. The ethylester (2-2) and the methylester (2-3) were similarly prepared. The ethylester (2-4) with methoxide or ethoxide, followed by treatment with HCl, gave the chloride [2-14, 8'-8''-Me] and the bis-methylthio [2-14, 8'-8''-Me] compounds, respectively.

The 8-chloro-9-methylpyridazine [2-5] was converted (2-4) into the hydrochloride [2-6].
isolated as the hydrochloride [although nuclear reductions of the pyrimidine ring usually occur under acidic conditions (Smith and Christensen, 1955) such reactions can sometimes proceed in the presence of a base (Davies and Piggott, 1945)]. When an alcohol was used as solvent, in the presence of a base, the 4-alkoxy compound (2-10) was formed in considerable quantity. Treatment of the ester (2-7) with one mole of sodium hydroxide gave sodium 2-(pyrimidin-2'-yl)acetate (2-9). Sodium 2-(4',6'-dichloropyrimidin-2'-yl)acetate (2-6; R=Na) was made similarly from the acetate.

The dichloro ester (2-6; R=Me) was mono-methoxylated in methanolic sodium methoxide to give the chloromethoxy ester (2-11) which on dehalogenation gave the methoxy ester (2-12) and subsequently the methoxy acid (2-13). Hydrolysis of the ester (2-11) with sodium hydroxide gave the methoxychloro acid (2-14; R'=OMe, R''=Cl) and forced replacement of both chloro groups of (2-6) with methoxide or ethyl mercaptide, followed by saponification, gave the dimethoxy (2-14; R'=R''=OMe) and the bisethylthio (2-14; R'=R''=SEt) acids, respectively.

Ethyl cyanoacetate was converted into ethyl 3-imino-3-methoxypropanoate hydrochloride (2-15; R'=OEt, R=OMe) characterized for the first time (cf. Pinner and Oppenheimer, 1895; McElvain and Schroeder, 1944) and thence into amidinoacetamidine hydrochloride (2-15; R'=R=NH₂) by treatment with ethanolic ammonia (McElvain and Tate, 1951). This material provided access into the 4'-alkylated and arylated 2-(pyrimidin-2'-yl)acetic acids. Condensation of
(2-6) \[ \text{MgO}/H_2 \] \[ \text{OH}^- \]

(2-8) \[ \text{ROH}/\text{BASE}/H_2 \]

(2-9) \[ \text{Na} \]

(2-10)
the amide with ethyl benzoate (13b; 8×8) over.

A mixture of 2-[(1,2)-dihydro-3-phenyl]

1,3-oxazin-2-yl)dimethylphosphonate (2-11; 9×9) together with the choline

pyridine (2×10; 4×4). After crystallization (acetone,

acetone) from boiling ethanol yielded two crystalline types

separated by hand, a chunky rhombical form (the pyridine)

and delicate plates (the pyridine). Careful crystallization

crystalization (acetone) was essential in separating

the crystals. The overall yield of (2-12) was 50%

produced (to lower proportion) than 8×8 and 9×9.

However, the ratios were evidently distributed.

The proportions of each form turned out to be

the molar ratio of condensation was constant for all cases.

attaining at 25°C in acetone with the presence of sodium

equivalent for 1×9. The proportions were studied by 1H NMR.

The products (the pyridine and pyridine) were well

separated. It is apparent that the cyclic nature of a single
diastereomeric of pyridine was formed in the ratio of pyridine:

phenylalanine of 3:1. Unfortunately, the code of pyridine

has been summarized by Newson (1983) and the presence of Bu

groups adjacent to a carbonyl appears to reduce reactivity
directly; thus the ketone (2-12) was reported not to form

an ester (Deady and Saper, 1911). Deady (1967) has given

several examples of stable resistance to condensation in

the Knoevenagel reaction. Thus, pyridine (2-12) gave a

yield of 5-methylpyrazole (2-21) under conditions where

pyridine produced a mixed condensation to the ketone

product (Trout, 1967). Condensation was the active
the amidine with ethyl benzoylacetate (2-16; R=Ph) gave a 1:1 mixture of 2-(1',6'-dihydro-6'-oxo-4'-phenylpyrimidin-2'-yl)acetamide (2-17; R=Ph) together with the isomeric pyridine (2-18; R=Ph). Slow crystallization (overnight) from boiling ethanol yielded two crystalline types separated by hand, a chunky rhomboidal form (the pyridine) and delicate needles (the pyrimidine). Careful fractional crystallization from ethanol was successful in separating the components of the mixture, but the overall yield of pure pyrimidine was poor. The pyridines (2-18), were also produced (in lesser proportion) when R=Me and Et; however, no pyridine was evident when R=Pr³ or Bu⁴. The proportions of each isomer formed are indicated in Table I. The conditions of condensation were the same for all cases: stirring at 25° in ethanol with one mole of sodium hydroxide for 2 days; proportions were judged by ¹H n.m.r. spectra of crude products (H5 in the pyridine and pyrimidine are well separated). It is apparent that the steric bulk of R determined the ratio of pyrimidine to pyridine. Steric effects in the addition reactions of ketones have been summarized by Newman (1963) and the presence of bulky groups adjacent to a carbonyl appears to reduce reactivity markedly: thus the ketone (2-19) was reported not to form an oxime (Haller and Bauer, 1913). Jones (1967) has given several examples of steric resistance to condensation in the Knoevenagel reaction. Thus pinacolone (2-21) gave a 48% yield of dicyanoethylene (2-22) under conditions where acetone produced a 90% conversion to the corresponding product (Prout, 1953). Condensation via the active
(2-19)

(2-20)

(2-21)

(2-22)

(2-23)
methylened and the imino group of the guanino to give the pyridine (2-20) will become unstable as the bulkiness of R increases and interacts with the guanido group.

Assignment of structure (2-19) rather than the isomer (2-19A) was based on the identity (m.p., 1H n.m.r.) of the Me (isomer (2-19; R=Me) with the compound by Imbach (1960). We made 2-amino-1,6-dihydro-6-ethyl-6-oxopyrididine (2-21) from 1,6-dihydropyridine (2-18; R=H) unambiguously from 1,6-dihydropyridazine (2-21). The structure assignment when R=Ph was made by analogy, however, additional evidence may be obtained from spectra (see Chapter 9).

TABLE I

<table>
<thead>
<tr>
<th>R</th>
<th>% PYRIM</th>
<th>% PYRID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>Et</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>Pr</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Bu</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Ph</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

The pyrimidinylmeclosta (2-17) and 1,6-dihydropyridazine (2-18) are shown. (1,6-Dihydropyridazine (2-18) is indicated in Scheme 10) as indicated in Scheme 10. The structure described and all substances used were independent of the previous dealing with low boiling solids, but were important, avoided complications due to decarboxylation which appeared to be unusually facile. Thus 2-(4'-butoxypyrrolidin-2'-yl)acetate (2-39) decarboxylated spontaneously at 80°C in 15 minutes to 4-(butoxypyrrolidin-2'-yl)acetate (2-39), characterized as the picrates. Electro-donating substituents appeared to accelerate the decarboxylation.

Thus it proved impossible to isolate the free acid from solution 2-(4'-methoxypyrimidin-2'-yl)acetate (2-31) without stabilization by the 4-methoxy-pyrimidine. Taylor (1974), Beeck and Rosen (1974) and Dunn and Thome (1974) have...
methylene and the imino group of the amidine to give the pyridine (2-20) will become unfavourable as the bulkiness of R increases and interacts with the α amido group. Assignment of structure (2-18) rather than the isomeric (2-18A) was based on the identity (m.p., $^1$H n.m.r.) of the Me isomer (2-18; R=Me) with the compound by Imbach (1970). He made 2-amino-1,6-dihydro-4-methyl-6-oxopyrid-3-ylformamide (2-18; R=Me) unambiguously from 3,6-dihydroxy-4-methylpyrazolo[3,4-b]pyridine (2-23). The structure assignment when R=Ph was made by analogy; however, additional evidence may be obtained from $^1$H n.m.r. spectra (see Chapter 3).

The pyrimidinylacetamides (2-17) were then converted to sodium 2-(4'-substituted pyrimidin-2'-yl)acetates (2-18) as indicated in Scheme 1. The acids so far described and all subsequent ones were isolated, characterized, and used as their sodium salts. This avoided dealing with low melting solids, but more importantly, avoided complications due to decarboxylation which proved to be unusually facile. Thus 2-(4'-t-butylpyrimidin-2'-yl)acetic acid (2-29) decarboxylated quantitatively at 90° in 15 minutes to 4-t-butyl-2-methylpyrimidine (2-30), characterized as the picrate. Electron-donating substituents appeared to accelerate the decarboxylations: thus it proved impossible to isolate the free acid from sodium 2-(4'-methoxypyrimidin-2'-yl)acetate (2-31) without contamination by the 2-methylpyrimidine. Taylor (1972), Brown and Moser (1971) and Dunn and Thimm (1977) have
SCHEME 1

\[(2-17) \xrightarrow{\text{POCl}_3} \text{Cl} \quad \xrightarrow{\text{MeOH/HCl}} \text{Cl} \quad \xrightarrow{\text{NaOH}} \text{OMe} \]

\[(2-24) \xrightarrow{\text{H}_2\text{O/}40^\circ} \text{Cl} \quad \xrightarrow{\text{H}_2} \text{CH}_2\text{CO}_2\text{Me} \]

\[(2-26) \xrightarrow{\text{NaOH}} \text{CH}_2\text{CO}_2\text{Na} \]

\[(2-28) \]
An important precursor to 2-(pyrimidin-4′-yl)acetate (2-32), chloropyrimidin-5′-ylacetate (2-33) with an excess of sodium hydroxide gave methyl 2-(pyrimidin-4′-yl)acetate (2-34). It was hoped that treatment of this with phosphoryl chloride would give the chloro acid (2-35) and with phosphorus oxychloride (2-36). Under the conditions of the first decomposition, the only detectable substance was 2-chloropyrimidin-5′-ylacetamide (2-37). Nitric acid was unsuccessful in that decomposition occurred and only boring material was detected.

Methyl 2-(4′-chloropyrimidin-5′-yl)acetate (2-38) was made by the chlorination of methyl 2-(4′-dimethylaminopyrimidin-5′-yl)acetate (2-39). Selective reduction of the 4′-chloro group would yield the required compound, but treatment of (2-38) with Raney nickel or zinc dust gave only the pyrimidine (2-40). Hydrogenation was investigated by passing hydrogen through the catalyst occurred after a very short period and no
studied decarboxylation of heterocyclic acetic acids in some detail.

An important precursor to 2-(pyrimidin-2'-yl)acetic acids substituted in the 4'-position was methyl 2-(4'-chloropyrimidin-2'-yl)acetate (2-32). A number of synthetic routes was tried before a successful one was found. Thus treatment of methyl 2-(4'-methoxypyrimidin-2'-yl)acetate (2-33) with an excess of sodium hydroxide gave sodium 2-(1',6'-dihydro-6'-oxopyrimidin-2'-yl)acetate (2-34). It was hoped that treatment of this with phosphoryl chloride would give the chloro acid (2-35) via the acid chloride (2-36). However, under the strongly acidic conditions, the only product detected and isolated was the decarboxylated material (2-37) in about 40% yield.

Permanganate oxidation of 2-(1',6'-dihydro-4'-methyl-6'-oxopyrimidin-2'-yl)acetamide (2-17; R=Me) to the acid (2-38) was achieved in poor yield. Attempts to decarboxylate the acid to the potential intermediate (2-39) were unsuccessful in that decomposition occurred and only starting material was detected.

Methyl 2-(4'-chloro-6'-ethylthiopyrimidin-2'-yl)acetate (2-40) was made by partial ethylthiation of methyl 2-(4',6'-dichloropyrimidin-2'-yl)acetate (2-6; R=Me). Selective reduction of the ethylthio group would yield the required compound, but treatment of (2-40) with Raney nickel or zinc dust gave only the pyrimidine (2-41). The possibility of removing the chloro group selectively by catalytic hydrogenation was investigated but poisoning of the catalyst occurred after a very short period and no
Depolymerization of methyl 2-(4-deoxy-d-erythro-pentopyranosyl)-2'-deoxy-d-erythro-pentopyranosylacetate (2-12) to methyl 2-(1,3,5-tri-0-acetyl-d-glucosaminyl-2'-deoxy-d-erythro-pentopyranosyl)acetate (2-40) (5% high yield) with anhydrous hydrogen bromide in benzene provided the natural product for the pyranosidic acetates. The latter was isolated as the hydrobromide. A proposed mechanism for the reaction is indicated (2-43) taking into account the ease leaving group capacity of the unsubstituted pyranose and the enhanced acidity of the 4-hydroxy group. This is also suggested by the analogy of 2-12 with the methyl glycoside the rest was due to attack at CO₂.

This was analogous to the mechanism proposed by Glinshtet
(1941) in the degradation of 2,4-dimethylpyrimidines
with sodium iodide in acetic acid.

The exopyranosidylacetate (2-40) gave methyl 2-(1,3,5-tri-0-acetyl-d-glucosaminyl-2'-deoxy-d-erythro-pentopyranosyl)acetate (2-38) on treatment with sodium iodide in acetic acid.

(2-17) → CO₂

(2-38)

(2-40) → CO₂

(2-41)
Dechlorinated material was detected. Demethylation of methyl 2-(4'-methoxypyrimidin-2'-yl)acetate (2-12) to methyl 2-(1',6'-dihydro-6'-oxopyrimidin-2'-yl)acetate (2-42) (in high yield) with anhydrous hydrogen bromide in benzene provided the natural precursor for the chloropyrimidinylacetate. The latter was made by treatment of the oxopyrimidine (2-42) with phosphoryl chloride. Hydrogen bromide as a demethylating agent is generally used in the form of a 48% aqueous solution (Burwell, 1954) but use of anhydrous hydrogen bromide is also well documented (Burwell and Fuller, 1957). Under the mild conditions (25-30°; benzene), no hydrolysis of the ester function was observed and the product was isolated as the hydrobromide. A proposed mechanism is indicated (2-43) taking into account the good leaving group capability of the protonated pyrimidine and the enhanced nucleophilicity of bromide ions in the apolar solvent. Daniels et al. (1965) studied the demethylation of 2-methoxypyrimidines in dilute sulphuric acid and concluded that about 8% of the product arose through nucleophilic attack of $H_2O$ on the aliphatic carbon of the methyl group (the rest was due to attack at C2). This was analogous to the mechanism proposed by Ulbricht (1961) in the dealkylation of 2,4-dimethoxypyrimidines with sodium iodide in acetic acid.

The oxopyrimidinylacetate (2-42) was converted into methyl 2-(4'-bromopyrimidin-2'-yl)acetate (2-44) with phosphoryl bromide in toluene; the chloro ester (2-32) gave methyl 2-(4'-iodopyrimidin-2'-yl)acetate (2-45) on treatment with potassium iodide in acetone.
(2-12) \[ \text{HBr/Benzene} \rightarrow \]

\[
\begin{align*}
\text{(2-42)} \\
\text{POCl}_3 \\
\text{POBr}_3 \\
\text{(2-44)} \\
\text{I}^-/\text{HI} \\
\text{(2-45)}
\end{align*}
\]
containing a trace of hydriodic acid.

Treatment of methyl 2-(4'-chloropyrimidin-2'-yl)acetate (2-32) with trimethylamine in anhydrous benzene gave 2-methoxycarbonylmethylpyrimidin-4-yl trimethyl ammonium chloride (2-46). This quaternary salt was converted into methyl 2-(4'-fluoropyrimidin-2'-yl)acetate (2-47) by the method of Brown and Waring (1974). This involved the use of potassium hydrogen difluoride in water at 5°; the fluoropyrimidine was continuously extracted into ether from the aqueous layer as the reaction proceeded. Interestingly, potassium fluoride gave no fluoro compound when used in place of the difluoride. All four methyl 2-(4'-halogenopyrimidin-2'-yl)acetates were converted into the corresponding sodium acetates by treatment with one mole of sodium hydroxide in water at 0°.

The sodium salt of ethyl mercaptan in methanol at 0° was used to convert the chloropyrimidinylacetate (2-32) into methyl 2-(4'-ethylthiopyrimidin-2'-yl)acetate (2-48). Some transesterification was observed (mass spectra) to give the thioester if an excess of ethyl mercaptide was used. Saponification with sodium hydroxide yielded the required acid (2-49). Oxidation of (2-48) with meta chloroperbenzoic acid in chloroform at 25° gave methyl 2-(4'-ethylsulphonylpyrimidin-2'-yl)acetate (2-50). This ester was treated at 0° with one mole of sodium hydroxide in water over a period of one hour. Two compounds were present in the reaction mixture and sodium 2-(4'-ethylsulphonylpyrimidin-2'-yl)acetate (2-51) was isolated by fractional crystallization. A second
(2-32) \[\rightarrow\] \[
\begin{array}{c}
\text{N(Me)}_3\text{Cl}^- \\
\end{array}
\]

(2-46) \[\rightarrow\] \[
\begin{array}{c}
\text{F} \\
\end{array}
\]

(2-47)

\[
\begin{array}{c}
\text{SEt} \\
\end{array}
\]

(2-48)

\[
\begin{array}{c}
\text{SO}_2\text{Et} \\
\end{array}
\]

(2-49)

\[
\begin{array}{c}
\text{SO}_2\text{Et} \\
\end{array}
\]

(2-50)

\[
\begin{array}{c}
\text{SEt} \\
\end{array}
\]

(2-51)

\[
\begin{array}{c}
\text{NH} \\
\end{array}
\]

(2-52)
component, identified by comparison with authentic material, was methyl 2-(1',6'-dihydro-6'-oxopyrimidin-2'-yl)acetate.

2-Methoxycarbonymethyl-6'-methylpyrimidin-4'-ylammonium chloride (2-52) was made from the chloropyrimidine (2-26; R=Me) and trimethylamine. This material gave a low yield (<5%) of methyl 2-(4'-cyano-6'-methylpyrimidin-2'-yl)acetate (2-53), when treated with potassium cyanide in molten acetamide (cf. Davies et al., 1964). Similarly (2-46) gave a very low yield of a mixture of two components, tentatively identified as the nitrile (2-54) and the dimethylamino compound (2-55). Extensive decomposition appeared to occur during the reaction.

2-Amino-5-bromopyrimidine (English et al., 1946) was converted into 5-bromo-2-fluoropyrimidine (2-56) by diazotization with fluoroboric acid (cf. Brown and Waring, 1974). It was hoped that condensation of this material with the anion of malonic ester would yield the adduct (2-57) which could be partially hydrolysed to the acid (2-58) and thence decarboxylated to methyl 2-(5'-bromopyrimidin-2'-yl)acetate (2-59). The condensation was attempted numerous times in benzene, acetonitrile, acetone and dimethylformamide with no success. Even with purified, dried reagents the mixture darkens after about 30 minutes and no product was detectable. The fluoro compound was chosen in view of its enhanced reactivity over other halogens (Brown and Waring, 1974) and, although the chloro compound was tried, it too failed to react.
some success was achieved by treatment with the Brønsted acids of the compound shown. However, treatment of the base with a mixture of perchloric acid and perchloric anhydride 3h resulted in a yellow product which was characterized by mass spectrometry. The mass spectrum showed a peak at m/z 275 corresponding to the molecular ion of the product. Further studies on the structure of this compound are currently underway.

Direct acylation of methyl 3-(pyrimidine-2-yl)acetate with acetic anhydride or acetic anhydride in pyridine gave the desired product in good yield. The product was purified by recrystallization from ethanol.

In its hydrolysis, the product gave a yellow compound with a peak at m/z 275 in the mass spectrum, consistent with the molecular ion of the product.

27a

\[
\begin{align*}
\text{Cl}^{-}(\text{Me})_3^+ & \xrightarrow{\text{CH}_2\text{CO}_2\text{Me}} \\
\text{CN} & \xrightarrow{\text{NMMe}_2} \\
\text{Br} & \xrightarrow{\text{CH}(\text{CO}_2\text{Et})} \\
\text{Br} & \xrightarrow{\text{OH}^-} \\
\text{CO}_2\text{Na} & \xrightarrow{\text{CH}_2\text{CO}_2\text{Me}}
\end{align*}
\]
Some success was achieved using the potassium salt of diethyl malonate in acetonitrile in the presence of a crown ether. Treatment of the dihalogenopyrimidine (2-56) in this way gave a low yield of dimethyl 2-(5'-bromopyrimidin-2'-yl)malonate (2-57) contaminated with a quantity of malonic ester. This material was purified by fractionation and treated with exactly one mole of sodium hydroxide. However, even at 20° the latter reaction did not appear to stop after saponification of one ester function and gave a mixture (3 components by t.l.c.) of (2-58), the ester (2-59), and its sodium salt. The low yield of (2-57) and complications in its hydrolysis caused this route to be abandoned.

Direct bromination of methyl 2-(pyrimidin-2'-yl)acetate yielded a mixture (not separated) of methyl 2-bromo-2-(pyrimidin-2'-yl)acetate (2-60) and methyl 2,2-dibromo-2-(pyrimidin-2'-yl)acetate (2-61).
2-[(1'-bromo-1'-methyl ethyl)pyrimidin-4-yl]pyrimidinone (2-60) was condensed with diethyl malonate to give 6-bromo-2-isopropylpyrimidin-4(3H)-one (2-61) in 55% yield (cf. Park et al., 1964; 245). This was converted into 2-chloroisopropylpyrimidinone (2-64), previously described by Park et al. (1964) in preparative details, upon treatment of 2(2-65) and 2-bromo substituents giving 2-isopropylpyrimidinone (2-66) was brominated in the ε-position with 6-bromoacetamide giving 2-[(1'-bromo-1'-methyl ethyl)pyrimidin-4-yl]pyrimidinone (2-69). Treatment of (2-64) with one mole of sodium methoxide in methanol gave the chloroisopropylmethoxy pyrimidinone (2-66) which underwent dechlorination and bromination giving 2-[(1'-bromo-1'-methyl ethyl)pyrimidin-4-yl]pyrimidinone (2-69). 2-Isopropyl-4-methoxy pyrimidinone (2-67) was demethylated using anhydrous hydrogen bromide in benzene, giving 2-isopropylpyrimidinone-4(3H)-one (2-68) which was treated with phosphoryl chloride giving the chloropyrimidine (2-70). Amination of the latter gave 2-[(1'-bromo-1'-methyl ethyl)pyrimidin-4-yl]pyrimidinone (2-71). The chloropyrimidine (2-70) was converted to the 4-fluoropyrimidinone (2-73) via the quaternary salt (2-72) which gave 2-[(1'-bromo-1'-methyl ethyl)pyrimidin-4-yl]pyrimidinone (2-74) after treatment with 3-bromo-
SECTION II

2-(1'-Bromo-1'-methylethyl)pyrimidines

Isobutyramidine (2-62), made from isobutyronitrile (McElvain and Nelson, 1942; Drozdov and Bekhli, 1944), was condensed with diethyl malonate to give 6-hydroxy-2-isopropylpyrimidin-4(3H)-one (2-63) in 55% yield (cf. Gershon et al., 1964; 24%). This was converted into the dichloroisopropylpyrimidine (2-64), previously described by Gershon et al. (1964) without preparative details. Catalytic hydrogenation removed both chloro substituents giving 2-isopropylpyrimidine which was brominated in the α position with N-bromosuccinimide giving 2-(1'-bromo-1'-methylethyl)pyrimidine (2-65).

Treatment of (2-64) with one mole of sodium methoxide in methanol gave the chloroisopropylmethoxypyrimidine (2-66) which underwent dechlorination and bromination giving

2-(1'-bromo-1'-methylethyl)-4-methoxypyrimidine (2-68).

2-Isopropyl-4-methoxypyrimidine (2-67) was demethylated using anhydrous hydrogen bromide in benzene, giving

2-isopropylpyrimidin-4(3H)-one (2-69) which was treated with phosphoryl chloride giving the chloropyrimidine (2-70).

Bromination of the latter gave 2-(1'-bromo-1'-methylethyl)-4-chloropyrimidine (2-71). The chloropyrimidine (2-70) was converted to the 4-fluoropyrimidine (2-73) via the quaternary salt (2-72) which gave 2-(1'-bromo-1'-methylethyl)-4-fluoropyrimidine (2-74) after treatment with N-bromo-succinimide.
Condensation of isobutyraldehyde with

\[
\begin{align*}
\text{HO} & \quad \text{Me} \\
\text{C} & \quad \text{Me} \\
\text{Cl} & \quad \text{Me}
\end{align*}
\]

Table 2 gives the reaction times for the isolation of the five isopropylpyridines studied. Reaction conditions were identical and solutions were monitored frequently by thin layer chromatography (silica/ethylene dichloride). NMR and IR spectra showed that only one product (i.e., olefin) was present. The authors give the most reliable account of the relative rates of reaction of the five compounds. The increase in rate of reaction with the halogen compounds appears to be at variance with the results for substituted amines where the reverse is true for substitution.

This result will be considered again in Chapter 4.

Three of the bromo compounds (2-64, 2-65, and 2-66) were isolated in a good percentage of the reaction mixture. Thus, they may be treated in the same way.
Condensation of isobutyramidine hydrochloride with ethyl benzoylacetate gave 2-isopropyl-6-phenylpyrimidin-4(3H)-one (2-75) which was subsequently converted (Scheme 2) into 2-(1'-bromo-1'-methylethyl)-4-phenylpyrimidine (2-76).

Table 2 indicates reaction times for the completion of bromination of the five isopropylpyrimidines studied. Reaction conditions were identical and solutions were monitored frequently by thin layer chromatography (silica/methylene dichloride). Yields were 80-90% (undistilled) and $^1$H n.m.r. spectra showed that no side products (e.g. olefins) were present. The times given are thus reliable estimates of the relative rates of reaction with N-bromosuccinimide. The marked decrease in reactivity of the 4-methoxy compound and the apparent increase in rate of reaction for the halogeno compounds appears to be at variance with the results for substituted toluenes where the reverse is true in free radical brominations. This result will be considered again in Chapter 4.

Three of the bromo compounds (2-65, -68, and -76) were solvolysed in methanol under preparative conditions and the products isolated and characterized. Thus 2-(1'-bromo-1'-methylethyl)pyrimidine (2-65) was refluxed in methanol for 48 hours to yield the ether (2-77) together with a small (5%) quantity of the olefin, apparently formed by acid-catalysed elimination. When the 4-methoxy compound (2-68) was treated in the same way,
SCHEME 2

\[
\begin{align*}
\text{C=O} & \quad \text{C=O} \\
\text{CH}_2 & \quad \text{NH}_2 \\
\text{OEt} & \quad \text{Me}
\end{align*}
\]

\[+\]

\[
\begin{align*}
\text{HCl} & \quad \text{NH}_2 \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{POCl}_3 & \\
& \quad \text{NBS} \\
& \quad \text{H}_2
\end{align*}
\]

\[
\begin{align*}
(2-75) & \\
(2-76)
\end{align*}
\]
TABLE 2

<table>
<thead>
<tr>
<th>R</th>
<th>TIME (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>4</td>
</tr>
<tr>
<td>OCH₃</td>
<td>16</td>
</tr>
<tr>
<td>Ph</td>
<td>2.5</td>
</tr>
<tr>
<td>Cl</td>
<td>0.75</td>
</tr>
<tr>
<td>F</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Because of the relatively slow rate of solvolysis, it was decided to examine a selection of the 4-bromo compounds under elimination conditions. Thus the parent compound (2-03) was treated with acetic anhydride in methanol at 60°C for 24 hours giving 2-isopropenylpyrimidinone (2-01; R=H; 65%). The presence of 5-10% of the methyl ether was detected by ¹H n.m.r. spectra. Similar results were obtained when R=Me and Ph.
a considerable amount (~15\%) of (1'-methoxy-1'-methyl-ethyl-pyrimidin-4(3H)-one (2-78) was formed via acid cleavage of the heteroaryl methoxy group. Addition of sodium hydrogen carbonate prevented the formation of the pyrimidinone (2-78) but caused the formation of an appreciable quantity of the olefin (2-79; 30\%). Clear conversion of 2-(1'-bromo-1'-methylethyl)-4-phenyl-pyrimidine (2-76) into the ether (2-80), was achieved by stirring at 50° for 3 days in methanol with apparent pH maintained at 6.8-7.0 by the automatic addition of potassium hydroxide. No olefin was produced under these conditions. The resistance to solvolysis of the t-bromo compounds was no doubt due to the destabilizing effect of the electron-withdrawing pyrimidine on the incipient carbonium ion. Protonation of the pyrimidine will further enhance this effect and this is illustrated by the fact that stirring the 4-phenyl compound (2-76) in 95\% aqueous formic acid at 80° for 24 hours resulted in recovery of the pyrimidine unchanged.

Because of the relatively slow rate of solvolysis, it was decided to examine a selection of the t-bromo compounds under elimination conditions. Thus the parent compound (2-65) was treated with sodium methoxide in methanol at 60° for 24 hours giving 2-isopropenyl-pyrimidine (2-81; R=H; 85\%). The presence of 5-10\% of the methyl ether was detected by $^1$H n.m.r. spectra. Similar results were obtained when R=OMe and Ph. Elimination with no concomitant solvolysis was achieved
by the use of potassium fluoride in acetonitrile in the presence of a crown ether.

In one instance, the tertiary alcohol (2-82) was made to check the solvolysis products in mixed aqueous solutions. Thus 2-(1'-acetoxy-1'-methylethyl)-4-phenylpyrimidine (2-83) was made from the bromo compound and silver oxide in acetic acid in 50% yield, accompanied by about 20% elimination to the olefin. Simple hydrolysis of this material gave 2-(1'-hydroxy-1'-methylethyl)-4-phenylpyrimidine (2-82).

Treatment of 2-isopropyl-4-phenylpyrimidine with m-chloroperoxybenzoic acid in chloroform gave 2-(1',2'-epoxy-1'-methylethyl)-4-phenylpyrimidine (2-84). No N-oxide was detectable.

Treatment of 4,6-dichloro-2-isopropylpyrimidine (2-64) with 1 mole of piperidine followed by dechlorination gave 2-isopropyl-4-piperidinopyrimidine (2-85). This material, after treatment with N-bromosuccinimide gave only 5-bromo-4-piperidino-2-isopropylpyrimidine (2-86); no α-brominated product was observed.
(2-77)

$$\text{OMe} \quad \text{NO} \quad \text{Me}$$

(2-78)

$$\text{OMe} \quad \text{Me}$$

(2-79)

$$\text{OMe} \quad \text{Me}$$

(2-80)
The ultra-violet spectra of the pyridine and pyridine carboxylic acids and their methyl esters were reported for the detection and quantitative determination of pyridine and its methyl esters. Because of the large differences between the spectra of neutral and protonated pyridines, a method of determining the spectrum at various pH values via titration of the corresponding acid with N-methylimidazolium hydroxide is used. It will be necessary to evaluate the spectrum of the ester in a non-aqueous solvent; however, it will be necessary to the "neutral" acid becomes greater (Nimrose and Serjeant, 1971). Table 3 lists the pKa values determined spectrophotometrically (by back titration of the acid solution), potentiometrically, and by the method of Albert and Serjeant (1971). Further investigations of the properties of these compounds are given in Chapter 3.

The pKa of methyl 2-(2-pyridyl)acetate and the carboxy group are expected to be lower than 2 in the neutral effect since the carboxyl group is not expected to be ionized for the acid in the neutral effect.
ULTRA VIOLET SPECTRA AND IONIZATION CONSTANTS

The ultra-violet spectra of the 2-(pyrimidin-2'-yl)acetic acids and their methyl esters were necessary for the detection and quantitative determination of zwitterionic species. Because of the large differences between the spectra of neutral and protonated pyrimidines, a useful procedure involves comparison between the spectra of each acid at various pH values with those of the corresponding methyl ester over the same range. In such a method for detecting zwitterions, it is assumed that the spectrum of the "neutral" acid will closely resemble that of the ester if the former is non-zwitterionic; however, it will approach that of the ester cation as the zwitterionic contribution to the "neutral" acid becomes greater (Albert and Serjeant, 1971). Table 3 lists the pK\(_a\) values as determined. pK\(_a^1\) (i.e. protonation of the pyrimidine ring) was determined spectrophotometrically; pK\(_a^2\) (protonation of the acid anion), potentiometrically, according to the method of Albert and Serjeant (1971). Further details of the measurements are given at the end of Chapter 5.

The pK\(_a\) of methyl 2-(pyrimidin-2'-yl)acetate is 0.53 and the carboxy group would be expected to have a base-weakening effect similar to that of the methoxycarbonyl group. Thus the (basic) pK\(_a^1\) for the acid is expected to be about 0.5; its measured value is 0.58. The measured (acidic) pK\(_a^2\) for the acid is 3.65, thus since the basic
**TABLE 3**

$pK_a$ Values of 4-Substituted Pyrimidin-2-ylacetic Acids and Methyl Esters $^a$

<table>
<thead>
<tr>
<th>4-R</th>
<th>$pK_a^1$</th>
<th>$pK_a^2$</th>
<th>$pK_E$</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>0.58</td>
<td>3.65</td>
<td>0.53</td>
</tr>
<tr>
<td>Me</td>
<td>1.35</td>
<td>3.86</td>
<td>1.42$^e$</td>
</tr>
<tr>
<td>Pr$^i$</td>
<td>1.56</td>
<td>3.90</td>
<td>1.58</td>
</tr>
<tr>
<td>Bu$^t$</td>
<td>1.75</td>
<td>3.95</td>
<td>1.74</td>
</tr>
<tr>
<td>Ph</td>
<td>1.45</td>
<td>3.73</td>
<td>1.45</td>
</tr>
<tr>
<td>OMe</td>
<td>1.81</td>
<td>4.22</td>
<td>2.05</td>
</tr>
<tr>
<td>SEt</td>
<td>1.96</td>
<td>4.15</td>
<td>1.97</td>
</tr>
<tr>
<td>SO$_2$Et</td>
<td></td>
<td>3.47</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td></td>
<td>3.63</td>
<td></td>
</tr>
<tr>
<td>Cl</td>
<td></td>
<td>3.60</td>
<td>-0.77$^f$</td>
</tr>
<tr>
<td>Br</td>
<td></td>
<td>3.67</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>-0.37</td>
<td>3.68</td>
<td>-0.57$^f$</td>
</tr>
</tbody>
</table>
### TABLE 3 (page 2)

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\delta_1$</th>
<th>$\delta_2$</th>
<th>$\delta_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>4,6-C\textsubscript{12}</td>
<td>3.34</td>
<td>-2.6</td>
<td>$f$, $g$</td>
</tr>
<tr>
<td>4,6-(OMe)\textsubscript{2}</td>
<td>1.23</td>
<td>3.89</td>
<td>1.07</td>
</tr>
<tr>
<td>4,6(SEt)\textsubscript{2}</td>
<td>1.23</td>
<td>4.04</td>
<td>1.13 $f$</td>
</tr>
<tr>
<td>4-Cl-6-OMe</td>
<td>3.66</td>
<td>-1.44</td>
<td>$f$, $g$</td>
</tr>
<tr>
<td>4-Cl-6-Me</td>
<td>3.75</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### FOOTNOTES TO TABLE 3

- $a$ $t = 21.5^\circ$.
- $b \pm 0.03$ or better.
- $c \pm 0.06$ or better.
- $d \pm 0.04$ or better.
- $e$ ethyl ester.
- $f$ in 5% aqueous methanol.
- $g \pm 0.2$. 

Any substituent which was base-strengthening was, in principle, likely to give rise to a certain amount of s
twitter since any effect on the carboxyl group, because of its more remote location, would be proportionately less. 
For example, the alkyl groups increased the base strength by up to 1.2 units while decreasing the acid strength by only 0.3 units. Thus some s
twittering contribution was
\( pK_a \) is more than three units below that of the acidic \( pK_a \), the presence of any zwitterion appears unlikely.

Comparison of the spectrum of 2-(pyrimidin-2'-yl)acetic acid with that of its methyl ester confirmed this (see Fig.1): at pH 2.5 the shape and absorbance maximum of the acid closely resembled those of the ester. At this pH, only 1% of the molecules will exist in the cationic form and >90% will be the neutral molecules. The infra-red spectra of the sodium salt of the acid and of the free acid confirmed the absence of any significant zwitterionic contribution (see later). The spectrum of the anion resembled that of the neutral molecule with a slight reduction in intensity. It was reasonable to assume that any pyrimidin-2-ylacetic acid containing a base-weakening substituent would exist similarly in a non-zwitterionic form: this was confirmed by spectral comparisons. For example, Fig.2 shows the spectrum of sodium 2-(4'-iodopyrimidin-2'-yl)acetate (\( pK_a \) 3.68) and its methyl ester. An absorption at about 290 nm was evident at \( H_0 \) -1 due to the protonated species. The iodopyrimidine decomposed at lower \( H_0 \) values and the absorbance of the cation was therefore obtained by extrapolation (see Experimental Section).

Any substituent which was base-strengthening was, in principle, likely to give rise to a certain amount of zwitterion since any effect on the carboxyl group, because of its more remote location, would be proportionately less. For example, the alkyl groups increased the base strength by up to 1.2 units while decreasing the acid strength by only 0.3 units. Thus some zwitterionic contribution was
FIG. 2

A

\[ \text{A} \]

\[ \lambda \text{(nm)} \]

1. H<sub>2</sub>O -1
2. pH 2.5

\[ \text{CH}_2\text{CO}_2\text{Na} \]

\[ \text{CH}_2\text{CO}_2\text{Me} \]

\[ \text{H}_2\text{O} \]
likely in this case. However simple spectral comparisons became difficult because of the possibility of overlapping pK_a values. This is indicated in Fig. 3 which shows spectral curves for the 4-phenyl acid and its methyl ester. The basic pK_a of the ester was 1.45 and this would be close to (but not the same as) the analogous value for the acid. The second pK_a of the acid was 3.73 and thus at pH 3.0, the acid would be 85% protonated and the pyrimidine ring about 2% protonated. At lower pH values there would be a greater contribution from the cationic species; thus although it is apparent that the spectrum of the neutral species would resemble that of the ester, a small proportion of zwitterionic species could not be ruled out. The same kind of dilemma was found in the 4-alkylpyrimidinylacetic acids, except that the absorbance maxima of the anion, neutral molecule, and cation were about the same, making any estimation of the spectrum of the neutral molecule even more inexact. The situation was even less clear in the case of 2-(4'-methoxypyrimidin-2'-yl)acetic acid, illustrated in Fig. 4. At pH 4.82, the spectrum of the acid resembled that of the neutral ester but at pH 3.0 it was impossible to gauge the contribution from zwitterion and the protonated acid (pK_a c. 2.0). Green and Tong (1956) determined the zwitterionic ratios for the pyridine-carboxylic acids using the assumption that the basic pK_a values of the esters were equal to those of the acids. Blanch (1966) used the same assumption in treating the pyridylacetic acids. This assumption, initially due to Ebert (1926) and Wegscheider (1902) has been shown to be
FIG. 3

1. pH 6.7
2. pH 3.0
3. cation

1. pH 6.7
2. pH 3.0
3. cation
incorrect (Bryson et al. 1963; Serjeant, 1969). An alternative method was used to determine the amounts (if any) of zwitterion present at the isoelectric point. Fig. 5 indicates schematically the situation to be considered. The equilibrium constants $K_\delta$, $K_\beta$, etc. are the true "microscopic" values for the equilibria indicated. $K_Z$ is the zwitterionic equilibrium constant and is a ratio of the relative concentrations of (3-1) and (3-2). It has already been illustrated that when $R=H$, $K_Z=0$ and $pK_a^1=pK_\beta^1$. From Table 3 it is seen that $pK_\beta - pK_E = 0.05$ for the unsubstituted compound (3-2; $R=H$). In general, determination of $pK_a^1$ was complicated by the fact that the value for the absorbance of the neutral-molecular species, $A_m$, could not be obtained directly because of contributions from anionic and cationic species. This was true even for the unsubstituted compound (3-2; $R=H$) where no zwitterion was present. Since the overlap of $pK_a$ values was not great (at worst about 2.2 units for the 4-ethylthio acid) the absorbance for the neutral species was determined by an extrapolation procedure using the value for the absorbance of the cation together with values of $A$ measured in the region of the $pK_a$. From this absorbance, a value for the extinction coefficient for the molecular species, $\varepsilon_m$, could be calculated. When $K_Z$, the zwitterionic equilibrium constant was zero, the value of $\varepsilon_m$ would be equal to the value for the neutral acid, $\varepsilon_0$, but in general it would be a composite value derived from a mixture of (3-1) and (3-2). The assumption was then made that the extinction coefficient,
Fig. 5

\[ \text{(3-1)} \]

\[ \text{(3-2)} \]
£ of the neutral molecule was equal to that for the ester, \( \varepsilon_{\text{ester}} \). This seemed a reasonable assumption and it was supported by the data for those acids which showed no zwitterion character. The zwitterionic ratio was then calculated from the expression:

\[
K_Z = \frac{\varepsilon_{\text{ester}} - \varepsilon_m}{\varepsilon_m - \varepsilon_{\text{cation}}}.
\]

This was essentially the method of Bryson et al. (1963) using an alternative method to calculate \( \varepsilon_m \). Detailed examples of calculations are shown at the end of Chapter 5. Table 4 shows the ultra-violet spectral data for the acids. In the cases where zwitterions were present, the value of the extinction coefficient, \( \varepsilon_m \) for the neutral species was an extrapolated value and a composite figure from neutral and zwitterionic forms of the acid. The "microscopic" equilibrium constants, \( K_\alpha, K_\beta, K_\gamma, K_\delta \) could then be evaluated using the experimentally determined \( pK_a^1 \) and \( pK_a^2 \) values and the relationships first derived by Adams (1916):

\[
K_a^1 = K_\alpha + K_\beta
\]

\[
\frac{1}{K_a^2} = \frac{1}{K_\gamma} + \frac{1}{K_\delta}
\]

\[
K_Z = \frac{K_\alpha}{K_\beta} = \frac{K_\gamma}{K_\delta}
\]

The values of \( pK_\alpha, pK_\beta, pK_\gamma \) and \( pK_\delta \) determined in this way are tabulated in Chapter 4, together with the zwitterionic ratios where the factors affecting these equilibria are discussed. The basic \( pK_a \) values of the 4-fluoro and 4-ethylsulphonyl compounds were too unstable in acidic media to be measured.
### TABLE 4

ULTRAVIOLET SPECTRA OF 4-SUBSTITUTED PYRIMIDINES AND METHYL ESTERS IN WATER

<table>
<thead>
<tr>
<th>4-R</th>
<th>Species&lt;sup&gt;a&lt;/sup&gt;</th>
<th>(\lambda \text{&lt;sup&gt;b&lt;/sup&gt;}&lt;br&gt;\log c)</th>
<th>ACID</th>
<th></th>
<th>Ester</th>
<th>(\lambda \text{&lt;sup&gt;b&lt;/sup&gt;}&lt;br&gt;\log c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>-</td>
<td>248, 256, 244</td>
<td>3.42, 3.29, 3.36</td>
<td>248, 256, 244</td>
<td>3.44, 3.29, 3.36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>246</td>
<td>3.43&lt;sup&gt;d&lt;/sup&gt;</td>
<td>246, 274, 240</td>
<td>3.55, 3.39, 2.46</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>250</td>
<td>3.63</td>
<td>250</td>
<td>3.64</td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>-</td>
<td>248, 275</td>
<td>3.55, 2.70</td>
<td>248, 275</td>
<td>3.57, 2.54</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>248</td>
<td>3.57&lt;sup&gt;d&lt;/sup&gt;</td>
<td>248, 275</td>
<td>3.57, 2.54</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>250</td>
<td>3.75</td>
<td>250</td>
<td>3.75</td>
<td></td>
</tr>
<tr>
<td>Pr&lt;sup&gt;1&lt;/sup&gt;</td>
<td>-</td>
<td>250, 275</td>
<td>3.54, 2.49</td>
<td>250, 275</td>
<td>3.60, 2.65</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>250</td>
<td>3.59&lt;sup&gt;d&lt;/sup&gt;</td>
<td>250, 275</td>
<td>3.57, 2.54</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>250</td>
<td>3.75</td>
<td>250</td>
<td>3.75</td>
<td></td>
</tr>
<tr>
<td>Bu&lt;sup&gt;1&lt;/sup&gt;</td>
<td>-</td>
<td>250, 275</td>
<td>3.58, 2.60</td>
<td>250, 275</td>
<td>3.60, 2.65</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>250</td>
<td>3.59&lt;sup&gt;d&lt;/sup&gt;</td>
<td>250, 275</td>
<td>3.57, 2.54</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>250</td>
<td>3.75</td>
<td>250</td>
<td>3.75</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>-</td>
<td>276, 250</td>
<td>4.01, 3.80</td>
<td>276, 250</td>
<td>4.07, 3.82</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>276, 248</td>
<td>4.01, 3.76&lt;sup&gt;e&lt;/sup&gt;</td>
<td>276, 250</td>
<td>4.07, 3.82</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>310</td>
<td>4.17</td>
<td>310</td>
<td>4.10</td>
<td></td>
</tr>
<tr>
<td>OMe</td>
<td>-</td>
<td>252</td>
<td>3.59</td>
<td>250</td>
<td>3.58</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>250</td>
<td>3.69&lt;sup&gt;d&lt;/sup&gt;</td>
<td>250</td>
<td>3.58</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>240</td>
<td>3.82</td>
<td>240</td>
<td>3.82</td>
<td></td>
</tr>
<tr>
<td>SET</td>
<td>-</td>
<td>256, 284</td>
<td>3.84, 3.89</td>
<td>258, 285, 300</td>
<td>3.85, 3.89, 3.24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>258, 286</td>
<td>3.79, 3.88&lt;sup&gt;d&lt;/sup&gt;</td>
<td>258, 285, 300</td>
<td>3.85, 3.89, 3.24</td>
<td></td>
</tr>
<tr>
<td>SO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>-</td>
<td>260, 254, 265</td>
<td>2.49, 2.44, 2.43</td>
<td>256, 253, 264</td>
<td>3.56, 3.53, 3.44</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>256, 253, 264</td>
<td>2.56, 2.53, 2.43</td>
<td>256, 253, 264</td>
<td>3.56, 3.53, 3.44</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Cl</td>
<td>Br</td>
<td>F</td>
<td>4,6-C1₂</td>
<td>4,6-(OEt)₂</td>
</tr>
<tr>
<td>--------</td>
<td>---------</td>
<td>----------</td>
<td>----------</td>
<td>---------</td>
<td>----------</td>
<td>------------</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>264</td>
<td>256</td>
<td>256</td>
<td>242</td>
<td>258,254,264</td>
<td>248</td>
</tr>
<tr>
<td></td>
<td>3.75</td>
<td>3.56</td>
<td>3.60</td>
<td>3.42</td>
<td>3.66,3.65,3.54</td>
<td>3.39</td>
</tr>
<tr>
<td></td>
<td>262</td>
<td>252</td>
<td>252</td>
<td>242</td>
<td>3.70,3.66,3.55</td>
<td>252</td>
</tr>
<tr>
<td></td>
<td>3.78</td>
<td>3.57</td>
<td>3.61</td>
<td>3.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>3.76°</td>
<td></td>
<td></td>
<td>3.61°</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>300,254</td>
<td>3.90</td>
<td></td>
<td>3.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>300,254</td>
<td></td>
<td>4.03°</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FOOTNOTES TO TABLE 4

a  Neutral species; +, cation; -, anion. Spectra were measured 3pH units from the pKₐ unless otherwise noted.

b Shoulders and inflections are underlined.

c Obtained by extrapolation.

d Ester in 5% aqueous methanol.
INFRARED SPECTRA

(a) Sodium pyrimidinylacetates

The infrared spectrum of sodium 2-(pyrimidin-2'-yl) acetate and the free acid (obtained by neutralization with DCl) were measured in D$_2$O and are shown in Fig.6. The salt showed the characteristic absorption at 1555 cm.$^{-1}$ for the $-\overset{\equiv}{C}\overset{\equiv}{O}_{\text{as}}$ asymmetric stretching vibration. Acetate salts absorb strongly between 1600 and 1550 cm.$^{-1}$ (Vratny et al. 1961). The upper trace of Fig.6 shows a broad absorption at 1710-1720 cm.$^{-1}$ due to the carbonyl of the group. The remaining band at 1580 cm.$^{-1}$ must be due, at least in part to the skeletal vibration of the pyrimidine ring (Short and Tompson, 1952). The presence of any zwitterion would be revealed by an absorption due to the pyrimidinium species. The peak at 1610 cm.$^{-1}$ might conceivably be a small contribution from a protonated species. The second trace of Fig.6 was taken after 2 h and it can be seen that the 1610 cm.$^{-1}$ absorption has increased relative to the carbonyl band. This suggests that it may have been due to a pyrimidine ring vibration and that the change in spectrum was a consequence of decarboxylation.

The spectrum of sodium 2-(4'-methoxypyrimidin-2'-yl) acetate (Fig.7) similarly showed a strong absorption at 1585 cm.$^{-1}$ due to the ionized carboxylate group. However, neutralization in this case produced, as well as a band at 1710 cm.$^{-1}$ due to the carbonyl group, a sharp band at
FIG. 6

[Graph depicting infrared spectra with wavenumbers in cm⁻¹ and absorbance values]
FIG. 7

The bands between 1600 and 1800 cm$^{-1}$ in the figure composite, mostly from pyridazine skeletal vibrations and those due to the
unsaturated contribution. The spectrum of the compounds rests in that it illustrates the effect of intramolecular hydrogen bond formation on the carbonyl frequencies. The carbonyl frequencies can also be attributed to the
intramolecular hydrogen bond formation.
1635 cm\(^{-1}\) which must reasonably be attributed to the protonated pyrimidine ring. The bands between 1550 and 1600 cm\(^{-1}\) in Fig.7 were composite, mostly from pyrimidine skeletal vibrations and those due to the \(-\text{C}^=\text{O}\)- group. Thus the infra-red spectrum of the unsubstituted acid supported the evidence from the ultraviolet spectra for lack of substantial zwitterion in the parent acid and indicated a significant zwitterionic contribution in the 4-methoxy acid.

(b) Methyl 2-(1',6'-dihydro-6'-oxopyrimidin-2'-yl)acetate

The spectrum of this compound proved interesting in that it illustrated the effect of intramolecular hydrogen bond formation on a carbonyl absorption in the infra-red region. Fig.8 compares its spectrum (in KBr) with that of the 4-chloro ester (neat liquid). The usual strong band at 1750 cm\(^{-1}\) due to the carbonyl of the ester group was absent in the 4-oxo compound. This can be ascribed to hydrogen bonding of the carbonyl oxygen to the proton on the ring nitrogen as indicated in (3-3) with subsequent displacement of the absorption by \(\text{ca. 50 cm}\(^{-1}\); it was indicative of a quite strong hydrogen bond (Nakanishi, 1962).
In Chapter 2, the assignment of structure (3-4) to the second product of condensation of ethyl benzylacetate with amidoguanidine rather than (3-5) was based on analogy with the 4-ethyl compound. The 1H NMR spectrum of the phenyl compound was also consistent with this structure. Fig. 3 shows the spectrum (in the scheme proton notation) of the pyridine compared with that of the unknown pyridine. The spectrum clearly showed two complex sets of signals in the intensity ratio 2:3. The autopisochronous low field was well resolved, that is, higher field to the α- and β-protons (Murrell et al. 1960). In contrast, the pyridine showed a broadened singlet. This was understandable in the light of work by Murrell et al. (1960) who showed that C-phenyl rings attached to the nitrogen atom of a heterocyclic ring (e.g., C-phenylpyridine) gave rise to α-proton signals well separated from those of the α- and β-protons, giving a pattern similar to that in Fig. 3b. This indicated that the phenyl ring in the pyridine (3-4) was not α to the ring nitrogen and that α- and β-protons therefore have been in the 4-position. The difference between the signals due to the α- and β-protons has been given the symbol Δ. This value for the pyridine in Fig. 3b is 0.50 ppm. Such a separation has been attributed to several causes (Murrell et al. 1960; Chattopadhyay and Basu, 1967; Bergmann et al. 1979): (i) a long range ring current effect, (ii) changes in σ electron densities.
NUCLEAR MAGNETIC RESONANCE SPECTRA

In Chapter 2, the assignment of structure (3-4) to the second product of condensation of ethyl benzoylacetate with amidinoacetamide rather than (3-5) was based on analogy with the 4-methyl compound. The n.m.r. spectrum of the phenyl compound was also consistent with this structure: Fig.9 shows the spectrum (in the aromatic proton region) of the pyridine compared with that of the isomeric pyrimidine. The pyrimidine clearly showed two complex sets of signals in the intensity ratio 2:3. The multiplet at low field was assigned to the o-protons, that at higher field to the m- and p-protons (Murrell et al. 1965). In contrast, the pyridine showed a broadened singlet. This was understandable in the light of work by Murrell et al. 1965: they showed that o-phenyl rings attached α to the nitrogen atom of a heterocyclic ring (e.g. 2-phenylpyridine) gave rise to o-proton signals well separated from those of the m- and p-protons, giving a pattern similar to that in Fig.9B. This indicated that the phenyl ring in the pyridine (3-4) was not α to the ring nitrogen and that it must therefore have been in the 4-position. The difference between the signals due to the o- and m/p-protons has been given the symbol Δ. This value for the pyrimidine in Fig.9B is 0.50ppm. Such a separation has been attributed to several causes (Murrell et al. 1965; Spotswood and Tanzer, 1967; Bergmann et al. 1974): (i) a long range ring current effect; (ii) changes in π electron densities;
In a study by Hückel (1968) the difference to different orientations of the attached groups were also examined. The orientation of the neighbouring ring and the electrostatic field effect of the amine group was equally effective in describing the spectra relative to the amine-proton of the attached ring.

The electrostatic field effect of the amine group on the screening of a hydrogen atom was observed through the screening of a hydrogen atom on the amine group. The effect is a combination of ring current and localized effects of nitrogen atom indicated in a comparison of the spectra of 6-chlorophenyl, 4-nitrophenyl, and 4-chloro-phenyl derivatives (Fig. 9).

While the values of the NMR spectra and H appeared in the spectra of the amine groups, and no region remained the spectra with regard to the H groups.
(iii) nitrogen magnetic anisotropy; (iv) perturbation of the electronic environment by CH···N interaction; (v) solvent effects; and (vi) changes in the degree of co-planarity of the two rings. Thus Bergmann (1974) in a study of 8-phenylpurines attributed the difference to different orientations of the phenyl ring brought about by steric interactions with N-substituents in the imidazole ring. Murrell et al. (1965) in a study of azabiphenyls also argued that the phenyl rings assumed different orientations with respect to the second ring, although they also took account of other effects mentioned above. Spotswood and Tanzer however proposed that diamagnetic anisotropy of the neighbouring ring and the electrostatic field effect of the nitrogen lone pair [(iv) above] were equally effective in deshielding the o-protons relative to the m/p-protons of the attached ring.

The electrostatic field effect of a polar molecule on the screening of a hydrogen atom was first discussed by Buckingham (1960) and could produce deshielding or shielding depending on its direction along the C-H bond in question. That the effect is a combination of ring current and localized effects of nitrogen was indicated in a comparison of the spectra of 5-chloro-2-phenyl, 2-amino-5-phenyl and 2-isopropyl-4-phenylpyrimidine (Fig.10) where the values of $\Delta$ are 1.03 and 0.60 for the 2- and 4-phenyl compounds, respectively. The spectrum of the 5-phenyl compound was not resolvable into distinct o- and m/p-regions and resembled the spectrum of biphenyl.
(DMSO did not noticeably affect the spectrum of 4-phenylpyrimidines when substituted for carbon tetrachloride as solvent.) For the 4-phenylpyrimidines, the value of $\Delta$ was independent of the substituents about the ring when measured in carbon tetrachloride and had a value of 0.58 ± 0.02. The non-equivalence of the 5-phenyl protons in Fig.10C was presumably mainly due to ring current effects and inductive electron withdrawal of the pyrimidine ring. The ring current effect in six-membered nitrogen heterocycles is 95-98% that of benzene and is presumably constant at constant distance from the ring (Hall et al. 1962). Gil and Murrell (1964) have showed that the o-proton on one ring will be little affected by the magnetic anisotropy of the nitrogen on the other.

In order to examine the possible origin of this effect more closely, the spectrum of 2-isopropyl-4-phenylpyrimidine was measured in deuterated methanol at four temperatures down to -110°. This procedure was adopted in order to detect any possible "freezing out" of a preferred conformation of the phenyl ring. The four spectra at 100 MHz (Fig.11) showed little change from ambient temperature (32°) to -110° except for general broadening. The value of $\Delta$ is unaltered between the two extremes. The only effect appeared to be a downfield shift of H-5 relative to H-6 and this could be attributed to stacking of the rings at lower temperatures. A decoupling experiment was carried out at room temperature to test the equivalence of the o-protons. Fig.12 indicates the effect of irradiating the signals due to the m- and p-protons: the
FIG. 11

AROMATIC REGION
100 MHz
MeOH (d₄)
FIG. 11 Cont.
FIG. 12

The signal received for the aromatic nucleus due to decoupling with the proton resonance of the quaternary nitrogen was also about 1 Hz. The coupling between the two sets of the signal of H2 was shown by decoupling (Danon et al., 1962) and dephasing by a 180° pulse. A value of 5 Hz for the difference in chemical shift for the H1A and H1B nuclei (D'Andrea, 1977; Fople et al., 1980) suggests that the carbon to carbon bond is not equivalent. The fact that there was no change in the spectrum as the temperature was lowered suggests that the non-equivalence is not due to conformational effects. The non-equivalence might suggest that the phenyl rings are in a conformation which was energetically favored for all temperatures below -100°C. This conformation might be closer to ortho-phenol than biphenyl (interplanar angle 20°). In solution, (Ishii et al., 1979) reports of a temperature dependency of the phenyl protons. This has little effect on the shift of H2, but it is clear that a hydrogen atom (originally close to H2) can be less than a hydrogen atom (originally distant from H2) by about 1 Hz when decoupling is applied.
signal from the o-protons did not collapse to a singlet but showed a distinct AB quartet indicating that (at 32\(^0\)) the protons were not equivalent. The coupling between the two was of the order of 1Hz, i.e. normal \(m\)-coupling (Banwell, 1961) and the separation between the doublets was also about 1Hz. The signal resembled that obtained for non-equivalent nuclei due to slow rotation about a partial double bond close to the point of coalescence. A value of 1 Hz for the difference in chemical shifts gave an upper limit to \(k(= \pi \Delta V_0 \sqrt{2})\) where \(\Delta V_0\) is chemical shift difference) of about 2-3 \(\text{sec}^{-1}\) (cf. Gasparro and Kolodny, 1977; Pople et al. 1959). That the ortho protons were not equivalent contradicted the claim by Murrell et al. (1965) that there was rapid rotation about the single bond in 4-phenylpyrimidine based on the (unsubstantiated) claim that the o-protons of the phenyl ring were equivalent. The fact that there was little change in the spectrum as the temperature was lowered, together with the non-equivalence of the ortho-protons, might suggest that the phenyl ring had a preferred conformation which was energetically favoured for all temperatures between 32\(^0\) and -110\(^0\). This conformation might be closer to co-planarity than biphenyl (interplanar angle 20\(^0\) in solution; Suzuki, 1959) because of a lessening of o-hydrogen interaction. Because of the polarizability of the lone pair, "size" has little meaning (Armarego, 1977) but evidence has been presented indicating that the steric requirements of a nitrogen lone pair can be less than a hydrogen atom (Brignell et al. 1966, 1968). A greater
The contribution from canonical forms of type (3-6) would provide an incentive for calculation.

Spotswood and Tanzer (1967) examined the electron-donating effect of the nitrogen lone pair as a factor in determining the character of the spectra of bipyridyls. They claimed that, in strongly hydrogen bonding solvents, the contribution to the shielding of the high-proton by the 2:2'-bipyridyl is completely suppressed. Their investigation indicated a contribution of about 170 ppm due to the electron-donating nitrogen. The solvent effect was equally apparent with 2,6-diphenylpyrimidines. The spectrum of compound 9 in DMSO and that of the methyl ester in CaCl₂. To this extent, the effect of hydrogen bonding decreases on solvolysis by about 20 ppm. The addition of D₂O to the 9-dichloride did not noticeably affect the aromatic signals. If it was assumed that the hydrogen bonding removes the electron-donating effect of the lone pair, then the contribution to deshielding of 9₂ and 9₃₄ was about 80 ppm. However, this was only an average value due to the nitrogen affecting both protons. Thus when 9₂ "sees" the full effect of the nitrogen, 9₃₄ is far enough away to be unaffected. This is not true of 2,2'-bipyridyl, where the preferred conformation is some equatorial and 69(2') always "sees" a nitrogen atom. Thus for a comparison with Spotswood and Tanzer's work, the difference should be doubled giving 0.7 ppm. The agreement then becomes good.
contribution from canonical forms of type (3-6) would also provide an incentive for coplanarity.

Spotswood and Tanzer (1967) examined the electrostatic field effect of the nitrogen lone pair as a factor in determining the character of the spectra of bipyridyls. They claimed that, in strongly hydrogen bonding solvents, the contribution to deshielding of the H3(3') protons in 2,2'-bipyridyls by the nitrogen of the second ring was completely suppressed. This investigation indicated a contribution of about 0.75ppm due to the electrostatic dipole. The solvent effect was equally apparent with 4-phenylpyrimidines. Fig. 13 shows the spectrum of sodium 2-(4'-phenylpyrimidin-2'-yl)acetate in D₂O and that of its methyl ester in CDCl₃. In this instance, on going from chloroform to the strongly hydrogen bonding deuterium oxide as solvent the value of Δ decreases by 0.36ppm. Addition of DCl to the sodium salt did not noticeably affect the aromatic signals. If it was assumed that the hydrogen bonding removes the electrostatic effect of the lone pair, then the contribution to deshielding of H_A and H_B was 0.36ppm. However, this was only an average value due to one nitrogen affecting both protons. Thus when H_A "sees" the full effect of the nitrogen, H_B is far enough away to be unaffected. This is not true of 2,2'-bipyridyl, where the preferred conformation is trans coplanar and H3(3') always "sees" a nitrogen atom. Thus for a comparison with Spotswood and Tanzer's work, the difference should be doubled giving 0.72ppm: the agreement then becomes good.
A further example of the long-range deshielding effect of the nitrogen lone pair can be seen in the spectrum of 2-isopropenylpyrimidine (Fig.14) compared with the benzenoid analogue, α-methylstyrene. In the latter, the signals from \( H_A \) and \( H_B \) were separated by 0.31ppm, the signal at lower-field being assigned to \( H_A \). The difference between the two vinyl protons of the heterocyclic compound (3-7) was 0.97ppm. If it is assumed that ring current effects were producing the same difference in the chemical shifts of \( H_A \) and \( H_B \), then the difference between these two values (0.66ppm) might reasonably be attributed to the contribution from the dipole moment of the nitrogen lone pair. This value might in fact represent the lower limit to this contribution since it represents the difference in the effect between \( H_A \) and \( H_B \). The distance between \( H_A \) and the nitrogen of the heterocyclic ring was estimated to be about 2.7 Å using molecular models. This distance was very close to the distance between the α-protons of the 4-phenyl ring and N-3 of the pyrimidine in Fig.11. The contribution to deshielding by the lone pair was thus of the same magnitude for both, and the value of 0.66ppm was again consistent with the work of Spotswood and Tanzer.

Interestingly, the spectrum of the epoxide of 2-isopropyl-4-phenylpyrimidine (Fig.15) showed no apparent contribution from the nitrogen dipole to the difference in chemical shifts between \( H_A \) and \( H_B \). This latter value is 0.54ppm and that for styrene oxide 0.35ppm. The difference
FIG. 14

It is known that a cyclopropane ring has a preferred bimetric conformation when interacting with an electron-deficient centre (Eisma and Olan, 1966; Been et al., 1985; Braun and Cleveland, 1978). If this was so with the azepane ring, H_A and H_B would be "above" the plane of the ring and farther from the nitrogen lone pair. This might then lessen electrostatic effects, especially if they were sensitive to steric effects. However, the side-chain is likely to lie in the plane with the azepane ring to minimize overlap of orbitals.
was possibly in part due to extra shielding effects of the methyl group in the former. This reduced effect of the lone pair may lie in a conformational preference of the three-membered ring. It is known that a cyclopropane ring has a preferred bisected conformation when interacting with an electron-deficient centre (Pitman and Olah, 1965; Deno et al. 1965; Brown and Cleveland, 1976). If this was so with the epoxide ring, $H_A$ and $H_B$ would be "above" the plane of the ring and further from the nitrogen lone pair. This might then lessen electrostatic effects, especially if they were sensitive to orientation. The olefin side-chain is likely to be co-planar with the pyrimidine ring to maximize overlap of orbitals.
The mass spectra of 2-phenylpyridine is shown in Fig. 15. The intense base ion at m/z 167 and 165 peaks for this spectrum and for the 3-phenyl and 4-phenyl isopropylpyridines are collected in Table 6. These spectra had a number of features in common: (1) a prominent molecular ion m/z 167, (2) an m/z -1 peak of somewhat intensity and (3) a base peak corresponding to the sum of Intensities. The peak intensity of the peak in question was determined by the base peak of the molecular ion 167 (the target base peak). This method of presentation helps eliminate variations between individual spectra due to the composition of peak areas in different samples (whether meaningful (significant) or not). 

The intensity in the 2-phenyl spectrum is much greater than that derived from pyridine and its anologue. Wrench et al. (1968) reported a value of \( I_0 \) of only 0.49 and 0.56 for the peak at m/z 167. The presence of the hydrocarbon was described as the fact that loss of the tertiary hydroxyl would yield the carbonyl ion (165) which can be stabilized by rearrangement to a propylcation (163) only by migration of a methyl group.
2-Isopropylpyrimidines

The mass spectrum of 2-isopropylpyrimidine is shown in Fig.16. The intensity data of the \( M^+ \), \( M^+-1 \) and \( M^+-15 \) peaks for this spectrum and for the 4-methoxy and 4-chloro-2-isopropylpyrimidines are collected in Table 5. These spectra had a number of features in common: (a) a prominent molecular ion \( M^+ \), (b) an \( M^+-1 \) peak of comparable intensity and (c) a base peak corresponding to \( M^+-15 \). The peak intensities, \( I \), are given as the ratio between the intensity of the peak in question and \( \Sigma_{25} \), the latter representing the sum of intensities of all peaks (≥ 5% base peak) from mass 25 to the molecular ion (or the largest detectable ion).

\[
I_{M-X} = \frac{\text{Intensity of } M-X}{\Sigma_{25}} \times 100.
\]

This method of presentation helped eliminate variations between individual spectra and made comparison of peaks more meaningful (Biemann, 1962).

The intensity of the \( M^+-1 \) fragment was much greater than that derived from the homocyclic isopropylbenzene. Franck et al. (1968) reported a value of \( I_{M-1} \) of only 0.43% for this compound compared to 8.4% for the heterocyclic analogue. The low intensity of the \( M^+-1 \) peak of the hydrocarbon was ascribed to the fact that loss of the tertiary hydrogen would yield the carbonium ion (3-8) which can be stabilized by rearrangement to a tropylium ion (3-9) only by migration of a methyl group. Such migrations, it
## TABLE 5

**MASS SPECTRAL DATA FOR 4-SUBSTITUTED 2-ISOPROPYL PYRIMIDINES**

<table>
<thead>
<tr>
<th>4-Substituent</th>
<th>m/e</th>
<th>I(%)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>122</td>
<td>8</td>
<td>M⁺</td>
</tr>
<tr>
<td></td>
<td>121</td>
<td>9</td>
<td>M⁺-1</td>
</tr>
<tr>
<td></td>
<td>107</td>
<td>34</td>
<td>M⁺-15</td>
</tr>
<tr>
<td>OMe</td>
<td>152</td>
<td>9</td>
<td>M⁺</td>
</tr>
<tr>
<td></td>
<td>151</td>
<td>5</td>
<td>M⁺-1</td>
</tr>
<tr>
<td></td>
<td>137</td>
<td>29</td>
<td>M⁺-15</td>
</tr>
<tr>
<td>Cl</td>
<td>158</td>
<td>1</td>
<td>M⁺</td>
</tr>
<tr>
<td></td>
<td>157</td>
<td>2</td>
<td>M⁺-1</td>
</tr>
<tr>
<td></td>
<td>156</td>
<td>4</td>
<td>M⁺</td>
</tr>
<tr>
<td></td>
<td>155</td>
<td>6</td>
<td>M⁺-1</td>
</tr>
<tr>
<td></td>
<td>143</td>
<td>8</td>
<td>M⁺-15</td>
</tr>
<tr>
<td></td>
<td>141</td>
<td>28</td>
<td>M⁺-15</td>
</tr>
</tbody>
</table>
The trimethylbenzene ions are not shown (Baron and Dierksen, 1967). The trimethylbenzene ions are strongly formed and can be readily (M-15 was 57%), enabling migration of N and formation of a stable tropylium ion. Although the base peak in the trimethylbenzene spectrum was at M + 15 of the M + 1 peak for the isopropylbenzene, 157 compared to 158 for the isopropylbenzene. Stabilization of the ion (3-10) by resonance was not a favourable process. Thus the reduced rate of solvolysis of the 2-propylxylene (Chapter 4) indicated that (in solution) such carbocation ions are less stable than the carbocyclic analogues. In addition, the N + 18 peak of 4-ethylpyridine was very weakly formed by the base peak of the carbenium ion (3-12) was demonstrated by the absence of carbenium ion (3-13) by the ring nitrogen of the 4-ethylpyridine was quite prominent although the value of δH was 0.99 compared to 0.76 (Dexter and Sheeks, 1972) implying greater electron withdrawal from the 4-position.

The N + 1 peak of 4-ethylpyridine was the base peak of the spectrum and this has been attributed to special stabilization of the ion (3-12) by formation of a "resonance current" (Flesher, 1966). This could occur in the various ions of the pyridylidine system as indicated in (3-14) to (3-18). Formation of (3-14) implies that formation of (3-16) occurred on the aromatic chain.
was pointed out, are not common (Brown and Djerassi, 1967). The ionized isopropylbenzene loses a methyl group much more readily (M-15 was 57%), enabling migration of ·H and formation of a stable tropylium ion. Although the base peak in the heterocyclic compounds also arises from an M+15 fragment, it appeared that some feature was conferring extra stability to the M+1 fragment. Thus the ratio IM-15 to IM-1 for the isopropylbenzene was 133 compared to 4 for the isopropylpyrimidine. Stabilization of the carbonium ion (3-10) by resonance was not a favourable process. Thus the reduced rate of solvolysis of the t-bromides (Chapter 4) indicated that (in solution) such carbonium ions are less stable than the carbocyclic analogues. In addition, the M+15 peak of 2-ethylpyridine was very weak, attributed to instability of the carbonium ion (3-11) due to electron-withdrawal from the 2-position by the ring nitrogen (Ridd, 1963). This explanation seemed inadequate however, since the M+15 peak for 4-ethylpyridine was quite prominent although the value of σ4N is 0.96 compared to σ2N 0.75 (Deady and Shanks, 1972) implying greater electron withdrawal from the 4-position.

The M+1 peak of 2-ethylpyridine was the base peak of the spectrum and this has been attributed to special stabilization of the ion (3-12) by formation of a 4-membered ring which rearranges to the tautomer (3-13) (Spiteller, 1966). Such a process could obviously apply to the pyrimidine system as indicated in (3-14) and (3-15). However, formation of (3-14) implies that ionization has occurred on the aliphatic chain. It seemed likely that
less of an electron from the nitrogen lone pair would occur in preference to this. Bourne et al. (1964) have calculated that removal of a non-bonding electron from nitrogen was the most favoured primary process. The ionisation potential of a lone pair electron to pyridine is 9.6 eV (Water et al., 1970) compared to a value of 12.1 eV for methane. Scheme 3 indicates formation of a diazo-alkene ion from the molecule via one of either of the following pathways. Intermediates with nitrogen lone pairs have been observed (e.g. the nitrosomethyl cation, Schleyer and Wendehinte, 1971). Schleyer and coworkers have shown that although the fragmentation patterns for diazoalkanes and (3-17) are similar to that of pyridine itself (Hill et al., 1988). It has been observed that pyridines with a side chain of 2 carbon lose the chain with hydrogen shift to the nucleus (Spittler, 1984). This mode of fragmentation would give rise to an ionized pyrimidine molecule (3-18) fragmenting with sequential loss of HCN (Hick et al., 1960). The spectra of the remaining diisopropylpyridiniums are interpretable on the basis of similar breakdowns.
loss of an electron from the nitrogen lone pair would occur in preference to this. Omura et al. (1957) have calculated that removal of a non-bonding electron from nitrogen was the most favoured primary process. The ionization potential of a lone pair electron in pyridine is 9.8 ev (Baker et al. 1970) compared to a value of 13.1 ev for methane. Scheme 3 indicates formation of a diazatropylium ion from the molecular ion by loss of either H· or CH₃· occurring via a three membered ring intermediate. Bridgehead carbonium ions have been observed (e.g. the 1-adamantyl cation, Schleyer and Nicholas, 1961; Schleyer et al. 1964) and although objections to azatropylium ions have been raised (Biemann, 1962) there appears to be no solid evidence against their existence.

Loss of HCN from the ions (3-16) and (3-17) accounts for the peaks at m/e 94 and 80 respectively. Interestingly, the spectrum of 2-isopropylpyrimidine up to m/e 80 was very similar to that of pyrimidine itself (Rice, et al. 1965). It has been observed that pyridines with a side chain of 2 carbons lose the chain with hydrogen shift to the nucleus (Spiteller, 1966). This mode of fragmentation would give rise to an ionized pyrimidine molecule (3-18) fragmenting with sequential loss of HCN (Rice et al. 1965). The spectra of the remaining 2-isopropylpyrimidines are interpretable on the basis of similar breakdowns.
SCHEME 3

\[ \text{m/e 122} \]

\[ \text{m/e 122} \rightarrow \text{m/e 122} \]

\[ (\text{3-16}) \]

\[ (\text{3-17}) \]
The mass spectrum of 2-(3'-bromo-2'-methylethyl)pyridinedione and the 4-phenyl, methoxy and chloro analogues were distinctive in the complete lack of detectable molecular ions and a very facile loss of bromine. The spectrum of the parent compound (Fig. 1) was similar to that of the corresponding olefin suggesting less of the former under electron impact. Thermal decomposition, although the bromo compound was expected to be at least 100°C less stable than the parent, gave the usual type of peaks at m/e 53 and 80, corresponding to the loss of the bromo and the olefin. The olefin peak is in the spectrum of both the parent bromo compound and the olefin. No special instability proposed for this type of ion by formation of a four-membered ring was mentioned. The methoxy compound showed a base peak corresponding to \( \text{C}_3\text{H}_3\text{N}^+ \) at m/e 53, 80 and 105 (3-18). No special stabilization was conferred on this fragment by the 4-methoxy group. The base peak for this compound was at m/e 150, the olefin, due perhaps to stabilization of the ion (3-21) by electron donation from the 4-dioxy. The base peak of the 4-chloro compound (Fig. 18) corresponded to m/e 80 giving \( \text{m/e} \) 105 and 127. Since the 4-phenyl substituent destabilizes the carbonium ion (3-22) in solution (Chapter 4), it was apparent that
2-(1'-Bromo-1'-methylethyl)pyrimidines

The mass spectrum of 2-(1'-bromo-1'-methylethyl)pyrimidine and the 4-phenyl, methoxy and chloro analogues were distinctive in the complete lack of detectable molecular ions and a very facile loss of bromine. The spectrum of the parent compound (Fig.17) was similar to that of the corresponding olefin suggesting loss of HBr under electron impact. Thermal loss was likely although the bromo compounds were stable up to at least 100°. The peak at m/e 121 corresponded in part to the carbonium ion formed from direct cleavage of the C-Br bond. This latter fragmentation is usually the one most preferred in aliphatic bromides and occurs preferentially to loss of HBr + H⁺ (Budzikiewicz, et al. 1967). Loss of HBr via 1,2 elimination gave the allylic carbonium ion (3-19) as the base peak in the spectrum of both the parent bromo compound and the olefin. The special stability proposed for this type of ion by formation of a four membered ring was mentioned earlier. The 4-methoxy compound showed a peak of low intensity corresponding to M⁺-Br at m/e 151 (3-20). No special stability was conferred on this fragment by the 4-methoxy group. The base peak for this compound was m/e 150, the ionized olefin, due perhaps to stabilization of the ion (3-21) by electron donation from the 4-0Me. The base peak of the 4-chloro compound (Fig.18) corresponded to M⁺-Br giving m/e 155 and 157. Since the 4-chloro substituent destabilizes the carbonium ion (3-22) in solution (Chapter 4), it was apparent that
such simple considerations of solvent obviously do not account for the initial products of cleavage of these compounds under electron impact.

1-Methoxy-1-methylallylpyridinium

The spectrum of the parent compound and the methoxy, phenyl and one analogues are experimentally as in the case of 11, and an extremely slow reaction of the pyridine radical (3-20) and the pyridinium radical (3-22) is again observed. The methanes still persist.
such simple considerations of solution reactivity do not account for the initial products of cleavage of these compounds under electron impact.

2-(1'-Methoxy-1'-methylethyl)pyrimidines

The spectrum of the parent compound (Fig.19) and the 4-methoxy, phenyl and oxo analogues are characterized by a base peak of 73 and an extremely weak molecular ion. The peak at m/e 73 is apparently formed by a cleavage giving the pyrimidiny1 radical (3-23) and the charged species (3-24). In competition with this was the process indicated in Scheme 4 with successive loss of methyl radicals. No loss of methanol was observed to occur.
SCHMIE 4

\[
\begin{align*}
\text{m/e 152} & \\
\text{m/e 137} & \\
\text{m/e 122} & \\
\text{m/e 107} &
\end{align*}
\]
CHAPTER 4

DISCUSSION OF RESULTS

Section I

Introduction

The $pK_a$ values for the carboxylic acids are collected in Table 6. These are designated $pK_\alpha$, $pK_\beta$, $pK_\gamma$, and $pK_\delta$ according to the scheme of Fig. 20. Where there are no zwitterions present, the $pK_a$ values are the same as those in Table 3 of Chapter 3. No thermodynamic corrections have been made to the values in Table 6 which were determined potentiometrically at the same concentration for all compounds ($6.67 \times 10^{-3}$): hence corrections would be the same for each, and correlations based on differences between $pK_a$ values ($\log K/K_0$) would be unaffected. Values determined spectrophotometrically were considered sufficiently dilute ($< 10^{-4} M$) to warrant no correction. The zwitterionic ratio, $K_z$, and the $pK_a$ of the corresponding methyl ester are also recorded. The last column of the Table gives the difference between $pK_\beta$ (the basic $pK_a$ for the acid) and $pK_E$ (the basic $pK_a$ for the ester). This difference was positive for all acids except the 4-methyl compound; however, in this case only, the ethyl ester was used. This illustrates the inapplicability of the Ebert-Wegscheider assumption that the $pK_a$ of the ester would be equal to that of the acid. This assumption was shown to be incorrect by Bryson et al. (1963) and Serjeant (1969). The latter author showed that for $p$-aminobenzoic acid $pK_\beta = pK_E + 0.06$ using the methyl ester,
<table>
<thead>
<tr>
<th>4-R</th>
<th>pK₆</th>
<th>pK₇</th>
<th>pK₈</th>
<th>pK₉</th>
<th>pKₓ</th>
<th>k²</th>
<th>pK₇ - pKₓ</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>3.65</td>
<td>0.58</td>
<td>2.32</td>
<td>2.82</td>
<td>0.53</td>
<td>0</td>
<td>+0.05</td>
</tr>
<tr>
<td>Me</td>
<td>3.81</td>
<td>1.40</td>
<td>2.60</td>
<td>2.86</td>
<td>1.42</td>
<td>0.12</td>
<td>-0.02</td>
</tr>
<tr>
<td>Pr₁</td>
<td>3.80</td>
<td>1.60</td>
<td>2.60</td>
<td>2.86</td>
<td>1.58</td>
<td>0.10</td>
<td>+0.02</td>
</tr>
<tr>
<td>Bu₁</td>
<td>3.91</td>
<td>1.79</td>
<td>2.79</td>
<td>2.91</td>
<td>1.74</td>
<td>0.10</td>
<td>+0.05</td>
</tr>
<tr>
<td>Ph</td>
<td>3.66</td>
<td>1.52</td>
<td>2.26</td>
<td>2.91</td>
<td>1.45</td>
<td>0.18</td>
<td>+0.07</td>
</tr>
<tr>
<td>OMe</td>
<td>3.91</td>
<td>2.13</td>
<td>2.08</td>
<td>3.96</td>
<td>2.05</td>
<td>1.10</td>
<td>+0.08</td>
</tr>
<tr>
<td>SEt</td>
<td>3.98</td>
<td>2.13</td>
<td>2.44</td>
<td>3.67</td>
<td>1.97</td>
<td>0.49</td>
<td>+0.15</td>
</tr>
<tr>
<td>SO₂Et</td>
<td>3.47</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>3.63</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl</td>
<td>3.60</td>
<td></td>
<td></td>
<td></td>
<td>-0.77</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Br</td>
<td>3.67</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3.68</td>
<td>-0.37</td>
<td></td>
<td></td>
<td>-0.57</td>
<td>0</td>
<td>+0.20</td>
</tr>
<tr>
<td>4,6-C₁₂</td>
<td>3.34</td>
<td></td>
<td></td>
<td></td>
<td>-2.6</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4,6-(OMe)₂</td>
<td>3.89</td>
<td>1.23</td>
<td></td>
<td>1.07</td>
<td>0</td>
<td>+0.16</td>
<td></td>
</tr>
<tr>
<td>4,6-(SET)₂</td>
<td>4.04</td>
<td>1.23</td>
<td></td>
<td>1.13</td>
<td>0</td>
<td>+0.10</td>
<td></td>
</tr>
<tr>
<td>4-C₁-6-OMe</td>
<td>3.66</td>
<td></td>
<td></td>
<td></td>
<td>-1.44</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4-C₂-6-OMe</td>
<td>3.75</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FOOTNOTES TO TABLE 6

a ±0.03 or better.  b ±0.06 or better.  c ±0.04 or better.  d ethyl ester.  e ±0.3
f in 5% aqueous methanol.
FIG. 20

A second factor affecting the apparent spread of the pKₐ values was the ease of the acids in

hydrolyzing to the corresponding base. Although there was no noticeable difference for ethyl 2-(4'-methylphenoxy)acetate and the corresponding acid, A second factor

in hydrolyzing the acids was the ease of the carboxylate on electron withdrawal by the pyridine ring. The

difference is 0.8 units greater than that for pyridine-2-

hydroxyl acid (Henson, 1953) and reflects the greater
distance of the carboxyl group from the ring. Blech (1946)

determined the microscopic pKₐ values of 1-(pyrid-2'-yl) 3-

and 6-pyridineacetic acids. He determined a value of 4.30 for

the 2-pyridyl compound (4-11 which is compared with a

value of 4.30 for phenylacetic acid (Jaffe, 1933)).
and $pK_B = pK_E + 0.03$ using the ethyl ester. This small difference for the ethyl ester may account for the small negative difference for ethyl 2-(4'-methylpyrimidin-2'-yl) acetate and the corresponding acid. A second factor affecting the assessment of the $pK_B$ values was the ease at which the acids decarboxylated. Although there was no observable spectral change of the carboxylic acids in strongly acidic media, no account could be taken of a small amount of decarboxylation affecting the $pK_B$ values. Hence these values may not be precise and although they parallel those of the esters, in general, any correlations were based on the values for the esters. However, the differences between $pK_B$ and $pK_E$, although small in some cases were considered significant. The fact that the differences varied considerably depending on the substituents in the ring was consistent with the work of Bryson et al. (1963) on N-(substituted)phenylglycinates, who showed that the difference was dependant on the $\sigma$ value of the substituent.

The value for $pK_\delta$ of the parent acid was considerably lower than that of phenylacetic acid ($pK_a 4.31$). This could be accounted for by stabilization of the anion by inductive electron-withdrawal by the pyrimidine ring. The value is 0.8 units greater than that for pyrimidine-2-carboxylic acid (Mason, 1959) and reflects the greater distance of the carboxy group from the ring. Blanch (1966) has measured the microscopic $pK_a$ values of 2-(pyrid-2', 3', and 4'-yl)acetic acids. He determined a value of 4.26 for the 2'-yl compound (4-1) which he compared with a value of 4.30 for phenylacetic acid (Jaffé, 1953).

*A change of $\pm 0.5$ in a $pK_a$ value corresponds approximately to 3.2 fold change in the equilibrium constant.*
Using the $\rho$ value for the ionization of phenylacetic acids (0.49; Jaffé, 1953) a value of +0.07 was derived for $\sigma_{2N}$. This very low value (due to a difference of only 0.04 units between the pyridyl- and phenyl-acetic acids) was ascribed to a significant amount of hydrogen bonding, stabilizing the neutral form of the acid (4-2). The situation in the pyrimidine case was quite different. Interpolation of the value of 3.65 into the data for the substituted phenylacetic acids gives a value of $(4.30 - 3.65)/0.489 = 1.35$ for the combined effects of the two "ortho" nitrogens. Thus half this value, 0.68 gives an estimate of the effect of one nitrogen on the $pK_a$ value. This value was very close to the one derived by Blanch of 0.71 from systems which do not hydrogen bond in the neutral form (*e.g.* ionization of pyridinealdoximes in water gave a value of 0.73) for the nitrogen "ortho" to the side chain. Thus, it appeared that, at least for the unsubstituted pyrimidine, hydrogen bonding was much less important in determining the acid strength of the carboxylic acid. This is understandable in the light of the relative basicities of the unsubstituted pyrimidine (0.58) and pyridine (~4). It also suggests that, in this respect, the effects of the nitrogen are additive.

The 4-alkyl groups produced a progressive increase in the value of $pK_\delta$ on going from Me to Bu+. The acid-weakening effect was in the normal inductive order (*i.e.* not hyperconjugative; Taft and Lewis, 1956). The value of $pK_\delta$ for the 4-phenyl acid was very close to that of the parent.
This is also true of the 4-halogen acids where variation from the value for the parent acid were not greater than 0.08 units. This was somewhat unexpected given the fact that the $pK_a$ value of 4-chlorophenylacetic acid was less than the parent phenylacetic acid by about 0.7 units and the same was true of the other 4-halogenophenyl acetic acids. The 4-methoxy and 4-ethylthio groups showed a significant acid weakening effect and this was the reverse of that observed for the 2-methoxy and 3-ethylthio groups. If the reaction of o-methoxyphenylacetic acid increases the strength of the acid by 1.8 units [Birkeland and Brown, 1955]. The 4-ethylsulphonylphenylacetic acid showed the expected acid-strengthening effect due to the large inductive electron-withdrawing capacity.

Addition of a second methoxy group giving 2-(4',6'-dimethoxyphenylimidazol-2'-yl)acetic acid (4-3; $\text{R}^1$=H, $\text{R}^2$=OMe) left the $pK_a$ of the acid virtually unchanged although there was a dramatic decrease in the basic $pK_a$ the bis-ethylthio compound (4-4; $\text{R}^1$=OMe, $\text{R}^2$=SET) showed a small increase in $pK_a$ over the mono-substituted compound. The dichloro acid (4-5; $\text{R}^1$=CH$_2$, $\text{R}^2$=Cl) showed a considerable decrease (9.26 units) over the mono-chloro acid and this was the trend drop exhibited in the acidic $pK_a$ of the methoxy (4-3; $\text{R}^1$=H, $\text{R}^2$=OMe) when a chloro substituent was introduced into position-6 giving (4-7; $\text{R}^1$=Cl, $\text{R}^2$=OMe). These preliminary observations indicated that the substituent effects on the $pK_a$ values were not simply additive.
This is also true of the 4-halogeno acids where variation from the value for the parent acid were not greater than ±0.05 units. This was somewhat unexpected given the fact that the $pK_a$ value of 4-chlorophenylacetic acid was less than the parent phenylacetic acid by about 0.2 units and the same was true of the other 4-halogenophenyl acetic acids. The 4-methoxy and 4-ethylthio groups showed a significant acid weakening effect and this was the reverse of that expected if they were considered as formally meta to the reaction site. A $m$-methoxy group in benzoic acid increases the strength of the acid by 0.12 units (McDaniel and Brown, 1958). The 4-ethylsulphonyl groups showed the expected acid strengthening effect due to its large inductive electron-withdrawing capacity.

Addition of a second methoxy group giving 2-(4',6'-dimethoxypyrimidin-2'-yl)acetic acid (4-3; $R^1=R^2=0\text{Me}$) left the $pK_a$ of the acid virtually unchanged although there was a dramatic decrease in the basic $pK_a$. The bisethylthio compound (4-3; $R^1=R^2=\text{SEt}$) showed a small increase in $pK_\delta$ over the monosubstituted compound. The dichloro acid (4-3; $R^1=R^2=\text{Cl}$) showed a considerable decrease (0.26 units) over the monochloro acid and this was the same drop exhibited in the acidic $pK_a$ of the methoxy (4-3; $R^1=\text{H}$, $R^2=0\text{Me}$) when a chloro substituent was introduced into position-6 giving (4-3; $R^1=\text{Cl}$, $R^2=0\text{Me}$). These preliminary observations indicated that the substituent effects on the acidic $pK_a$ values were not simply additive.
The basic $pK_a$ values of the esters, $pK_a$, showed a greater sensitivity to changes in substituents than the acidic $pK_a$ values. The alkyl groups caused a progressive base-strengthening effect in the inductive order. The 4-methoxy and 4-ethyl substituted groups produced substantial increases in the basic strength, while the two 4-halogeno esters measured were the expected sharp drop in basicity. It can be seen that the addition of a second group into the ring giving a 4,6-disubstituted pyrimidine caused a slight decrease in the basic strength regardless of the nature of the group. For example, insertion of a chlorine substituent into the 6-position of the 4-methoxy ester reduced the basic strength by 1.5 units. Similarly, a methoxy group in the same position caused a drop of nearly 1 unit. These dramatic effects are produced when both substituents were near to one of the ring nitrates and the added proton necessarily went on a nitrogen standing a to a substituent. This effect, the so-called abnormal $pK_a$ effect, has been mentioned in Chapter 1. An example in the pyrimidine series was given by Khromov-Danielev (1968) with the observation that a 4-methoxy group increased the basic strength of pyrimidine ($pK_a 1.3$) to 2.0 while a 2-methoxy group decreased it by 0.5 units to 0.60. Steric effects have been unlikely to be the cause since only transfer of a proton is involved and Charton (1964, 1968) has attempted to explain them in terms of short-range induction effects.
Basic $pK_a$ values

The basic $pK_a$ values of the esters, $pK_E$ showed a greater sensitivity to change in substituent than the acidic $pK_a$ values. The alkyl groups caused a progressive base-strengthening effect in the inductive order. The 4-methoxy and 4-ethylthio groups produced substantial increases in the basic strength, while the two 4-halogeno esters measured showed the expected sharp drop in basic $pK_a$. It can be seen that the addition of a second group into the ring giving a 4,6-disubstituted pyrimidine caused a sharp decrease in the base-strength regardless of the nature of the group. For example, insertion of a chloro substituent into the 6-position of the 4-methoxy ester reduced the base strength by 3.5 units. Similarly, a methoxy group in the same position caused a drop of nearly 1 unit. These dramatic effects are produced when both substituents were ortho to one of the ring nitrogens and the added proton necessarily went on a nitrogen standing $\alpha$ to a substituent. This effect, the so-called abnormal $\alpha$ effect, has been mentioned in Chapter 1. An example in the pyrimidine series was given by Khromov-Borisov (1968) with the observation that a 4-methoxy group increased the basic strength of pyrimidine ($pK_a$ 1.3) to 2.0 while a 2-methoxy group decreased it by 0.8 units to 0.50. Steric effects seem unlikely to be the cause since only transfer of a proton is involved and Charton (1964, 1969) has attempted to explain them in terms of short range inductive effects.
The basic $pK_a$ values of the monosubstituted esters ($pK_E$) are shown in Fig. 21 plotted against $\sigma_p$ values. The latter were from the compilation of Exner (1966, 1972) based on the ionization of benzoic acids. It can be seen that although the $pK_a$ values for the $4$-$\text{OMe}$, $\text{Me}$, $\text{Pr}^i$, $\text{But}^t$, $\text{Cl}$ and $I$ esters showed a rectilinear relationship with $\sigma_p$ values ($r = 0.992$) the phenyl and ethylthio substituents were anomalous. The value of $\sigma_p$ for $\text{SMe}$, based on the ionization of benzoic acids is $+0.01$. (This is the value for $\text{SMe}$ and change in the alkyl group from $\text{Me}$ to $\text{Et}$ was assumed to have little effect.) A similar plot (Fig. 22) shows the basic $pK_a$ values of $4$-substituted pyridines (Perrin, 1965) plotted against the corresponding values for nine $2$-(4$'$-substitutedpyrimidin-2$'$-yl)acetates. Only the 4-methoxy, methyl, iodo, and chloro substituents lay on a line passing through the origin. This line had a slope of 0.99 (by a least-squares best fitting procedure): thus these four substituents elicited the same effect on protonation of the heterocyclic ring in each case. All other substituents showed an exalted effect over that expected from the pyridine data. The value of $pK_E$ for the ethylthio ester ($1.97$, giving $\Delta pK_a=1.44$) was consistent with the value for $4$-ethylthiopyrimidine of 2.65 (giving $\Delta pK_a=1.35$) determined by Brown and Foster (1966). This is in contrast with a value of 5.94 for $4$-methylthiopyridine ($\Delta pK_a=0.75$; Albert and Barlin, 1959) compared to that of the $4$-methoxypyridine of 6.47 giving $\Delta pK_a=1.28$. The enhancement in the pyrimidine series thus appeared to be
FIG. 22

In order to attempt a correlation with $p^+$ values, which are known's greater resonance contributions. The non-linear relationship within a plot is evident from Fig. 22. A tentative correlation of ionization constants of substituted pyridines with $p^+$ values derived from additivity rules (Ellis and Johnson, 1964) has led to the recognition of enhanced effects over certain substituents which are capable of donating electrons to the nitrogen atom (e.g. OMe). Both me and Topper (1962) have suggested the use of $p^+$ values and have correlated $p^+$ values with $p$ values. The dual substitution parameter approach was discussed for reasons to be mentioned below. Also, a number of data were subjected to treatment by means of correlation described by Moroney (1965). They resulted in the following equation:

$$Y = (\frac{p}{p^+}) = 5.34 + 0.72X$$

This result is very similar to the correlation.
a real one. One possible solution to the anomaly might be to attempt a correlation with $\sigma_{p}^{+}$ values, i.e. Brown's electrophilic substituent constants which should allow for a greater resonance contribution. The non-linear nature of such a plot is evident from Fig. 23.

Attempts to correlate ionization constants of 4-substituted pyridines with $\sigma$ values derived from substituted benzoic acids (Ellam and Johnson, 1971; Fischer et al. 1964) has led to the recognition of enhanced effects due to substituents which are capable of strong mesomeric electron-donation to the nitrogen atom (i.e. NH$_2$, OMe). Brownlee and Topsom (1972) have criticized the use of $\sigma$ values and have correlated $pK_{a}$ changes using the Dual Substituent Parameter approach with $\sigma_{I}$ and $\sigma_{R}^{+}$ values, the latter accommodating any enhanced resonance donation. In order to see if this approach was possible in the case of the pyrimidine system five 4-substituted pyrimidines were subjected to this type of analysis. Lack of values for $\sigma_{R}^{+}$ prevented the incorporation of the isopropyl and $t$-butyl groups and the phenyl compound was deleted for reasons to be mentioned later. Although only a small number of data points was available, they were subjected to treatment by multiple correlation as described by Moroney (1953). This resulted in the following equation:

$$\log \left( \frac{K}{K_{o}} \right) = 5.3\sigma_{I} + 3.0\sigma_{R}^{+}.$$  

equation 13.

This was very similar to the equation derived by Brownlee and Topsom (1972)(Equation 8, Chapter 1) to describe the
FIG. 23

The equation predicted a value of 0.38 for the 4-phenyl substituted pyrimidine. This was well below the experimentally determined value of 1.45 which implies a much greater resonance contribution from the phenyl than was hypothetically realized. This discrepancy may be due to three causes:

(i) a non-additive effect of the second nitrogen,
(ii) protonation on both N-1 and N-3, or (iii) an enhanced resonance effect of the 4-phenyl substituent. Experimental evidence, based on n.m.r. studies has been given by Parmar and Cavallin (1969) that 4-phenylpyrimidine protonates essentially on N-1. The presence of a methoxy group in an adjacent chain should hardly affect this result. Chatterton (1964, 1969), in a study of the ortho effect has shown that $pK_a$ differences in nine disubstituted pyrimidines were correlated best with either $\sigma^+_{p}$ or $\sigma^+_{p}$, respectively. The correlation using data for thirteen 2-substituted pyrimidines from the latter of these studies (1969) showed.
ionization of 4-substituted pyridines with coefficients 5.15 and 2.69 respectively. The ratio of inductive to resonance contribution \((\lambda)\) in Equation 13 is 1.8, that in Brownlee and Topsom's 1.9. Table 7 compares the predicted to the experimentally determined \(pK_E\) values. The fact that similar equations described ionization constants for both pyridine and pyrimidine strongly suggests that for the five substituents in question (OMe, SET, Me, I, Cl) protonation occurs on N-1 of the pyrimidine ring. Further, that the second nitrogen of the pyrimidine ring contributes a constant amount to the "\(pK_a\)" of N-1 of 4.58 ± 0.5 pK units relative to the pyridine.

The equation predicted a value of 0.90 for the 4-phenyl substituted ester. This was well below the experimentally determined value of 1.45 which implied a much greater resonance contribution from the phenyl than was normally realized. This anomaly may be due to three causes: 

(i) a non-additive effect of the second nitrogen,  
(ii) protonation on both N-1 and N-3, or (iii) an enhanced resonance effect of the 4-phenyl substituent. Experimental evidence, based on n.m.r. studies has been given by Gil and Sarmento (1969) that 4-phenylpyrimidine protonates essentially on N-1. The presence of a methoxycarbonyl methyl side chain should hardly affect this result.

Charton (1964, 1969), in a study of the ortho effect, has shown that \(pK_a\) differences in nine 2-substituted pyridines were correlated best with either \(\sigma_m\) or \(\sigma_I\). Re-examination of this correlation using data for thirteen 2-substituted pyridines from the literature (Perrin, 1965) shows again
TABLE 7

<table>
<thead>
<tr>
<th>4-R</th>
<th>PREDICTED</th>
<th>FOUND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>1.49</td>
<td>1.42</td>
</tr>
<tr>
<td>OMe</td>
<td>2.16</td>
<td>2.05</td>
</tr>
<tr>
<td>SET</td>
<td>1.74</td>
<td>1.97</td>
</tr>
<tr>
<td>Cl</td>
<td>-0.82</td>
<td>-0.77</td>
</tr>
<tr>
<td>I</td>
<td>-0.79</td>
<td>-0.57</td>
</tr>
<tr>
<td>(Ph)</td>
<td>(0.90)</td>
<td>(1.45)</td>
</tr>
</tbody>
</table>
a good correlation with $\sigma_I$ (Equation 14):

$$\log \left( \frac{K}{K_0} \right) = 11.7 \sigma_I - 0.81 \ (n=13, \ S.D.=0.04, \ r=0.98)$$  

and poor correlation with $\sigma_P$. A similar treatment of literature data for nine 2-substituted pyrimidines gave equation 15:

$$\log \left( \frac{K}{K_0} \right) = 9.4 \sigma_m - 0.97$$  

(S.D. = 0.06, $r = 0.95$, $n = 9$).

Fig. 24 gives a graphical representation of these data. Thus, given a value of +0.06 for $\sigma_m$ of the phenyl substituent, it would be expected to exert a substantial base weakening effect on N-3 and protonation would hence be favoured on N-1. This rules out (ii) above.

Although conceivable, it seems unlikely that N-3 should exert an extra base-strengthening effect in the presence of an adjacent phenyl substituent. This leaves (iii) as a possible cause. The ability of the phenyl group to engage in orbital overlap of the type indicated in the canonical structure (4-4) implies its ability to attain co-planarity with the pyrimidine ring. That this can be achieved is evident from ultraviolet spectral studies. However, such excited state spectra may not provide the correct means to diagnose ground state effects such as ionization constants. Thus, biphenyl is not co-planar in solution (Suzuki, 1959) and it was suggested that 2,2'-bipyridyl existed preferentially in the trans conformation and that the two rings are more nearly
FIG. 24

$\text{pK}_a$ Values for 2-Substituted Pyrimidines

- Cl
- Br
- SMe
- OMe
- OEt
- OH
- Me
- NH$_2$
- N(Me)$_2$

Log($K/K_0$) vs. $\sigma_m$
In particular, the CH...HC interactions are atomistically more favourable than CH...N interactions. This view has been discussed in Chapter 3. Steric Interactions in supramolecular interaction has been well documented, especially by the work of Brown and Martin (1967) and Martin and Cleveland (1976). It is clearly shown that a phenyl ring can be prevented from a supramolecular interaction with an electron-deficient group on a second ring because of interference from a lone pair. Thus, it is conceivable that replacement of the o-hydrogens by a lone pair might, through steric effects, enable a quinoline mesomorphic interaction of the phenyl group with the pyridazine ring (4-4). The presence of a lone pair on the second ring only is unsuitable for application to the pyridazine series.

The marked reduction in base strength observed upon introduction of a second substituent into the pyridazine ring to give a 4,6-disubstituted compound was clearly a consequence of the "abnormal" effect discussed by Martin (1964, 1969). A proton next add to a nitrogen is a substituent and the basicity of such a nitrogen is greatly reduced according to Equation 14. A more appropriate to this problem might be to combine Equation 13 and Equation 14 giving Equationashing.
co-planar than in biphenyl (Murrell et al. 1965). In particular, that CH····HC interactions are sterically more unfavourable than CH····N interactions. This point has been discussed in Chapter 3. Steric interference to mesomeric interaction has been well documented (Beavan, 1958) and the work of Brown and Inukai (1962) and Brown and Cleveland (1976) has clearly shown that a phenyl ring can be prevented from full mesomeric interaction with an electron-deficient centre on a second ring because of interference from $\sigma$-hydrogens. Thus it is conceivable that replacement of one of the $\sigma$-hydrogens by a lone pair might, through relief of steric effects, enable a greater mesomeric interaction of the phenyl group with the pyrimidine ring (4-4). Thus values of $\sigma_R^+$ for the phenyl substituent derived from reaction series in which the substituent is "flanked" by $\sigma$-protons on the second ring may be unsuitable for application in the pyrimidine series.

The marked reduction in base strength observed upon introduction of a second substituent into the pyrimidine ring to give a 4,6-disubstituted compound was clearly a consequence of the "abnormal" $\alpha$ effect discussed by Charton (1964, 1969). A proton must add to a nitrogen $\alpha$ to a substituent and the basicity of such a nitrogen is sharply reduced according to Equation 14. A naive approach to this problem might be to combine Equation 13 and Equation 14 giving Equation 16.
\[
\log \left( \frac{K}{K_0} \right) = [5.3\sigma_I + 3.0\sigma_R^+] + [11.7\sigma_I - 0.810] \\
\text{equation 16}
\]

This gave the following 
\[pK_a\] values for the 4,6-dichloro and 4,6-dimethoxy esters: -5.3 and -0.20 compared with -2.6 and 1.07 respectively. It was too much to expect that the effects would be additive and it was reasonable to suppose that the presence of a second substituent will increase the contribution of canonical structures of the type (4-5) by induction. For example, an \(o\)-methoxy group will increase the rate of deuterium exchange by 500-fold over that for unsubstituted benzene. This increased resonance contribution will vary depending on the nature of the substituent.

Both the basic \(pK_a\) values \((pK_B)\) for the esters and, to a lesser extent, the acidic \(pK_a\) values \((pK_a)\) for the carboxylic acids showed an increase in effective electron-donation from methyl to \(t\)-butyl. This was the normal inductive order. However, the use of the \(\sigma_R^+\) of Ehrenson et al. (1973), based as they are (in part) on Brown's electrophilic substituent parameters, should give the hyperconjugative order to this series. Thus Brown and Okamoto (1958) gave values of \(\sigma_P^+\) for Me, Et, Pr\(^i\) and Bu\(^t\) of -0.311, -0.295, -0.280 and -0.256 respectively. The 'normal' unexalted values for \(\sigma_P\) are -0.170 for Me and -0.197 for Bu\(^t\) (McDaniel and Brown, 1958).

Interestingly, Brown and Mihn (1955) give virtually identical values for the basic \(pK_a\) values of 4-Me, Et, Pr\(^i\) and Bu\(^t\) pyridines (6.02 ± 0.02). The data for the
Analytical pyrolysis might suggest that py values are not the most suitable for correlation to other series.

In previous work (1972) in proposing their four scales of py values (Chapter 3) included reactivity to the pyridine series as a type base fitted by py values, it has pointed out that resonance interaction with electron-deficient bonds is not as strong as for example with a carbonyl group.

The substituent py values for various substituted benzoic acids cannot be treated as formally dual to the reaction centres of N. This was clearly indicated by a plot of py values against acid log p. (pH/pKa) (Fig. 14). It was unlikely that electronic effects had been 'reversed', and so a secondary effect must be operating to cause this anomalous behaviour. The most likely source of this effect was internal hydrogen bonding. Thus, in the general case (4-5), the existence of such intramolecular hydrogen bonding, facilitated by an unstrained six-membered ring, will stabilize the neutral form of the acid over the anion. This type of effect is well known in organic chemistry: for example, p-hydroxybenzoic acid has pKa 2.98 compared with values for the m- and n-isomers of 4.80 and 4.69, respectively. The greater acid strength of the n-isomer was attributed to stabilization of the anion by hydrogen bonding to the adjacent hydroxyl hydrogen.

It has already been indicated that hydrogen bonding may also operate as strongly to the pyridinyl carboxylic acids.
4-alkyl pyrimidines might suggest that $\sigma_R^+$ values are not the most suitable for correlation in this series. Ehrenson and co-workers (1972) in proposing their four scales of $\sigma_R$ values (Chapter 1) included reactivity in the pyridine series as a type best fitted by $\sigma_R^+$ values but pointed out that resonance interaction with the N atom may not be as strong as for example with a carbonium ion.

**Acidity pK$_a$ values**

The substituents of 2-(4'-substitutedpyrimidin-2'-yl)acetic acids cannot be treated as formally meta to the reaction centre. This was clearly indicated by a plot of $\sigma_m$ values against acid pK$_a$ (pK$_0$)(Fig. 25). It was unlikely that electronic effects had been "reversed", and so a secondary effect must be operating to cause this anomalous behaviour. The most likely source of this effect was internal hydrogen bonding. Thus, in the general case (4-6), the existence of such intramolecular hydrogen bonding, facilitated by an unstrained six-membered ring, will stabilize the neutral form of the acid over the anion. This type of effect is well known in organic chemistry: for example o-hydroxybenzoic acid has pK$_a$ 2.98 compared with values for the m- and p- isomers of 4.08 and 4.58, respectively. The greater acid strength of the o-isomer was attributed to stabilization of the anion by hydrogen bonding to the adjacent hydroxyl hydrogen. It has already been indicated that hydrogen bonding may not operate as strongly in the pyrimidinyl acetic acids.
as in the pyridilazetic acids. However, the existence of a strong electron-donor group (e.g., N' methyl) will have the effect of increasing charge density at R-1 and facilitating hydrogen bonding. Evidence for the presence of hydrogen bonding was indicated by the ease of deacetylation of these compounds and these thermolytic reactions were favourable (Brown and Mason, 1977) on complete protonation of the compounds (Pinnock and Wonnacott, 1977). In this case, there are three major effects of the substituent in the amiation of the carboxylic acid:

(i) the inductive effect of R-1
(ii) the indirect effect of increased charge density on R-1 due to mesomeric interaction with the strong electron-donor in the 4-substituent, and (iii) enhanced hydrogen bonding due to (ii). The effect of hydroxy group effects (i) and (iii) will both be acid-strengthening and affect (ii) acid-strengthening.

The inductive effect I, should operate in the same way to 4-substituted phenylazetic acids since the geometrical relationships are the same. It would be extremely difficult to separate effects (ii) and (iii) unless it could be shown that hydrogen bonding never occurred and thus only effect (ii) would operate. It has been pointed out (Kling, 1960) that a hydrogen bonding effect should be observed only when independent evidence for its existence can be produced. Such evidence was not available in this instance. However, that the indirect inductive effect of mesomeric electron-donation to R-1 does not appear to be very great, was suggested by the substituent effect for
as in the pyridylacetic acids. However, the existence of a strong electron-donor group (e.g., SET) will have the effect of increasing charge density at N-1 and facilitating hydrogen bonding. Evidence for the presence of hydrogen bonding was indicated by the ease of decarboxylation of the acids; mechanisms most favoured (in the pyridine series) involved a transition state with either strong hydrogen bonding (Brown and Moser, 1971) or complete proton transfer (Dunn and Thimm, 1977; Dyson and Hammick, 1937). Thus there will be three major effects of the substituent on the ionization of the carboxylic acid: (i) the inductive effect, (ii) the indirect effect of increased charge density on N-1 due to mesomeric interaction with a strong electron-donor in the 4-position, and (iii) enhanced hydrogen bonding due to (ii). For a 4-methoxy group effects (ii) and (iii) will both be acid-weakening and effect (i) acid-strengthening.

The inductive effect I, should operate in the same way as in m-substituted phenylacetic acids since the geometrical relationships are the same. It would be extremely difficult to separate effects (ii) and (iii) unless it could be shown that hydrogen bonding never occurred and thus only effect (ii) would operate. It has been pointed out (King, 1965) that a hydrogen bonding effect should be invoked only when independent evidence for its existence can be produced. Such evidence was not available in this instance. However, that the indirect inductive effect of mesomeric electron-donation to N-1 does not appear to be very great, was suggested by the solvolysis data for
4-substituted 2-(1'-bromo-1'-methylethyl)pyrimidines discussed in a later section. Thus it seemed reasonable to suppose that some internal hydrogen bonding operated to weaken the acids.

The $pK_a$ data for eleven carboxylic acids (excluding the ethylsulphonyl acid) was examined for correlation with $\sigma_p^+$, Brown's electrophilic substituent constants. This seemed a reasonable choice since enhanced mesomeric electron-donation to N-1 might be expected. No value of $\sigma_p^+$ for the ethylsulphonyl group was available. By using a standard least squares fitting procedure, the data were best described by Equation 17:

$$\log \left( \frac{K}{K_0} \right) = 0.38\sigma_p^+ - 0.038$$

(n=11, S.D.=0.07, r=0.85).

The criteria of Jaffé (1953) have been used to evaluate the goodness of fittings by the Hammett equation and a value for the regression coefficient, r of < 0.9 is considered poor. Use of $\sigma_p$ values gives an even worse fit: McDaniel and Brown (1958), for example, gave a value of +0.03 for $\sigma_p$ for the ethylthio group ($c.f.$ -0.268 for $\sigma_p$ OMe).

The data for nine 4-substituted acids were analysed by the Dual Substituent Parameter treatment yielding Equation 18

$$\log \left( \frac{K}{K_0} \right) = 0.34\sigma_I + 0.31\sigma_R^+$$

(n=9, r=0.92, S.D.=0.07)
Table 8 shows the calculated and measured values of the \( pK_a \) using this Equation. The fit was probably no better than that of Equation 17 using \( \sigma_p^+ \) values. (In Equation 18 the \( \sigma_R^+ \) value for SEt was taken as being the same as that for SMe.) The values of \( \sigma_R^+ \) (and \( \sigma_p^+ \)) for the isopropyl and \( t \)-butyl groups of -0.21 and -0.18 would suggest an acid-strengthening rather than an acid-weakening in the order methyl, isopropyl, \( t \)-butyl (\( \sigma_R^+ \) Me is -0.25).

This was also true of the basic strengths which increase significantly in the order Me, Pr\(^i\), Bu\(^t\). Thus, it appeared as if no particular substituent constant was suitable for general correlations in this series of compounds. Mention should also be made of the status of \( \sigma_R^+ \) for SEt. This was taken as being equal to -0.81, a value derived from the solvolysis of \( t \)-cumyl chlorides. However Ehrenson et al. (1973) have indicated the apparent variable nature of the alkylthio group when in a reaction series of high electron-demand. The value of \( \sigma_R^+ \) varied from -0.55 to -0.95 depending on the defining reaction.

The difficulty in obtaining a better correlation of ionization constants may lie in the problem of separating hydrogen bonding effects and indirect inductive effects due to mesomeric donation to the nitrogen. The physical justification for using Equation 18 may lie in the blend of inductive and resonance effects. In this instance it was very close to 1, being slightly larger for the inductive contribution. This "explains" the relative insensitivity of the \( pK_a \) to the halogeno substituents.
TABLE 8

<table>
<thead>
<tr>
<th>4-R</th>
<th>PREDICTED</th>
<th>FOUND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>3.74</td>
<td>3.81</td>
</tr>
<tr>
<td>Ph</td>
<td>3.71</td>
<td>3.66</td>
</tr>
<tr>
<td>OMe</td>
<td>3.88</td>
<td>3.91</td>
</tr>
<tr>
<td>SET</td>
<td>3.82</td>
<td>3.98</td>
</tr>
<tr>
<td>S02ET</td>
<td>3.48</td>
<td>3.47</td>
</tr>
<tr>
<td>F</td>
<td>3.66</td>
<td>3.63</td>
</tr>
<tr>
<td>Cl</td>
<td>3.61</td>
<td>3.60</td>
</tr>
<tr>
<td>Br</td>
<td>3.59</td>
<td>3.67</td>
</tr>
<tr>
<td>I</td>
<td>3.60</td>
<td>3.68</td>
</tr>
</tbody>
</table>
where the substituent constants are of the same order but different signs \((e.g. \sigma_I \text{ for } F \text{ is } +0.50 \text{ while } \sigma_R^+ \text{ is } -0.57)\). In the case of 4-halogeno substituents it seems unreasonable however to suppose that significant hydrogen bonding was occurring. It has been pointed out that hydrogen bonding for the unsubstituted pyrimidinyl acetic acid was much less than for the pyridylacetic acid and this could be attributed to a greater base strength of the latter. Thus, although it might be reasonable to suppose that some hydrogen bonding occurs in 2-(4'-methoxypyrimidin-2'-yl)acetic acid with basic \(pK_a\) about 2, it would be unlikely to occur in the 4'-iodo acid with \(pK_a\) -0.37. Thus, the contribution to acid-weakening by intramolecular hydrogen bonding would be variable and depend on the nature of the substituent, greater for a 4-methoxy group than for a 4-ethylsulphonyl group, being close to zero in the latter. This was similar to a situation in which a change in mechanism as the substituent was altered causes the Hammett relationship to fail completely \((e.g. \text{ the solvolysis of benzyl chlorides and tosylates; Exner, 1966, 1972})\).

In the light of the above observations it would be difficult to make any semi-quantitative correlations of the acidic \(pK_a\) values for the di-substituted pyrimidinyl acetic acids. The values for the dimethoxy and bisethylthio acids are little different from the corresponding monosubstituted compounds which seemed unusual in that a further inductive effect would be
expected to strengthen the acid directly and by reducing any hydrogen bonding because of the drop in base strength. The lowering of the value for the 4-chloro acid by 0.26 units by the introduction of a further chloro substituent in the 6-position can be attributed to a further inductive effect. The effect of introducing a chloro substituent into the 6-position of the 4-methoxy acid lowers the acidic $pK_a$ by 0.25 units but the same substituent in the 6-position of the 4-methyl acid affects it by only 0.07 units. Clearly, the substituent effects are not additive.

Zwitterionic Ratios

The values of $pK_\alpha$, $pK_B$, $pK_\gamma$ and $pK_\delta$ (Fig. 20) gave insight into the manner in which a substituent affected the dissociation of the pyrimidinylacetic acids when a ring nitrogen was protonated. This is illustrated with reference to Fig. 20. When $R=O\text{Me}$, $pK_\delta$ was 3.91, and the acid was weaker than the parent by 0.26 pK units for reasons given earlier. However, $pK_\alpha$ has a value of 2.08. This could not be compared directly with the parent acid since the value of $pK_\alpha$ when $R=H$ was not known. Comparison with the 4-methyl acid ($pK_\alpha$ = 2.32) showed it was a stronger acid by 0.31 units. In (4-7) the substituent can no longer place a negative charge on N-1 by a mesomeric interaction and so the inductive effect of the substituent may dominate. It would be of some interest to obtain an estimation of $pK_\alpha$ when $R=H$. This could be done in the
Consider the reaction scheme of chemical reactions, where the equilibrium constants and pK_a values are discussed. If it can be assumed that the pK_a value is 0.03, then using the value of pK_a, the effective concentration can be inferred. This value can be used in the calculation of pK_b values, which are also consistent with an estimated value of 0.92 units for the 1-OMe constituent in the equilibrium (4-7) → (4-8) and does not support the notion that it was electron-donating by 5-7. The 4-OMe group provided the mechanism for acid dissociation in the species (4-9). If in (4-7) when R = CH_3, the ring nitrogen was considered as a substituent, and the effects of the protonated nitrogen and the second nitrogen were additive, then of log(K_b) as log(K_b) = log(K_b)_protonated + log(K_b)_second nitrogen, using log(K_b) = 0.92, 0.03, and the estimated value for pK_a when N-CH_3, a value of 32.8 was found. This was of the same order of magnitude found by Blanch (1996) from perfluorinated acids.
following way. Consider the equilibria shown in Fig. 26. When $X = \text{H}$, $pK_a = 2.30$ (Khromov-Borisov, 1968), when $X = \text{CO}_2\text{Me}$, $pK_a = 0.53$ and $X = \text{CO}_2\text{H}$, $pK_a = 0.58$. If it can be assumed that $\log(K/K_0) = \rho \sigma_m$ for 2-substituted pyrimidines (c.f. previous discussion): then, using the values of $\sigma_m$ for $\text{CO}_2\text{Me}$ and $\text{CO}_2\text{H}$ indicated in Fig. 26, $\rho$ takes on a value between 5.4 and 5.7. The value of $\sigma_m$ for $\text{CO}_2^-$ has been estimated as +0.01 (Serjeant, 1969). Jaffé (1953) suggested a value of $0 \pm 0.02$. Taking a value for $\sigma_m$ of $\text{CO}_2^-$ as +0.01 and $\rho = 5.5$, a value for $pK_a$ when $X = \text{CO}_2^-$ in Fig. 26 of 2.24 is obtained. This would correspond to $pK_Y$ in Table 6 when $R = \text{H}$. Since $K_z = K_\delta/K_\gamma = K_\alpha/K_\beta$ and using the value of $pK_\delta$, a value for $K_z$ when $R = \text{H}$ of $\sigma_\alpha$. 0.03 was estimated. This value, together with $pK_\beta$ enabled an estimation of $pK_\alpha$ of 2.1. This calculation must be considered at best, crude. It was consistent with an acid strengthening effect of 0.02 units for the 4-0Me substituent in the equilibria $(4-7) \rightleftharpoons (4-8)$ and does support the notion that it was electron-donation to N-1 by the 4-0Me group which provided the mechanism for acid weakening in the species $(4-9)$. If in $(4-7)$ when $R = \text{H}$, the ring nitrogen was considered as a substituent, and the effects of the protonated nitrogen and the second nitrogen were additive, then if $\log(K/K_0) = \rho (\sigma_{2N} + \sigma_{2 NH^+})$ a value for $\sigma_{2 NH^+}$ may be calculated. Using $\sigma_{2N} = 0.68$, $\rho = 0.49$ and the estimated value for $pK_\alpha$ when $R = \text{H}$, a value of $\sigma_{2 NH^+}$ of +3.8 was found. This was of the same order as that found by Blanch (1966) from pyridylacetic acids of 3.41. In the light of the variability of such values
FIG. 26

\[
\begin{array}{c}
\text{X} \\
\text{H} \\
\text{CO}_2\text{Me} \\
\text{CO}_2\text{H} \\
\text{CO}_2^- \\
\end{array}
\begin{array}{c}
\sigma_m \\
0 \\
0.33 \\
0.30 \\
0.01 \\
\end{array}
\begin{array}{c}
pK_a \\
2.30 \\
0.53 \\
0.58 \\
\text{X} \\
\text{H} \\
\text{CO}_2\text{Me} \\
\text{CO}_2\text{H} \\
\text{CO}_2^- \\
\end{array}
\]

69a
given to a protonated ring nitrogen (Ridd, 1971) the agreement was reasonable. The value of $pK_\alpha$ for (4-7) of 2.1 when $R=H$ however implies that the acid was still weakened when $R=SEt$, $pK_\alpha$ for the latter being 2.44. This can be attributed to the crudeness of the above calculations but also to the fact that canonical structures of the type shown in (4-10) may be important and the direction of their effects difficult to gauge. Further, simple consideration of polar effects alone, particularly with charged substituents (e.g. 4-7) often do not account for relative acid strengths. Solvation effects in particular may be important, and any full treatment should be made on the basis of entropy and enthalpy changes (King, 1960, 1965; Calder and Barton, 1971).
Section 11

The rate data for the solvolyses of 4-(1-bromo-4-methylpyridinium) are collected in Table 9. Rates for the reactions were determined at various temperatures in order to ascertain the activation parameters for the solvolysis. The 2-thiopyridinium was unstable and decomposed within 2-3 days even at 0°C and only one rate constant could be determined on the reaction mixture. Further details of the procedures used will be found in the Experimental Section.

An obvious feature of the data was the wide range in which the 1-bromo pyridinium solvolyses were observed. The parent compound has a half-life of 33 h at 20°C in 95% acetic acid solution, while its 4-phenyl derivative was established to have a half-life of at least ten days in 50% acetic acid at the same temperature (or 2 h at 0°C). In contrast, the rate of solvolysis of a 1-bromo-4-phenyl-2-methylpyridinium cation at 55°C has been measured as 1 x 10^{-10} s^{-1} at 0°C (Bates et al., 1949). A phenyl group should be much less effective as two methyl groups in stabilizing the cation than (Stevenson, 1958; and given the 1-bromo-4-methyl-4-phenylbenzene would solvolysed faster because the quinolone suggested by Marcus and Eisenstein (1949)
Section II

The solvolysis of 2-(1'-bromo-1'-methylethyl)pyrimidines

The rate data for the solvolysis in 50% (v:v) aqueous methanol at constant pH for the five bromopyrimidines studied are collected in Table 9. Rates for all compounds except the fluoropyrimidine were determined at three temperatures in order to ascertain the activation parameters for the solvolyses; these are indicated in Table 10. The 4-fluoropyrimidine was unstable and decomposed over 2-3 days even at 0° and only one rate constant (at 53.1°) was determined on freshly distilled material. Further details of the procedures used will be found in the Experimental Section.

An obvious feature of the data was the slow rate at which the t-bromo pyrimidines solvolysed when compared with other t-bromo compounds. The parent was estimated to have a half-life of 36 h at 20° in 50% aqueous methanol while its 4-phenyl derivative was estimated to have a half-life of at least ten days in pure methanol at the same temperature (or 27 h at 53.1°). In contrast, the rate of solvolysis of t-butyl bromide in 80% aqueous ethanol at 55° has been measured as 1 x 10^{-2} sec (t_{1/2} 69 sec.) (Bateman et al., 1940). A phenyl group should be about as effective as two methyl groups in stabilizing a carbonium ion (Streitwieser, 1956) and thus the 1-bromo-1-methyl-ethylbenzene would solvolyse faster. Using the equation suggested by Grunwald and Winsten (1948)

\[ \log k = \log k_0 + mY \]
TABLE 9

RATES OF SOLVOLYSIS OF 4-SUBSTITUTED-
2-(1'-BROMO-1'-METHYLETHYL)PYRIMIDINES
IN 50% AQUEOUS METHANOL.

<table>
<thead>
<tr>
<th>4-R</th>
<th>t°</th>
<th>k x 10^-4 sec^-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>36.4</td>
<td>0.420</td>
</tr>
<tr>
<td></td>
<td>41.8</td>
<td>1.80</td>
</tr>
<tr>
<td></td>
<td>53.1</td>
<td>3.78</td>
</tr>
<tr>
<td>Ph</td>
<td>61.1</td>
<td>0.299</td>
</tr>
<tr>
<td></td>
<td>0.417</td>
<td></td>
</tr>
<tr>
<td>OMe</td>
<td></td>
<td>6.46</td>
</tr>
<tr>
<td>Cl</td>
<td></td>
<td>0.526</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.0671</td>
</tr>
<tr>
<td>F</td>
<td></td>
<td>2.57</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.47</td>
</tr>
</tbody>
</table>

In brackets are given in sec^-1.


**TABLE 10**

ACTIVATION PARAMETERS FOR SOLVOLYSIS OF 4-SUBSTITUTED-
2-(1'-BROMO-1-METHYLETHYL)PYRIMIDINES
IN 50% AQUEOUS METHANOL

<table>
<thead>
<tr>
<th>R</th>
<th>$\Delta H$ $^a$</th>
<th>$\Delta S^+$ $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>23.2</td>
<td>-6.8</td>
</tr>
<tr>
<td>OMe</td>
<td>23.4</td>
<td>-5.6</td>
</tr>
<tr>
<td>Ph</td>
<td>23.6</td>
<td>-4.6</td>
</tr>
<tr>
<td>Cl</td>
<td>23.8</td>
<td>-8.7</td>
</tr>
</tbody>
</table>

$^a$ In kcals mole$^{-1}$; accurate to ±1 kcal mole$^{-1}$

$^b$ In cal deg$^{-1}$ mole$^{-1}$; accurate to ±0.5
cals deg$^{-1}$ mole$^{-1}$.
where log \( k \) is the rate in 20\% aqueous ethanol, log \( 8 \) is the rate in a solvent characterized by a value of \( 8.8 \), the Hammett \( \rho \) value, and \( b \) is the sensitivity to solvent change. An estimation for the rate of aromatization of the ring towards the rate by over 4000 was attempted. The reactions were assumed to be unimolecular and not previously shown that the analogous Michael reaction products of 3- and 4-bromopyridinium ion bromide in a 20\% aqueous ethanol solution (Werten, 1934; Donn and Varion, 1970) gave a rate in agreement with the solvent dependence of the reaction. The observed substituent effects are shown to which contribute the solvolysis rate, the enhancing in concisely by groups not on the benzene ring. The 2-phenyl substituents in the benzene ring show the 4-phenyl substituents in the benzene ring to accelerate the rate of solvolysis. The rate with their inductive and resonance withdrawing capacity. The rate of 3- and 4-bromopyridinium ion bromide decreases in the effect of the parent pyrimidine ring is due to the rotation of the pyrimidine ring to stabilize the developing negative charge on the central carbon atom. Thus canonical forms such as (4-1b) with the negative charge delocalized in nitrogen are not favorable and only minor-some small extent of delocalization of the charge. The reluctance of the
where \( \log k_0 \) is the rate in 80% aqueous ethanol, \( \log k \) is the rate in a solvent characterized by a value of \( Y \) (the "ionizing power") and \( m \) is the sensitivity to solvent change, an estimation for the rate of solvolysis of \( t \)-butyl bromide in 80% aqueous methanol \( (Y = +2, \text{Grunwald and Winstein, 1948}) \) can be made. Using \( m = 0.94 \) (Winstein et al. 1951) a value of 0.8 sec\(^{-1}\) was estimated. Thus, the replacement of one methyl group with a pyrimidine ring retards the rate by over 4000-fold. The reactions were assumed to be unimolecular since it has previously been shown that the analogous primary bromo compounds, 2- and 4-bromomethylpyrimidines did not react in a 50% aqueous ethanol solution (Waring, 1974; Brown and Waring, 1974) and resistance to bimolecular attack by solvent would be further increased by the presence of two methyl groups on the saturated carbon.

The 4-methoxy and 4-phenyl substituents were shown to slightly accelerate the solvolysis. This was in contrast to \( meta \) substituents in the benzene series where the groups are rate retarding. The 4-halogeno substituents retarded the rate of solvolysis and this was consistent with their inductive electron-withdrawing capacity. The sharp decrease in the rate of solvolysis of the parent \( t \)-bromopyrimidine was presumably due to the reluctance of the pyrimidine ring to stabilize the developing positive charge on the central carbon atom. Thus canonical forms such as (4-11) with positive charge delocalized to nitrogen would not be favourable and only forms such as (4-12) would aid delocalization of the charge. The reluctance of the
bromine to ionize can also be formulated on purely electrostatic grounds. Thus, in (4-13) the dipoles of the lone pairs will give rise to an electric field which may have a component in the direction of the C-Br bond as shown. This will oppose the type of charge separation which must occur for ionization to proceed. It is interesting that Olah and Calin (1968) could not observe the carbonium ion generated from 2-(1'-hydroxy-1'-methyl-ethyl)pyridine in superacid media. The enhanced rates of solvolysis for the 4-methoxy and 4-phenyl compounds are no doubt due to contributions from resonance structures of the type (4-14). The incipient carbonium ion cannot partake of direct mesomeric interaction with the 4-OMe group, and so the slight rate acceleration must be due to an indirect inductive effect. Noyce et al. (1973) and Noyce and Virgilio (1973), as part of a general study of solvolysis in this type of heterocyclic system, studied solvolysis of substituted 2-, 3-, and 4-(1'-chloro-1'-methylethyl)pyridines, e.g. (4-15), in 80% aqueous ethanol at constant pH. In general, this study showed that rates could be correlated with the $\sigma_p^+$ values of Brown and Okamoto (1956). However, when $X$ in (4-15) was a 6-Me, 6-OMe, 6-Ph or 6-Cl, an enhanced rate of solvolysis was found over that expected if the substituents were considered meta to the reaction site. These results were qualitatively the same as for the pyrimidines although the rate enhancements were greater. Thus a 6-methoxy group in (4-15) increased the rate of solvolysis by a factor of 10 compared with 1.4 for the 4-methoxypyrimidine. This may
The latter is calculated faster than the parent molecule, which occurs because of a change in solvent. In any case the rates are not comparable because of a change in solvent. In both instances, it appeared that an intrinsic effect due to resonance contributions of the type (4-15) were responsible for the observed rates. Unfortunately, no data are available on a 4-chloro substituent. It can be seen that a 4-chloro substituent was slightly less rate-enhancing than a 4-methoxy substituent and a 4-methoxy substituent is consistent with a greater value for $\eta$ for $\gamma$-benzyl. The 2-phenyl substituent caused an 100% rate-enhancement over the range $2 < 0^\circ$ but the 4-methoxy group induced only a further 10% increase in $k$. This could be compared to the effect of a 3-methoxy group on the solvolysis of 3-chloro-1-methyl-2-propyloxazoline ("3-oxacyl chloride") which underwent solvolysis with almost equal rate as the parent. Conversion of 0.5-fold enhancement for phenethyl (Brown, 1969). Although the relative magnitude of the individual effects of negative charge on $\eta$ 2 (4-14), would be difficult to estimate it might appear that the phenyl group was about as effective as the methoxy group in placing charge on $\eta$. This was consistent with the $\eta$ value of section f.

The possibility of correlating these anomalous rates using a type of dual substituent parameter approach has been suggested by Maccoll and Grigg (1972). Brown (1969)
be a consequence of a change from the chloride to bromide. The latter do solvolyze faster than the former (Moelwyn-Hughes, 1962) and so may require less assistance from an electron-donating substituent. In any case the rates are not comparable because of a change in solvent. In both instances it appeared that an indirect effect due to resonance contributions of the type (4-14) were responsible for enhanced rates. Unfortunately, no data for a 4-methoxy substituent in the pyridine series was available. It can be seen that a 4-fluoro substituent was slightly less rate retarding than a 4-chloro substituent (Table 9) consistent with a greater value for $\sigma_R^+$ for F (-0.57) than for Cl (-0.36). The 4-phenyl substituent caused ca. 33% rate-enhancement over the parent at 53.1° but the 4-methoxy group produced only a further 10% increase in $k$. This could be compared to the effect of a $p$-methoxy group on the solvolysis of 1-chloro-1-methyl-ethylbenzene ("t-cumyl chloride") which underwent solvolysis 3400 times faster than the parent compared with only a 6.5-fold enhancement for $p$-phenyl (Brown, 1958). Although the relative magnitude of the indirect effect of negative charge on N-1 in (4-14) would be difficult to estimate it might appear that the phenyl group was about as efficient as the methoxy group in placing charge on N-1. This was consistent with the $pK_a$ data of Section I.

The possibility of correlating these anomalous rates using a type of Dual Substituent Parameter approach has been suggested by Noyce and Virgilio (1973). Brown (1958)
used the notion of independent inductive and resonance components in explaining the slight rate enhancement by \( p \)-fluoro in \( t \)-cumyl chlorides compared with a rate decrease for other \( p \)-halogeno \( t \)-cumyl chlorides. Ehrenson \textit{et al.}\,(1973) has given numerous examples. Equation 19, obtained by trial and error, successfully predicted the rate constants for the 4-OMe, 4-Cl and 4-F pyrimidines. These values are shown in Table 11.

\[
\log \left( \frac{k}{k_H} \right) = -2.36\sigma_I - 0.86\sigma_R^+ 
\]

\text{equation 19.}

This equation has no statistical justification whatsoever. However, it was consistent with the notion of a substantial resonance contribution from a formally \textit{meta} position. The negative signs for the coefficients indicate that electron-withdrawing groups retard the reaction and \textit{vice versa}. The equation predicted a much lower value for \( k \) when \( R = \text{Ph} \) than observed, which was consistent with the suggestion that the phenyl substituent may be more resonance-donating than anticipated on the basis of the \( \sigma_R^+ \) value (-0.30).

The major factor affecting the rate constants for the 4-OMe 4-Cl and 4-F compounds was the entropy change accompanying solvolysis shown in Table 10. For the parent, a large energy of activation contributes to its lesser reactivity compared to the corresponding benzene system. It has already been pointed out that the cation (4-11) would be a highly unstable species and a transition state of similar electronic structure would require a large amount of solvation to make its development energetically favourable. Such a structural ordering of
### TABLE 11

SOLVOLYSIS RATES FOR

![Chemical Structure](image.png)

at 53.1°

<table>
<thead>
<tr>
<th>R</th>
<th>FOUND</th>
<th>CALCULATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>1.80</td>
<td></td>
</tr>
<tr>
<td>OMe</td>
<td>2.57</td>
<td>2.85</td>
</tr>
<tr>
<td>Cl</td>
<td>0.299</td>
<td>0.31</td>
</tr>
<tr>
<td>F</td>
<td>0.417</td>
<td>0.37</td>
</tr>
<tr>
<td>Ph</td>
<td>2.38</td>
<td>1.90</td>
</tr>
</tbody>
</table>

The solvent would produce a large (unfavorable) positive entropy change. The value of -0.9 m.w. may be explained by a value of -0.9 m.w. for the solvolysis of 2-phenylchloride in 50% aqueous methanol (Hirsch and Fahey, 1967). Chlorides are known to be less solvated than bromides, whereas and nitro groups may induce an even more negative effect. The substituents may affect the entropy of activation in the following way:

A methoxy group in the 4-position will produce considerable base-strengthening of the 4-phenyl derivative. The rate of solvolytic reactions in a solvent of lower ionic strength (or "unreactive"

Thus the solvent will have a relatively more ordered state of hydrogen bonding in the ground state relative to the reactant. The developing carbocation will induce a greater amount of ordering of solvent about the reaction site and a more negative value of \( \Delta G^+ \) will result. In the light of the complex changes accompanying \( \Delta H^+ \) and \( \Delta S^+ \) with changes in solvent (Thorson, 1964) any further discussion should await the acquisition of more data.
the solvent would produce a large (unfavourable) negative entropy change. The value of -6.8 e.u. may be compared to a value of -0.6 e.u. for the solvolysis of t-butyl chloride in 50% aqueous methanol (Winstein and Fainberg, 1957). Chloride ion should be more strongly solvated than bromide (Harvey and Porter, 1963) so a change from bromide to chloride in the pyrimidine would produce an even more negative value of $\Delta S^+$. The substituents may affect the entropy of activation in the following way. A methoxy group in the 4-position will produce considerable base strengthening of the nitrogen atoms and increase hydrogen bonding in their vicinity in the ground state. Thus the solvent molecules, relatively more ordered in the 4-methoxy compound than in the parent, will experience a lesser amount of immobilization (or "electrostriction": Laidler, 1963, Schaleger and Long, 1962) on attainment of the carbonium ion-like transition state. This should result in a less negative value for $\Delta S^+$. The reverse holds for the 4-halogeno substituents, in which case base-weakening has reduced hydrogen bonding in the ground state relative to the parent. The developing carbonium ion will induce a greater amount of ordering of solvent about the reaction site and a more negative value of $\Delta S^+$ will result. In the light of the complex changes accompanying $\Delta S^+$ and $\Delta H^+$ with changes in solvent (Thornton, 1964) any further discussion should await the acquisition of more data.
In Chapter 2 mention was made of the ease of bromination of the 4-halogeno-2-isopropylpyrimidine and the reduced rate for the 4-OMe compound. This was the reverse of the order in substituted toluenes in which, for example, a m-bromo group decreases the rate of bromination (Stirling, 1965). Correlation of radical bromination rates has been achieved with \( \sigma^+ \) values (Russell, 1958). This has been attributed to the relatively low reactivity of the bromine atom and the consequent late transition state resembling products and having a fair degree of bond breaking. Russell (1958) proposed that resonance structures such as (4-16) will become important and the stabilizing effects of substituents on the positive carbon will determine the relative rates. Such carbonium ion-like transition states have been seen to be highly unstable for pyrimidines and, given the rate-accelerating effect of a 4-fluoro substituent in bromination, appear to play no part in the constitution of the transition state. It is reasonable to suggest that the transition state occurs earlier for compounds of type (4-17) compared to toluenes and it is the strength of the C-H bond which determines rate. Weakened by electron-withdrawal from the pyrimidine ring, the C-H bond will be further weakened by electron-withdrawing halogen substituents and strengthened by electron-donating substituents.
In conclusion, it appears that spectroscopic acidic and unsaturated effects are attributable to an unsaturated reaction site on the ring because of the generation of variable intramolecular conjugation. Data from this work suggest that the compounds examined are unstable compounds which can strongly interact in a resonance way with the ring nitrogen, thus generating negative charge by an inductive effect. Some substituents, in particular, Me and Ph, appear to stabilize negative charge by an inductive resonance interaction in a greater extent than others. It would be worthwhile to examine these effects in other more stable teaching systems such as axial and equatorial protons. It is possible to probe for enhanced electronic effects in the side-chain of unsaturated x-d deficit heterocycles.

(4-16)

\[
\begin{align*}
\text{C} & \quad \text{Me} \\
\text{Me} & \quad \text{H} \\
\text{X} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{C} & \quad \text{Me} \\
\text{Me} & \quad \text{H} \\
\text{X} & \quad \text{Me}
\end{align*}
\]

(4-17)
In conclusion, it appeared that pyrimidinylacetic acids are unsuitable for probing the "transmission" of substituent effects to an insulated reaction site on the ring because of the possibility of variable intramolecular hydrogen bonding. Both the data from this work and those for the solvolysis of 2-(1'-bromo-1'-methylethyl)pyrimidines however indicate that substituents which can strongly interact in a mesomeric way with the ring nitrogen will modify side-chain reactivities by an indirect inductive effect. Some substituents, in particular Ph and SEt, appear to donate negative charge by a resonance interaction to a greater extent than expected. It would be useful to examine these effects using ground state methods such as $^{13}\text{C}$ and $^{19}\text{F}$ magnetic resonance to probe for enhanced electronic effects in the side-chain of substituted $\pi$-deficient heterocycles.
CHAPTER 5

EXPERIMENTAL

SECTION I

Microanalyses were carried out by the Australian National University Analytical Services Unit. Solids for analysis were dried at 100° under a vacuum of 0.1 mmHg unless otherwise stated. Melting points are uncorrected.

Where possible, all compounds were examined for the presence of impurities by thin layer chromatography (silica or alumina in chloroform/methanol 10:1 or ethyl acetate).

$^1$H N.m.r. spectra were run at 60 MHz at 35° with a Varian T60-A instrument. The solvent used was CDCl$_3$ unless otherwise indicated. Tetramethylsilane or the sodium salt of 3-(trimethylsilyl)propanesulphonic acid in water was used as an internal standard. Mass spectra were run on an A.E.I. MS9 instrument.

New compounds were measured in potassium bromide discs (unless otherwise indicated) on a Unicam SP1000 instrument. Ultraviolet spectra were recorded on a Unicam SP8000 and peaks checked on a Unicam SP1700 instrument.

New compounds are underlined at their first mention in this Chapter.

Methyl and ethyl 2-(4',6'-dichloropyrimidin-2'-yl)acetimidate

$^2$-(1',6'-Dihydro-4'-hydroxy-6'-oxopyrimidin-2'-yl)acetamide (Brown, 1956; McElvain and Tate, 1951) was converted into 2-(4,6'-dichloropyrimidin-2'-yl)acetonitrile by treatment (McElvain and Tate, 1951) with phosphoryl chloride. A solution of
the nitrile (1.0 g) in anhydrous ether (20 ml), anhydrous benzene (20 ml), and absolute ethanol (2 ml) was saturated with dry hydrogen chloride at 0°. After a further 12 h at 5°, the ethyl acetimidate hydrochloride (90%) was filtered off, washed with ether, and dried at 50°. It had m.p. 141-143° (Found: C, 35.6; H, 3.9; N, 15.3. 
C₈H₁₀Cl₃N₃O requires C, 35.5; H, 3.7; N, 15.5%); νmax. 1655 (C=N stretching).

The use of absolute methanol instead of ethanol gave similarly the methyl acetimidate hydrochloride (88%), m.p. 136-137° (Found: C, 33.1; H, 3.3; N, 16.2. 
C₇H₈Cl₃N₃O requires C, 32.8; H, 3.1; N, 16.4%).

**Methyl and ethyl 2-(4',6'-dichloropyrimidin-2'-yl)acetate**

The above ethyl acetimidate hydrochloride (230 mg) was stirred in water (2 ml) at 40° for 4 h. The solution was extracted with ether (5 x 10 ml). The dehydrated extract was evaporated to give the ethyl ester (120 mg), m.p. 50-51° (from light petroleum) (Found: C, 41.0; H, 3.5; N, 12.0. 
C₈H₈Cl₂N₂O₂ requires C, 40.9; H, 3.4; N, 11.9%); νmax. 1730 (C=O); n.m.r. 1.30 (t, ~8, Me of Et), 4.10 (s, 2-CH₂), 4.30 (q, ~8, CH₂ of Et), 7.50 (s, H5').

Similarly, the methyl acetimidate hydrochloride gave the methyl ester, m.p. 62-63°, in comparable yield (Found: C, 38.3; H, 2.6; N, 12.5. 
C₇H₆Cl₂N₂O₂ requires C, 38.0; H, 2.7; N, 12.7%).
Ethyl 2-(pyrimidin-2'-yl)acetate

The foregoing ethyl ester (800 mg) was hydrogenated at atmospheric temperature and pressure in water (40 ml) containing sodium carbonate (740 mg; 2 mol.) and 10% palladium-on-charcoal (160 mg). The theoretical uptake (180 ml) occurred in ~1 h. The filtered solution was extracted with chloroform (5 x 20 ml). Dehydration of the extract and evaporation gave the ethyl pyrimidinylacetate (68%), b.p. 96-98°/3 mm (Found: C, 58.0; H, 6.1; N, 16.8. \( \text{C}_8\text{H}_{10}\text{N}_2\text{O}_2 \) requires C, 57.8; H, 6.1; N, 16.9%); n.m.r. 1.23 (t, \( \delta \) 8, Me of Et), 4.00 (s, 2-\text{CH}_2), 4.20 (q, \( \delta \) 8, \text{CH}_2 of Et), 7.20 (t, \( \delta \) 5, H5'), 8.70 (d, \( \delta \) 5, H4'+H6'). A comparable result was obtained by using sodium hydrogen carbonate as base.

2-(Pyrimidin-2'-yl)acetic acid

The above ethyl pyrimidinylacetate (480 mg) was boiled under reflux in water (10 ml) containing sodium hydroxide (130 mg) until t.l.c. (silica; ethyl acetate) indicated that saponification was complete (~30 min). The solid from evaporation recrystallized from ethanol to give the sodium pyrimidinylacetate (60%), m.p. 220° (dec.)(Found: C, 44.7; H, 3.6; N, 17.2. \( \text{C}_6\text{H}_5\text{N}_2\text{NaO}_2 \) requires C, 45.0; H, 3.2; N, 17.5%); n.m.r. (D\(_2\)O) 4.87 (s, \text{CH}_2), 7.23 (t, \( \delta \) 5, H5'), 8.50 (d, \( \delta \) 5, H4'+H6').

Ethyl 2-(1',4',5',6'-tetrahydropyrimidin-2'-yl)acetate

The ethyl dichloropyrimidinylacetate (1.12 g) was hydrogenated in ethanol (50 ml) containing sodium hydrogen carbonate (400 mg) and 10% palladium-on-charcoal (700 mg)
until uptake ceased. Filtration followed by evaporation left a brei from which the organic material was extracted with a little hot ethanol. Refrigeration of the extract gave the ethyl tetrahydropyrimidinylacetate hydrochloride (60%), m.p. 125-126° (Found: C, 46.9; H, 7.3; N, 13.4. \( \text{C}_8\text{H}_{15}\text{ClN}_2\text{O}_2 \) requires C, 46.5; H, 7.3; N, 13.6%); n.m.r. 1.17 (t, J 8, Me of Et), 1.93 (m, 4'-CH\(_2\) + 6'-CH\(_2\)), 3.40 (m, 5'-CH\(_2\)), 3.87 (s, 2-CH\(_2\)), 4.80 (q, J 8, CH\(_2\) of Et). The same result was obtained using magnesium oxide in place of sodium bicarbonate.

Methyl 2-(4'-chloro-6'-methoxypyrimidin-2'-yl)acetate

Methyl dichloropyrimidinylacetate (2.0 g) was stirred at 25° for 6 h with methanolic sodium methoxide (methanol, 10 ml; sodium, 120 mg). The residue from evaporation in vacuo at 40° was extracted with ether. Distillation of the extract gave the methyl chloromethoxypyrimidinylacetate (1.5 g), b.p. 116-118°/1.5 mm (Found: C, 44.6; H, 4.4; N, 13.0. \( \text{C}_8\text{H}_{9}\text{ClN}_2\text{O}_3 \) requires C, 44.4; H, 4.2; N, 12.9%); n.m.r. 3.70 (s, CO\(_2\)Me), 3.90 (s, CH\(_2\)), 3.93 (s, 6'-OMe), 6.63 (s, H5'); \( \nu_{\text{max}} \) 1740 (C=O). m.x.

Methyl 2-(4'-methoxypyrimidin-2'-yl)acetate

(a) The foregoing methyl chloromethoxypyrimidinylacetate (1.3 g) was hydrogenated in methanol (60 ml) containing sodium carbonate (650 mg) and 10% palladium-on-charcoal (150 mg). The filtered solution was evaporated and the residue was distilled to give the methyl methoxypyrimidinylacetate (950 mg), b.p. 100-102°/1.5 mm (Found: C, 52.8;
H, 5.9; N, 15.5. $C_8H_{10}N_2O_3$ requires C, 52.7; H, 5.5; N, 15.4%; n.m.r. 3.70 (s, CO$_2$Me), 3.87 (s, CH$_2$), 3.90 (s, 4'-OMe), 6.57 (d, J 5, H5'), 8.33 (d, J 5, H6'); $\nu_{max}$ 1740 (C=O).

(b) Ethyl 2-(4',6'-dichloropyrimidin-2'-yl)acetate (500 mg) was hydrogenated in methanol containing sodium hydroxide (170 mg) and palladium-on-charcoal (170 mg). The filtered solution was distilled to give a product (255 mg) identical with that from (a) in n. m. r., i.r., and analysis (Found: C, 53.1; H, 5.9%).

2-(4'-Methoxypyrimidin-2'-yl)acetic acid

The above ester (200 mg) was stirred for 12 h at 70º in a mixture of methanol (5 ml), water (0.5 ml), and sodium hydroxide (44 mg). Evaporation and crystallization of the residue from ethanol gave the sodium methoxypyrimidinylacetate (180 mg), m.p. >300º (dec.) (Found: C, 44.3; H, 4.1; N, 14.7. $C_7H_7N_2NaO_3$ requires C, 44.2; H, 3.7; N, 14.7%); n.m.r. (D$_2$O) 3.73 (s, CH$_2$), 3.97 (s, CO$_2$Me), 6.83 (d, J 5, H5'), 8.43 (d, J 5, H6').

2-(4',6'-Dichloropyrimidin-2'-yl)acetic acid

Methyl dichloropyrimidinylacetate (1.0 g) was stirred at 50º in water (20 ml) containing sodium hydroxide (185 mg) for 4 h, during which time the solution became homogeneous. Evaporation in vacuo and recrystallization from ethanol gave the sodium dichloropyrimidinylacetate (700 mg), m.p. >320º (dec.) (Found: C, 31.6; H, 1.5; N, 11.9. $C_6H_3Cl_2N_2NaO_2$ requires C, 31.5; H, 1.3; N, 12.2%); n.m.r. (D$_2$O) 3.73 (s, CH$_2$), 7.50 (s, H5'); $\nu_{max}$ 1560 (C=O), 1590.
Ethyl methoxyformimidoylacetate hydrochloride

Ethyl cyanoacetate (30 g), anhydrous methanol (12.2 ml), and anhydrous ether (300 ml) were saturated with dry hydrogen chloride at $< 5^\circ$ and then allowed to stand at 0-5$^\circ$ for 18 h. The white solid was filtered off, washed with ether, and dried in vacuo. The hydrochloride (63%) had m.p. 88-90$^\circ$ (Found: C, 39.7; H, 6.7. $C_6H_{12}ClNO_3$ requires C, 39.7; H, 6.7%).

2-(1',6'-Dihydro-6'-oxo-4'-phenylpyrimidin-2'-yl)acetamide and 2-amino-1,6-dihydro-6-oxo-4-phenylpyridine-3-carboxamide

The above ethyl methoxyformimidoylacetate hydrochloride was converted (McElvain and Tate, 1951; Brown et al.1977) into amidinoacetamide hydrochloride in 73% yield. The amidine hydrochloride (10 g), ethyl benzoylacetate (14.6 g), and ethanol (100 ml) containing sodium hydroxide (2.9 g) were stirred together for 14 h at 25$^\circ$. The residue from evaporation of the slurry was added to ice water (50 ml) and the solution was adjusted to pH 3. The precipitated solid (c. 8 g) was dissolved in boiling methanol (150 ml). After standing at 20-25$^\circ$ for 1 h, the oxophenylpyrimidinylacetamide (2.0 g) was filtered off. It had m.p. 251-253$^\circ$ (from methanol)(Found: C, 62.9; H, 4.9; N, 18.4. $C_{12}H_{11}N_3O_2$ requires C, 62.9; H, 4.8; N, 18.3%); n.m.r. [(CD$_3$)$_2$SO] 3.70 (s, CH$_2$), 6.9 (s, H5'), 7.55 (m, H3"+H4"+H5" of Ph), 8.10 (m, H2"+H6" of Ph)]. Refrigeration of the filtrate at -5$^\circ$ for 3 h gave the phenylpyridinecarboxamide (4.5 g), m.p. 244-245$^\circ$ (from methanol)(Found: C, 62.9; H, 4.9; N, 18.7.
$\text{C}_{12}\text{H}_{11}\text{N}_{3}\text{O}_{2}$ requires C, 62.9; H, 4.8; N, 18.3\%; n.m.r.

$[(\text{CD}_{3})_{2}\text{SO}] 5.60 \text{ (s, H5)}, 7.60 \text{ (s, Ph)}. \text{Evaporation of the}

mother liquors and fractional crystallization of the residue
gave more of each compound. The total yields were
pyrimidine (15\%) and pyridine (33\%).

2-(4'-Chloro-6'-phenylpyrimidin-2'-yl)acetonitrile

The above hydroxyphenylpyrimidinylacetamide (2.0 g),
NN-diethylaniline (1.3 g), and phosphoryl chloride (60 ml)
were heated under reflux for 1 h. Evaporation of 70-80\%
of the phosphoryl chloride and quenching of the residue in
ice gave the yellow chlorophenylpyrimidinylacetonitrile
(1.5 g), m.p. 134-135° (from ethanol)(Found: C, 63.1;
H, 3.9; N, 18.0. $\text{C}_{12}\text{H}_{8}\text{ClN}_{3}$ requires C, 62.8; H, 3.5;
N, 18.3\%); n.m.r. 4.10 (s, CH$_2$), 7.53 (m, H3"+H4"+H5"),
7.66 (s, H5"'), 8.10 (m, H2"+H6").

Methyl 2-(4'-chloro-6'-phenylpyrimidin-2'-yl)acetimidate

A mixture of the foregoing nitrile (4 g), ether (100 ml),
and benzene (150 ml) was saturated at 0° with dry hydrogen
chloride and then allowed to stand for 12 h at 5°. The
crystalline methyl chlorophenylpyrimidinylacetimidate
hydrochloride (3.8 g) was filtered off and washed with ether.
It had m.p. 110-112° (dec.)(Found: C, 52.4; H, 4.6;
N, 14.2. $\text{C}_{13}\text{H}_{13}\text{Cl}_{2}\text{N}_{3}\text{O}$ requires C, 52.4; H, 4.4; N, 14.1\%).

Methyl 2-(4'-chloro-6'-phenylpyrimidin-2'-yl)acetate

The preceding acetimidate hydrochloride (3.7 g) was
stirred in water (100 ml) at 50° for 45 min. An ether extract
(3 x 40 ml) was washed with 5\% aqueous sodium hydrogen
carbonate (2 x 5 ml) followed by water (2 x 5 ml) and then dried over sodium sulphate. Evaporation gave the methyl chlorophenylpyrimidinylacetate (3.0 g), as a low (c. 31°) melting solid (from light petroleum) (Found: C, 59.4; H, 4.1; N, 10.8. \(\text{C}_{13}\text{H}_{11}\text{ClN}_{2}\text{O}_{2}\) requires C, 59.4; H, 4.2; N, 10.7%); n.m.r. 3.70 (s, Me), 4.0 (s, \(\text{CH}_2\)), 7.40 (m, H5'+H3"+H4"+H5"), 7.90 (m, H2"+H6").

**Methyl 2-(4'-phenylpyrimidin-2'-yl)acetate**

The foregoing chloro derivative (1.2 g) was hydrogenated (2 h; uptake, 110 ml) in methanol (50 ml) containing sodium carbonate (500 mg) and 10% Pd/C (150 mg). Evaporation of the filtered solution gave the methyl phenylpyrimidinylacetate (900 mg) (Found: C, 68.7; H, 5.4; N, 12.2. \(\text{C}_{13}\text{H}_{12}\text{N}_{2}\text{O}_{2}\) requires C, 68.4; H, 5.3; N, 12.3%); n.m.r. 3.70 (s, Me), 4.10 (s, \(\text{CH}_2\)), 7.47 (m, H5'+H3"+H4"+H5"), 8.06 (m, H2"+H6"), 8.86 (d, \(J = 5\), H6').

**2-(4'-Phenylpyrimidin-2'-yl)acetic acid**

The above ester (900 mg) was boiled in 0.3N sodium hydroxide (15 ml) for 3 h. Evaporation gave the sodium phenylpyrimidinylacetate (55%), m.p. 250-255° (dec.) (from ethanol) (Found: C, 60.6; H, 4.5. \(\text{C}_{12}\text{H}_{10}\text{N}_{2}\text{NaO}_{2}\) requires C, 60.8; H, 4.2%); n.m.r. (\(\text{D}_2\text{O}\)) 3.86 (s, \(\text{CH}_2\)), 7.47 (m, H5'+H3"+H4"+H5"), 7.67 (m, H2"+H6"), 8.40 (d, \(J = 5\), H6').
2-(1',6'-Dihydro-4'-methyl-6'-oxopyrimidin-2'-yl)acetamide
and 2-amino-1,6-dihydro-4-methyl-6-oxopyridine-3-carboxamide

Amidinoacetamide hydrochloride (10 g) and ethyl acetoacetate (9.5 g) were condensed in ethanolic sodium hydroxide as described for the phenyl homologue. The crude product (10 g) was recrystallized from boiling methanol (300 ml). After removing a first crop (6 g), the filtrate was evaporated to 100 ml which was then left at 20-25° for 1 h to give a second crop (1.2 g). The combined solids were recrystallized from water to give the methyl oxopyrimidinylacetamide, m.p. 245-247° (lit. 235-252°; Dornow and Neuse, 1954)(Found: N, 24.9. Calc. for C₇H₉N₃O₂: N, 25.1%); n.m.r. [(CD₂)₂SO] 2.13 (s, Me), 3.43 (s, CH₂), 6.00 (s, H₅'). Evaporation of the mother liquors and recrystallization from water gave the pale yellow isomeric pyridinecarboxamide, m.p. 263-265° (dec.) (lit. 263-265,252°; Imbach et al., 1970; Dornow and Neuse, 1954, respectively)(Found: C, 50.4; H, 5.4; N, 25.0. Calc. for C₇H₆N₂O₂: C, 50.3; H, 5.4; N, 25.1%); n.m.r. [(CD₂)₂SO] 2.10 (s, Me), 5.30 (s, H₅). When the original condensation was done in boiling ethanolic sodium ethoxide, the main product (5.0 g) was the pyridinecarboxamide.

2-(4'-Methylpyrimidin-2'-yl)acetic acid and intermediates

By methods similar to those described for its 4'-phenyl homologue, the above methyl oxopyrimidinylacetamide was converted successively into 2-(4'-chloro-6'-methylpyrimidin-2'-yl)acetonitrile (82%), m.p. 78-79° (Found: C, 50.2; H, 3.9; N, 25.0. C₇H₆ClN₃ requires C, 50.2; H, 3.6; N, 25.1%; n.m.r. 2.53 (s, Me), 4.03 (s, CH₂), 7.16 (s, H₅').)
methyl 2-(4'-chloro-6'-methylpyrimidin-2'-yl)acetimidate hydrochloride (77%), m.p. 105-106° (dec.) (Found: C, 40.3; H, 5.0. \( \text{C}_{8}\text{H}_{11}\text{Cl}_{2}\text{N}_{3}\text{O} \) requires C, 40.7; H, 4.7%) and also (by using ethanol) ethyl 2-(4'-chloro-6'-methylpyrimidin-2'-yl)acetimidate hydrochloride (80%), m.p. 129-131° (Found: C, 43.0; H, 5.3. \( \text{C}_{9}\text{H}_{13}\text{Cl}_{2}\text{N}_{3}\text{O} \) requires C, 43.2; H, 5.2%); ethyl 2-(4'-chloro-6'-methylpyrimidin-2'-yl)acetate (89%), m.p. 59-60° (Found: C, 50.1; H, 5.3; N, 12.9. \( \text{C}_{9}\text{H}_{11}\text{ClN}_{2}\text{O}_{2} \) requires C, 50.4; H, 5.2; N, 13.0%); the liquid ethyl 2-(4'-methylpyrimidin-2'-yl)acetate (81%) (Found (after dissolution in light petroleum, treatment with charcoal, double filtration, and evaporation): N, 15.7. \( \text{C}_{9}\text{H}_{12}\text{N}_{2}\text{O}_{2} \) requires N, 15.6%) [n.m.r. 1.23 (t, \( \tilde{J} \) 8, Me of Et), 2.47 (s, 4'-Me), 3.90 (s, 2-CH\(_2\)), 4.17 (q, \( \tilde{J} \) 8, CH\(_2\) of Et), 7.00 (d, \( \tilde{J} \) 5, H5'); 8.47 (d, \( \tilde{J} \) 5, H6')] and sodium 2-(4'-methylpyrimidin-2'-yl)acetate (53%), m.p. 257-261° (dec.) (Found: N, 16.2. \( \text{C}_{7}\text{H}_{7}\text{N}_{2}\text{NaO}_{2} \) requires N, 16.1%).

2-(4'-t-Butyl-1',6'-dihydro-6'-oxopyrimidin-2'-yl)acetamide

A mixture of amidinoacetamide hydrochloride (6.7 g), ethyl pivaloylac etate (8.6 g), and ethanolic sodium ethoxide (ethanol, 30 ml; sodium, 1.1 g) was heated at 70° with stirring for 24 h. The residue from evaporation was suspended in water (15 ml) and adjusted to pH 3. The resulting solid (3.7 g) was recrystallized first from isobutyl methyl ketone and then from ethanol to give the t-butyloxopyrimidinylacetamide, m.p. 200-202° (Found: C, 57.5; H, 7.0; N, 20.2. \( \text{C}_{10}\text{H}_{15}\text{N}_{3}\text{O}_{2} \) requires C, 57.4; H, 7.2; N, 20.1%); n.m.r. [(CD\(_3\))\(_2\)SO] 1.75 (s, Bu\(^t\)), 3.50 (s, CH\(_2\)), 6.10 (s, H5'), 7.1 (br, NH), 7.5 (br, NH).
2-(4'-t-Butylpyrimidin-2'-yl)acetic acid and intermediates

Like its phenyl analogue, the above 6-t-butylhydroxy-
pyrimidinylacetamide was converted sequentially into
2-(4'-t-butyl-6'-chloropyrimidin-2'-yl)acetonitrile (73%),
m.p. 41-42° (Found: C, 57.2; H, 5.7; N, 20.0.
C_{10}H_{12}ClN_{3} requires C, 57.3; H, 5.8; N, 20.0%) [n.m.r.
1.33 (s, Bu), 4.03 (s, CH_{2}), 7.26 (s, H5')]; methyl
2-(4'-t-butyl-6'-chloropyrimidin-2'-yl)acetimidate hydro-
chloride (64%), m.p. 110-112° (dec.) (Found: C, 47.6;
H, 6.3; N, 14.8. C_{11}H_{17}ClN_{3}O requires C, 47.5; H, 6.2;
N, 15.1%); methyl 2-(4'-t-butyl-6'-chloropyrimidin-2'-yl)acetate
(55%), b.p. 94-96°/0.5 mm (Found: C, 55.0; H, 6.3; N, 11.9.
C_{11}H_{15}ClN_{2}O requires C, 54.4; H, 6.2; N, 11.5%)[n.m.r.
1.30 (s, Bu), 3.72 (s, Me), 3.97 (s, CH_{2}), 7.23 (s, H5')];
the liquid, methyl 2-(4'-t-butylpyrimidin-2'-yl)acetate
(74%) (Found: C, 63.0; H, 7.3. C_{11}H_{16}N_{2}O_{2} requires C, 63.4;
H, 7.7%); and sodium 2-(4'-t-butylpyrimidin-2'-yl)acetate
(60%), m.p. >300° (dec.) (Found: C, 55.4; H, 6.2; N, 12.8.
C_{10}H_{13}N_{2}NaO_{2} requires C, 55.5; H, 6.1; N, 12.9%).

2-(4'-Isopropylpyrimidin-2'-yl)acetic acid and intermediates

Condensation of amidinoacetamide hydrochloride with
ethyl isobutyrylacete, as for the t-butylpyrimidine, gave
2-(1',6'-dihydro-4'-isopropyl-6'-oxopyrimidin-2'-yl)acetamide
(64%), m.p. 164-165° (from ethanol) (Found: C, 55.3; H, 6.5;
N, 21.4. C_{9}H_{13}N_{3}O_{2} requires C, 55.4; H, 6.7; N, 21.5%);
[n.m.r. in (CD_{3})_{2}So: 1.13 (d, J 6, Me_{2}), 2.67 (sep., J 6,
Ch of Pr), 3.43 (s, CH_{2}), 5.97 (s, H5'), 7.10 and 7.50
(br, NH_{2}); \nu_{max}. 1610, 1660 (lactam), 1690 (C=O of amide),
3170 and 3420 (NH$_2$); 2-((4'-chloro-6'-isopropylpyrimidin-2'-yl)acetonitrile (61%), a liquid purified by dissolution in light petroleum and evaporation (Found: C, 54.9; H, 5.3; N, 21.2. C$_9$H$_{10}$ClN$_3$ requires C, 55.2; H, 5.2; N, 21.5%) [n.m.r. 1.30 (d, J 6, Me$_2$), 3.10 (sep., J 6, CH of Pr$^1$), 4.20 (s, CH$_2$), 7.37 (s, H5'); $\nu_{\text{max}}$ 1570, 2280 (CN)]; methyl 2-((4'-chloro-6'-isopropylpyrimidin-2'-yl)-acetimidate hydrochloride, a hygroscopic solid, m.p. 106-103$^\circ$ (from ethanol-ether) (Found: N, 15.8. C$_{10}$H$_{15}$Cl$_2$N$_3$O requires N, 15.9%) [$\nu_{\text{max}}$ 1670 (C=NH)]; methyl 2-((4'-chloro-6'-isopropylpyrimidin-2'-yl)acetate (92%), b.p. 110-112$^\circ$/1 mm (Found: C, 52.3; H, 5.9; N, 12.4. C$_{10}$H$_{13}$ClN$_2$O$_2$ requires C, 52.5; H, 5.7; N, 12.2%) [n.m.r. 1.30 (d, J 6, Me$_2$ of Pr$^1$), 3.03 (sep., J 6, CH of Pr$^1$), 3.77 (s, OMe), 4.03 (s, CH$_2$), 7.20 (s, H5'); $\nu_{\text{max}}$ 1740 (C=O)]; methyl 2-((4'-isopropylpyrimidin-2'-yl)acetate (85%), b.p. 120-122$^\circ$/6 mm (Found: C, 62.1; H, 7.0; N, 14.6. C$_{10}$H$_{14}$N$_2$O$_2$ requires C, 61.8; H, 7.3; N, 14.4%) [n.m.r. 1.26 (d, J 6, Me$_2$ of Pr$^1$), 3.03 (sep., J 6, CH of Pr$^1$), 3.77 (s, OMe), 4.03 (s, CH$_2$), 7.17 (d, J 6, H5'), 8.53 (d, J 6, H6'); $\nu_{\text{max}}$ 1740 (C=O)]; and the hygroscopic sodium 2-((4'-isopropylpyrimidin-2'-yl)acetate, m.p. 220-222$^\circ$ (dec.) (Found: C, 50.9; H, 5.9; N, 13.3. C$_9$H$_{11}$N$_2$NaO$_2$ + 0.5 H$_2$O requires C, 51.2; H, 5.7; N, 13.3%) [n.m.r. (D$_2$O) 1.23 (d, J 6, Me$_2$), 2.97 (sep., J 6, CH of Pr$^1$), 3.80 (s, CH$_2$), 7.20 (d, J 6, H5'), 8.47 (d, J 6, H6');].
2-(4'-Ethyl-1',6'-dihydro-6'-oxopyrimidin-2'-yl)acetamide

Ethyl 3-oxo-n-valerate (5 g) and amidinoacetamide hydrochloride (4.8 g) were stirred in absolute ethanol (30 ml) with one mole of sodium hydroxide for 16 h at 25°. The solid formed was filtered off, added to water (20 ml) at 0° and pH adjusted to 7. The precipitated solid was filtered and dried giving a mixture (4.5 g) of the pyrimidine and the isomeric 2-amino-4-ethyl-1,6-dihydro-6-oxopyridine-3-carboxamide in a 4:1 ratio (n.m.r.). The pure pyrimidine (1 g) could be obtained by fractional crystallization from ethanol and had m.p. 196-197° (Found: C, 52.6; H, 6.2; N, 23.0. \( \text{C}_{8}\text{H}_{11}\text{N}_{3}\text{O}_{2} \) requires C, 53.0; H, 6.1; N, 23.2%); n.m.r. \( \delta ($)\text{CD}_3\text{SO} \) 1.10 (t, J 8, Me); 2.43 (q, J 8, ethyl CH\(_2\)); 3.40 (s, CH\(_2\)); 6.00 (s, H5); 7.10, 7.63 (br, NH\(_2\) of amide).

The pyridine [\( \delta 5.37 \text{ (s, H5)} \)] was not isolated.

Methyl 2-(1',6'-dihydro-6'-oxopyrimidin-2'-yl)acetate

Anhydrous hydrogen bromide was generated by dropping bromine onto dry tetralin according to the method of Vogel (1956). The hydrogen bromide was passed directly into dry benzene. Methyl 2-(4'-methoxypyrimidin-2'-yl)acetate (1.05 g) was stirred in a 5% solution of hydrogen bromide in benzene (80 ml) at 50° for 16 hours. The solution was cooled and the white precipitate filtered. This material was dissolved in a mixture of methanol (20 ml) and water (5 ml) and neutralized with sodium bicarbonate at 0°. This solution was evaporated to dryness and extracted with boiling ethyl acetate (2 x 50 ml)
Evaporation of the solvent yielded 750 mg (80%) of the ester, m.p. 180-181\(^\circ\) (after recrystallization from ethyl acetate) (Found: C, 50.0; H, 4.7; N, 16.5. \(C_7H_8N_2O_3\) requires C, 50.0; H, 4.8; N, 16.7\%); \(\nu_{\text{max}}\) 1660, 1690 (C=O str); n.m.r. (CDCl\(_3\)) 3.83 (s, Me); 6.43 (d, \(J\ 6\), H5); 8.00 (d, \(J\ 6\), H6). The CH\(_2\) signal was not detectable in dry chloroform presumably due to rapid exchange with N-H. M\(^+\) 168.

**Methyl 2-(4'-chloropyrimidin-2'-yl)acetate**

Methyl 2-(1',6'-dihydro-6'-oxopyrimidin-2'-yl)acetate (750 mg) was refluxed with phosphorous oxychloride (60 ml) and diethylaniline (660 mg) for 30 minutes. The solution was cooled and excess phosphorous oxychloride removed in a rotary evaporator. The remaining liquid was poured onto crushed ice (~50 g) and extracted with diethyl ether (6 \(\times\) 30 ml). The ether was washed with a 5% sodium bicarbonate solution (2 \(\times\) 10 ml) and water (2 \(\times\) 10 ml) and dried over calcium sulphate. Evaporation of the ether yielded a yellow product (b.p. 86-88\(^\circ\)/0.4 mm). The yield was 350 mg (42\%, based on distilled material) (Found: C, 44.8; H, 3.8; N, 14.7. \(C_7H_7ClN_2O_2\) requires C, 45.1; H, 3.8; N, 15.0\%); \(\nu_{\text{max}}\) 1750 (ester C=O str); n.m.r. (CDCl\(_3\)) 3.77 (s, Me); 4.03 (s, CH\(_2\)); 7.33 (d, \(J\ 6\), H5); 8.67 (d, \(J\ 6\), H6).
2-((4'-Chloropyrimidin-2'-yl)acetic acid

Methyl 2-(4'-chloropyrimidin-2'-yl)acetate (90 mg) was stirred in water (20 ml) with sodium hydroxide (20 mg, 1 mole) for 30 minutes at 35°C after which time the hydrolysis was judged complete by t.l.c. The solution was evaporated to dryness in a rotary evaporator at < 35°C and further dried in a desiccator under a good vacuum overnight. The solid was recrystallized by dissolution in methanol (5-6 ml) at 20°C, addition of diethyl ether until the solution becomes faintly turbid followed by refrigeration overnight. This gave the sodium chloropyrimidinylacetate (80 mg), m.p. >300°C (Found: C, 36.4; H, 1.9; N, 14.0. C₆H₄ClN₂NaO₂ requires C, 37.0; H, 2.1; N, 14.4%).

Methyl 2-(4'-ethylthiopyrimidin-2'-yl)acetate

Ethylmercaptan (80 mg) was added to a sodium methoxide solution (made by dissolving 25 mg of sodium in 20 ml of methanol) and cooled to 0°C. Methyl 2-(4'-chloropyrimidin-2'-yl)acetate (200 mg) was added to this solution maintaining the temperature at 0°C for 6 hours. The solution was evaporated to dryness, triturated with diethyl ether (50 ml) filtered and the ether evaporated to yield the methyl ethylthiopyrimidinylacetate (190 mg) (b.p. 114-116°C/0.5 mm) (Found: C, 51.0; H, 5.7; N, 13.4. C₆H₁₂N₂O₂S requires C, 50.9; H, 5.7; N, 13.2%); vmax. 1760 (ester C=O str); n.m.r. (CDCl₃) 1.40 (t, J 8, Me of ethyl); 3.30 (q, J 8, CH₂ of ethyl); 3.80 (s, Me); 4.03 (s, CH₂); 7.13 (d, J 6, H5); 8.43 (d, J 6, H6).
2-(4'-Ethylthiopyrimidin-2'-yl)acetic acid

The above ester (73 mg) was stirred in water (8 ml) with sodium hydroxide (14 mg) for 60 minutes at 50°. Evaporation and recrystallization of the residue from ethanol gave the sodium ethylthiopyrimidinylacetate (65 mg) m.p.: >300° (dec.) (Found: C, 43.2; H, 4.1; N, 12.6. C₈H₉N₂NaO₂S requires C, 43.6; H, 4.1; N, 12.7%).

Methyl 2-(4'-ethylsulphonylpyrimidin-2'-yl)acetate

Methyl 2-(4'-ethylthiopyrimidin-2'-yl)acetate (450 mg) was stirred at room temperature with 80% m-chloroperbenzoic acid (920 mg, 2 moles) in chloroform (50 ml) for 4 h after which time the reaction was judged complete (t.l.c., alumina, methylene dichloride). The chloroform was washed successively with 10% sodium bisulphite (2 x 10 ml) 5% sodium carbonate (2 x 10 ml) and water (4 x 10 ml) dehydrated and evaporated to dryness to yield the methyl ethylsulphonylpyrimidinylacetate (200 mg, based on distilled material) b.p. 165-166°/0.7 mm (Found: C, 44.8; H, 4.9; N, 11.8. C₉H₁₂N₂O₄S requires C, 44.3; H, 4.9; N, 11.5%); ν_max 1750 (ester C=O str); 1325, 1130 (ν_as and ν_s SO₂ resp.); n.m.r. 1.37 (t, J 8, Me of ethyl); 3.53 (q, J 8, CH₂ of ethyl); 3.80 (s, Me); 4.23 (s, CH₂); 8.03 (d, J 6, H5); 9.20 (d, J 6, H6).

2-(4'-Ethylsulphonylpyrimidin-2'-yl)acetic acid

Sodium hydroxide (33 mg), dissolved in water (3 ml) was added to a stirred suspension of methyl 2-(4'-ethyl-sulphonylpyrimidin-2'-yl)acetate (200 mg) in water over
30 minutes at 0°. The solution was stirred at 5° for 60 minutes and stored overnight at 0°. The material was freeze dried and finally left overnight in an evacuated desiccator over P₂O₅. Thin layer chromatography showed the presence of a considerable portion (ca 50%) of methyl 2-(1',6'-dihydro-6'-oxopyrimidin-2'-yl)acetate. The material was dissolved in methanol (20 ml) at 0° and decolourised with activated charcoal, diethyl ether was added (30 ml) and the material refrigerated (-5°) for 4 days. In this way 10-15 mg. (5-7%) of pure sodium ethylsulphonylpyrimidinylacetate was obtained; m.p. > 300° (dec.)(Found: C, 36.8; H, 3.9; N, 10.6. C₈H₉N₂NaO₄S₁₂H₂O requires C, 36.8; H, 3.8; N, 10.7%).

Methyl 2-Methoxycarbonylpyrimidin-4-yltrimethylammonium chloride

Methyl 2-(4'-chloropyrimidin-2'-yl)acetate (550 mg) was dissolved in benzene (10 ml) and added to a 15% benzene solution of trimethylamine (35 ml) and left for 3 days at 20°. After this period the white solid was filtered off (600 mg), washed well with dry diethyl ether and dried in a vacuum at room temperature, m.p. 150-152° (dec.)(Found: C, 48.4; H, 6.8; N, 17.9. C₁₀H₁₆ClN₃O₂ requires C, 48.9; H, 6.6; N, 17.1%).

Methyl 2-(4'-fluoropyrimidin-2'-yl)acetate

Methyl 2-Methoxycarbonylpyrimidin-4-yltrimethylammonium chloride (550 mg) was added to an aqueous solution of potassium hydrogen difluoride (1 g, 20 ml) at 5°.
Immediately diethyl ether was added (60 ml) and the mixture stirred sufficiently to cause good mixing at the interface of the two liquids. After twenty minutes the ether was removed, washed with sodium bicarbonate solution (10%, 2 x 10 ml) and water (3 x 10 ml) and dehydrated over calcium sulphate. Fresh ether was added and the process continued for 2-5 h after which time little organic material was passing from the aqueous layer into the ether (as judged by t.l.c.).

The combined ether extracts were evaporated to yield the methyl fluoropyrimidinylacetate (50 mg, 12%) (Found: C, 49.8; H, 4.0; \( \text{C}_7\text{H}_7\text{FN}_2\text{O}_2 \) requires C, 49.4; H, 4.1%); \( \nu_{\text{max}} \) 1750 (ester \( \text{C}=\text{O} \) str); \( M^+ \) 170.

2-(4'-Fluoropyrimidin-2'-yl)acetic acid

The above ester (45 mg) was treated in water (10 ml) with one mole of sodium hydroxide (10 mg) for 1 h at 0°. The water was removed in a rotary evaporator at 10° and final traces removed by storage over \( \text{P}_2\text{O}_5 \) in a vacuum desiccator for 24 h. The white solid was dissolved in methanol (10 ml) at 5° and decolourized with activated charcoal. Diethyl ether (15 ml) was added and refrigeration (-5°) for 2 days gave the sodium fluoropyrimidinylacetate (35 mg); m.p. >300° (dec.) (Found: C, 40.7; H, 2.5; N, 15.10. \( \text{C}_6\text{H}_4\text{FN}_2\text{NaO}_2 \) requires C, 40.5; H, 2.2; N, 15.7%).
methyl
2-Methoxycarbonylpyrimidin-4-yltrimethylammonium chloride (200 mg) was added to a slurry of dry acetamide (2 g) and dry potassium cyanide (150 mg, 3 moles) heated to 85-90° over a period of 30 minutes. Bubbles rapidly were evolved and the molten mixture darkened quickly. After a further 15 minutes period of heating the melt was cooled in ice and dissolved in water (20 ml). The aqueous solution was extracted with diethyl ether (6 x 20 ml) and the latter dehydrated over calcium sulphate. The ethereal solution was evaporated to a small volume and chromatographed on a Merck silica preparative plate developed in ethyl acetate. The two major components were isolated as impure liquids (~20 mg each) and tentatively identified as methyl 2-(4'-cyanopyrimidin-2'-yl)acetate (M⁺ 177, νmax 1750) and methyl 2-(4'-dimethylaminopyrimidin-2'-yl)acetate (M⁺ 195, νmax 1750).

Methyl 2-(4'-bromopyrimidin-2'-yl)acetate
Methyl 2-(1',6'-dihydro-6'-oxopyrimidin-2'-yl)acetate (150 mg) was refluxed in toluene (8 ml) with phosphorus oxybromide (800 mg) for 1.5 h. The solution was cooled and poured onto crushed ice. The organic layer was separated and the aqueous layer extracted with diethyl ether (3 x 15 ml). The combined organic fractions were washed with sodium carbonate solution (5%; 2 x 10 ml) and water (2 x 10 ml) and finally dried over calcium sulphate. Evaporation of the solvent at 35° yielded,
after complete removal of toluene in vacuo, the methyl bromopyrimidinylacetate (50 mg, 24%); m.p. 50-55° (Found: C, 36.1; H, 3.1; N, 11.8. C₇H₇BrN₂O₂ requires C, 36.4; H, 3.0; N, 12.1%); n.m.r. 3.80 (s, Me); 4.10 (s, CH₂); 7.57 (d, J 6, H5); 8.64 (d, J 6, H6).

The above ester (30 mg) was treated with sodium hydroxide (5.5 mg, 1 mole) for 1.5 h in water (10 ml) at 0°. Evaporation in a "Rotovap" at 10° followed by recrystallization from methanol/ether gave 2-(4'-bromopyrimidin-2'-yl)acetic acid (30 mg) as its sodium salt; m.p. >300° (dec.) (Found: C, 29.9; H, 2.0. C₆H₄BrN₂NaO₂ requires C, 30.2; H, 1.7%).

Methyl 2-(4'-iodopyrimidin-2'-yl)acetate

Methyl 2-(4'-chloropyrimidin-2'-yl)acetate (200 mg) was refluxed in dry acetone (15 ml) with sodium iodide (170 mg) and two drops of concentrated hydriodic acid (S.G. 1.94) for 30 minutes. The solution was cooled in ice and water (½ ml) added. The mixture was neutralized with 5% sodium bicarbonate solution, evaporated to a small volume and extracted with ether (3 x 20 ml). The dried ethereal extract yielded 210 mg (70%) of the methyl iodopyrimidinylacetate; m.p. 59-61° (Found: C, 30.4; H, 2.9; N, 9.93. C₇H₇IN₂O₂ requires C, 30.2; H, 2.5; N, 10.1%). The foregoing iodo ester (100 mg) was treated with one mole of sodium hydroxide in water (20 ml) at 0°. Evaporation of the water and recrystallization from methanol/ether gave sodium 2-(4'-iodopyrimidin-2'-yl)acetate (100 mg); m.p. >300° (dec.) (Found: C, 25.7; H, 1.7; N, 10.1. C₆H₄IN₂NaO₂ requires C, 25.2; H, 1.4; N, 9.79%).
Methyl 2-(4',6'-dimethoxypyrimidin-2'-yl)acetate

Methyl 2-(4',6'-dichloropyrimidin-2'-yl)acetate (1 g) was refluxed with sodium methoxide (from 240 mg sodium) in methanol (25 ml) for 30 minutes. The methanol was removed in a rotary evaporator, diethyl ether (50 ml) added and precipitated salts removed and the ethereal solution evaporated to yield the methyl dimethoxypyrimidinylacetate (800 mg), b.p. 100-104°/0.5 mm (Found: C, 51.2; H, 6.1; N, 12.9. \(\text{C}_9\text{H}_{12}\text{N}_2\text{O}_4\) requires C, 50.9; H, 5.7; N, 13.20%); \(\nu_{\text{max}}\) 1750 (ester C=O str); n.m.r. 3.77 (s, Me of ester); 3.83 (s, \(\text{CH}_2\)); 3.93 (s, OMe); 5.90 (s, H5).

2-(4',6'-Dimethoxy pyrimidin-2'-yl)acetic acid

The foregoing ester (200 mg) was treated with sodium hydroxide (1 mole) in water at 50° for 30 minutes. Evaporation of the water and recrystallization of the solid from methanol/ether gave the sodium dimethoxypyrimidinylacetate (190 mg), m.p. 241-243° (Found: C, 43.7; H, 4.3; N, 12.7. \(\text{C}_8\text{H}_9\text{N}_2\text{NaO}_4\) requires C, 43.6; H, 4.1; N, 12.7%).

Methyl 2-(4',6'-bisethylthiopyrimidin-2'-yl)acetate

Methyl 2-(4',6'-dichloropyrimidin-2'-yl)acetate (1.0 g) was treated with sodium ethyl mercaptide (from 2 moles of sodium methoxide and 2.2 moles of ethyl mercaptan) in methanol (25 ml) at 50° for 2 h. The methanol was removed in the rotary evaporator, diethyl ether (50 ml) added and precipitated salts removed and the ethereal solution evaporated to yield the bisethylthiopyrimidinylacetate (1.2 g), b.p. 204-206°/2mm (Found: C, 48.4; H, 5.6;
N, 10.1. \( \text{C}_{11} \text{H}_{16} \text{N}_{2} \text{O}_{2} \text{S}_{2} \) requires C, 48.5; H, 5.9; N, 10.3%; \( \nu_{\text{max}} \) 1750 (C=O ester str.); n.m.r. 1.37 (t, \( J = 8 \), Me of S-ethyl); 3.17 (q, \( J = 8 \), CH\(_2\) of S-ethyl); 3.80 (s, Me); 3.93 (s, CH\(_2\)); 6.93 (s, H5). \( M^+ \) 272.

2-(4',6'-Bisethylthiopyrimidin-2'-yl)acetic acid

The above ester (1 g) was treated with sodium hydroxide (1 mole, 147 mg) in water (20 ml) for 2 h at 50\(^\circ\). Evaporation to dryness and recrystallization from methanol/ether gave the sodium bisethylthiopyrimidinylacetate (1 g), m.p. 165-166\(^\circ\) (dec.)(Found: C, 42.6; H, 4.9; N, 9.82; S; 22.7. \( \text{C}_{10} \text{H}_{13} \text{N}_{2} \text{NaO}_{2} \text{S}_{2} \) requires C, 42.8; H, 4.6; N,10.0; S, 22.9%).

2-(4'-Chloro-6'-methoxypyrimidin-2'-yl)acetic acid

Methyl 2-(4'-chloro-6'-methoxypyrimidin-2'-yl)acetate (650 mg) was treated with sodium hydroxide (1 mole, 120 mg) in water (25 ml) at 55\(^\circ\) for 2 h. Evaporation of the water and recrystallization of the solid from methanol/ether gave the sodium chloromethoxypyrimidinylacetate (650 mg), m.p. >300\(^\circ\) (Found: C, 37.8; H, 2.5; N, 12.1. \( \text{C}_{7} \text{H}_{6} \text{ClN}_{2} \text{NaO}_{3} \) requires C, 37.4; H, 2.6; N, 12.5%).

Methyl 2-(4'-chloro-6'-ethylthiopyrimidin-2'-yl)acetate

Methyl 2-(4',6'-dichloropyrimidin-2'-yl)acetate (1.0 g) was treated with sodium ethyl mercaptide (1 mole: from 1 mole of sodium methoxide and 1.1 moles of ethyl mercaptan) in methanol at 0\(^\circ\) for 6 h. The methanol was evaporated off and inorganic salts precipitated with diethyl ether,
the filtered ethereal solution was dried over calcium sulphate and evaporated to yield the methyl chloroethylthiopyrimidinylacetate (900 mg), b.p. 142-144°/2mm (Found: C, 44.0; H, 4.5; N, 11.4; S, 12.9. C\textsubscript{9}H\textsubscript{11}ClN\textsubscript{2}O\textsubscript{2}S requires C, 43.8; H, 4.4; N, 11.4; S, 13.0%); n.m.r. 1.37 (t, ~8, Me of ethyl); 3.20 (q, ~8, CH\textsubscript{2} of ethyl); 3.73 (s, Me); 3.93 (s, CH\textsubscript{2}); 7.10 (s, H5).

Treatment of this material with Raney nickel in water or ethanol gave only methyl 2-(pyrimidin-2'-yl)acetate. Hydrogenation did not proceed past 10% H\textsubscript{2} uptake even in the presence of a large excess of palladium catalyst.

**Sodium 2-(1',6'-dihydro-6'-oxopyrimidin-2'-yl)acetate**

Methyl 2-(4'-methoxypyrimidin-2'-yl)acetate (700 mg) was refluxed in water (30 ml) with sodium hydroxide (4.1 moles, 700 mg) for 6 h. The solution was cooled, 1N-hydrochloric acid added (2 moles, 9.0 ml) and the solution evaporated to dryness. The solid was extracted with boiling ethanol (2 x 30 ml) to give the sodium dihydrooxopyrimidinylacetate (550 mg), m.p. >300° (dec.) (Found: C, 40.6; H, 2.7. C\textsubscript{6}H\textsubscript{5}N\textsubscript{2}NaO\textsubscript{3} requires C, 40.9; H, 2.8%).

The foregoing sodium salt (1.0 g) was refluxed with phosphoryl chloride (30 ml) for 45 minutes. Excess phosphoryl chloride was removed, the slurry cooled and then quenched in ice. The cold aqueous solution was extracted with ether (6 x 20 ml) and the ether washed with cold water until the washings were neutral to litmus.
paper. The ethereal solution was dried and evaporated to give a material the i.r. and n.m.r. spectra of which were identical with authentic 4-chloro-2-methylpyrimidine.

2-Carbamoylmethyl-1,6-dihydro-6-oxopyrimidine-4-carboxylic acid

2-(1',6'-Dihydro-4'-methyl-6'-oxopyrimidin-2'-yl) acetamide (1 g) was treated with potassium permanganate (3.8 g) in water (30 ml) for 2 h at 55° by which time the permanganate colour is lost. The slurry was centrifuged, the clear supernatant liquid removed, the manganese dioxide sludge washed with water and the process repeated several times. The combined aqueous solution was adjusted to pH 1 and evaporated to yield a solid which was recrystallized (with difficulty) from methanol/water. The carbamoylmethylidihydrooxopyrimidine carboxylic acid had m.p. 248-250° (Found: C, 42.4; H, 3.6; N, 21.8. C₇H₇N₃O₄ requires C, 42.7; H, 3.5; N, 21.3%); ν max. 1660, 1670 (amide C=O str), 1700 (acid C=O str), 2800, 2850, 2940, 3000 (weak OH str and combinations).

Attempts to decarboxylate the above acid by heating at 100, 200 and 250° were not successful. Only starting material was obtained or charring destroyed any product.

2-Methoxycarbonylmethyl-6-methylpyrimidin-4-yltrimethylammonium chloride

Methyl 2-(4'-chloro-6'-methylpyrimidin-2'-yl)acetate (800 mg) was treated with trimethylamine (1 g) in dry benzene (60 ml) at 25° for 2 days. The precipitated ammonium salt (350 mg) was filtered, washed with diethyl
ether and dried at room temperature *in vacuo*, m.p. 134-137° (Found: C, 51.2; H, 7.3; N, 15.8. 

\[ C_{11}H_{18}ClN_3O_2 \] requires C, 50.9; H, 7.0; N, 16.2%).

**Methyl 2-(4'-cyano-6'-methylpyrimidin-2'-yl)acetate**

The foregoing quaternary salt (580 mg) was added to a melt of acetamide (2 g) and potassium cyanide (400 mg) at 70-75° over a period of 45 minutes. The solution was heated a further 15 minutes, cooled and dissolved in water (30 ml). The aqueous solution was extracted with diethyl ether (6 x 30 ml) the ether dehydrated over calcium sulphate and evaporated to give an oil (130 mg) which was chromatographed on a Merck silica preparative plate developed in ethyl acetate. Two compounds were isolated. The methyl cyanomethylpyrimidinylacetate (50 mg, 12%) had m.p. 55-56° (Found: C, 56.2; H, 4.9; N, 21.2. \[ C_{10}H_{11}N_3O_2 \] requires C, 56.5; H, 4.8; N, 22.0%); \[ \nu_{\text{max.}} 1750; \text{n.m.r.} 2.67 (s, Me); 3.80 (s, Me ester); 4.10 (CH\text{2}); 7.47 (s, H5). \] The second component of the mixture isolated, a liquid (~50 mg), was tentatively identified as methyl 2-(4'-dimethylamino-6'-methylpyrimidin-2'-yl)acetate. \[ \nu_{\text{max.}} 1750; \text{n.m.r.} 2.40 (s, CH\text{3}); 3.13 (s, Me\text{2}); 3.80 (s, Me of ester); 3.87 (s, CH\text{2}); 6.27 (s, H5). \]

**2-(4'-Chloro-6'-methylpyrimidin-2'-yl)acetic acid**

Methyl 2-(4'-chloro-6'-methylpyrimidin-2'-yl)acetate (400 mg) was stirred in water (30 ml) with sodium hydroxide (85 mg) for 25 minutes at 60°. The aqueous
solution was filtered, evaporated to dryness and the white solid recrystallized from ethanol (400 mg), m.p. >310° (Found: C, 40.7; H, 2.9; N, 13.5. \( \text{C}_7\text{H}_6\text{ClN}_2\text{NaO}_2 \) requires C, 40.3; H, 2.9; N, 13.4%).

**5-Bromo-2-fluoropyrimidine**

2-Amino-5-bromopyrimidine (34 g; made according to the method of Nishiwaki, 1966) was dissolved in concentrated fluoroboric acid (200 ml) and cooled to 0° in an alcohol/dry ice bath. Sodium nitrite (20 g) dissolved in water (100 ml) was added over a period of time sufficient to maintain a temperature of -5 to 0° (2-3 h). After this period, the aqueous solution was neutralized with concentrated sodium hydroxide solution and extracted with diethyl ether (6 x 50 ml). The ethereal solution was washed with sodium bicarbonate solution (2%, 4 x 20 ml) and water (4 x 20 ml), dehydrated and evaporated to give a yellow solid (13.0 g), m.p. 92-93° (Found: C, 26.8; H, 1.2; N, 15.5. \( \text{C}_4\text{H}_2\text{BrFN}_2 \) requires C, 27.2; H, 1.2; N, 15.8%); n.m.r. 8.70 (s, H4 and H6).

**Diethyl 2-(5'-bromopyrimidin-2'-yl)malonate.**

5-Bromo-2-fluoropyrimidine (500 mg) was refluxed in dry acetonitrile (20 ml) with the potassium salt of diethylmalonate (560 mg, prepared by adding a methanolic potassium hydroxide solution to a solution of diethylmalonate in diethylether) and 18-crown-6 (750 mg) for 10 h.
The solution was cooled and diethylether added (30 ml) and allowed to stand for 1 h. After this period the solution was filtered and the diethylether and acetonitrile removed in vacuo. This gave a viscous liquid from which the product was separated by fractional distillation, b.p. 150-152°C/2mm (200 mg, 22%) (Found: C, 42.2; H, 4.4). C_{11}H_{13}BrN_{2}O_{4} requires C, 41.7; H, 4.1%; n.m.r.

1.30 (t, J 8, Et); 4.37 (q, J 8, CH₂ of ester); 5.17 (s, methine); 8.84 (s, H4 and H6).

The above di-ester (150 mg) was treated with sodium hydroxide (19 mg, 1 mole) in water (8 ml) at 60°C for 16 h. The aqueous solution was evaporated to dryness (at <35°C). Subsequent examination by n.m.r. and chromatography indicated a mixture of at least three components.

Methyl 2-(pyrimidin-2'-yl)acetate (100 mg) was treated with N-bromosuccinimide in dry carbon tetrachloride and glacial acetic acid at reflux for varying times. No 5-bromopyrimidine could be identified in the products: only α-bromination at the side-chain occurred.

4-t-Butyl-2-methylpyrimidine

Methyl 2-(4'-t-butylpyrimidin-2'-yl)acetate (1 g) was refluxed with sodium hydroxide (16 ml, 0.5N) for 60 minutes. The solution was cooled, pH adjusted to 2 and the Cu(II) salt of the acid precipitated by the addition of Cu(II) sulphate. The blue salt (700 mg) was suspended in water and the copper precipitated as Cu(II) sulphide by
the addition of hydrogen sulphide. The sulphide was filtered off and the water evaporated down to a small volume in a rotary evaporator at 30°C. The water was cooled to 0°C giving 2-(4’-t-butylpyrimidin-2'-yl)acetic acid; m.p. 94-96°C (dec.) (Found: C, 61.0; H, 7.6; N, 14.2. \( \text{C}_{10}\text{H}_{14}\text{N}_{2}\text{O}_{2} \) requires C, 61.8; H, 7.3; N, 14.4%).

This material when heated at 90°C for 15 minutes gave a quantitative yield of 4-t-butyl-2-methylpyrimidine characterized as the picrate, m.p. 148-152°C (Found: C, 47.4; H, 4.6; N, 18.2. \( \text{C}_{15}\text{H}_{17}\text{N}_{5}\text{O}_{7} \) requires C, 47.5; H, 4.5; N, 18.5%).

**Methyl 2-(pyrimidin-2'-yl)acetate**

Methyl 2-(4',6'-dichloropyrimidin-2'-yl)acetate (300 mg) was hydrogenated at atmospheric pressure in water (20 ml) containing sodium carbonate (270 mg) and 10% palladium-on-charcoal (90 mg) as for the ethyl analogue. The filtered solution was extracted with chloroform (5 x 15 ml). Dehydration of the extract and evaporation gave the methyl pyrimidinylacetate (60%), b.p. 90-93°C/4mm (Found: C, 55.3; H, 5.2; N, 18.5. \( \text{C}_{7}\text{H}_{8}\text{N}_{2}\text{O}_{2} \) requires C, 55.3; H, 5.3; N, 18.4%); n.m.r. 3.80 (s, Me); 4.04 (s, \( \text{CH}_2 \)); 7.21 (t, \( \text{J} = 5 \), H5); 8.72 (d, \( \text{J} = 5 \), H4+H6) [cf. Chem. Abstr., 1976, 85, 142994]
EXPERIMENTAL

SECTION II

6-Hydroxy-2-isopropylpyrimidin-4(3H)-one

A solution of isobutyronitrile (150 g) in anhydrous ether (2 L) containing ethanol (125 ml) was saturated at 0° with hydrogen chloride and then allowed to stand at 0-5° for 36 h. The crystalline ethyl isobutyrimidate hydrochloride (190 g) was filtered off, washed with ether, and dried in a vacuum at room temperature. It had m.p. 99-101° (dec.) (Found: C, 47.8; H, 9.0; N, 9.4. Calc. for C₆H₁₄ClNO: C, 47.5; H, 9.3; N, 9.2%). This hydrochloride (150 g) was stirred in saturated ethanolic ammonia (1 l) at 20-23° for 24 h. The solid, obtained from evaporation at <30° in a vacuum, recrystallized from ethanol to give isobutyramidine hydrochloride (86 g; 41% on the nitrile), m.p. 164° (dec.) (lit. 167° Drozdiv and Bekli, 1944).

A mixture of the above amidine hydrochloride (40 g) and diethyl malonate (52 g) in ethanolic sodium methoxide (400 ml; sodium, 7.5 g) was heated under reflux for 6 h. After refrigeration the solid was filtered off and dissolved in ice-cold water (50 ml); the solution was adjusted to pH 3-4 and filtration gave the hydroxyisopropylpyrimidinone (61%), m.p. 313-315° (dec.) (from water) (lit. 296-297°, Gershon et al. 1964) (Found: C, 54.1; H, 6.5; N, 18.3. Calc. for C₇H₁₀N₂O₂: C, 54.5; H, 6.5; N, 18.2%); n.m.r. [(CD₃)₂SO] 1.20 (d, J 6, Me₂); 2.83 (sep., J 6, CH of Pr¹); 5.20 (s, H5).
2-Isopropylpyrimidine

The above hydroxypyrimidinone (3.7 g), phosphoryl chloride (12 ml), and \(\text{N,N-diethylaniline}\) (7.2 g) were heated under reflux for 1 h. The cooled mixture was added slowly to ice and stirred for 15 minutes. The resulting suspension was extracted with ether. The extract was washed with aqueous sodium hydrogen carbonate, dried over sodium sulphate, and distilled to give 4,6-dichloro-2-isopropylpyrimidine (2.6 g), b.p. 50-53\(^0\)/1mm (lit. 47-48\(^0\), Gershon et al. 1964)(Found: C, 44.5; H, 4.4; N, 14.8. Calc. for \(\text{C}_7\text{H}_8\text{Cl}_2\text{N}_2\): C, 44.0; H, 4.2; N, 14.7%); n.m.r. 1.37 (d, \(J\) 6, Me\(_2\)); 3.23 (sep., \(\sim 6\), CH of Pr\(^i\)); 7.33 (s, HS).

This material (1 g) was hydrogenated (c. 3 h) at 1 atm. in water (30 ml) containing sodium carbonate (1.2 g) and palladium-on-charcoal (10%; 0.15 g). The filtered solution was extracted with ether and evaporation of the dehydrated extract gave the isopropylpyrimidine (65%), b.p. 46-47\(^0\)/2mm (Found: C, 69.1; H, 8.4; N, 23.0. \(\text{C}_7\text{H}_{10}\text{N}_2\) requires C, 68.8; H, 8.3; N, 22.9%); n.m.r. 1.33 (d, \(J\) 6, Me\(_2\)); 3.33 (sep., \(J\) 6, CH of Pr\(^i\)); 7.07 (t, \(J\) 6, H5); 8.67 (d, \(J\) 6, H4 + H6).

2-(1'-Bromo-1'-methylethyl)pyrimidine

2-Isopropylpyrimidine (0.5 g) and \(\text{N-bromosuccinimide}\) (0.75 g) were heated under reflux for 4 h in carbon tetrachloride containing a trace of dibenzoyl peroxide. The residue from evaporation was distilled (b.p. 67-68\(^0\)/0.5mm) and then recrystallized from light petroleum to give the
bromopyrimidine (60%), liquid at 25° (Found: C, 42.1; H, 4.5; N, 13.6. \( \text{C}_7\text{H}_9\text{BrN}_2 \) requires C, 41.8; H, 4.5; N, 13.9%); n.m.r. 2.27 (s, \( \text{Me}_2 \)) ; 7.23 (t, J 6, H5); 8.83 (d, J 6, H4+H6).

2-Isopropyl-6-phenylpyrimidin-4(3H)-one

Isobutyramidine hydrochloride (40 g) and ethyl benzoylacacetate (31 g) were condensed as for the analogue above. The resulting phenylpyrimidinone (55%) had m.p. 233-234° (from water)(lit. 227°, Pinner, 1892)(Found: C, 72.9; H, 6.3; N, 13.1. Calc. for \( \text{C}_{13}\text{H}_{14}\text{N}_2\text{O} \): C, 72.9; H, 6.6; N, 13.1%); n.m.r. \((\text{CD}_3\text{)}_2\text{SO}\)
1.27 (d, J 6, \( \text{Me}_2 \)); 2.90 (sep., J 6, CH of \( \text{Pr}^1 \)); 6.63 (s, H5); 7.37 (m, H3′+H4′+H5′); 7.97 (m, H2′+H6′).

4-Chloro-2-isopropyl-6-phenylpyrimidine

The above pyrimidinone (15 g), phosphoryl chloride (100 ml) and \( \text{N,N} \)-diethylaniline (10.5 g) were boiled under reflux for 90 minutes. The cooled mixture was added slowly with stirring to ice (200 g). After 15 minutes, the solid was filtered off. The filtrate was extracted with chloroform (100 ml) to which the solid was added subsequently. The extract was washed with aqueous sodium hydrogen carbonate and then with water. Dehydration over calcium sulphate and distillation gave the chlorophenylpyrimidine (68%), b.p. 164-166°/9 mm (Found: C, 67.3; H, 5.5; N, 11.9. \( \text{C}_{13}\text{H}_{13}\text{ClN}_2 \) requires C, 67.1; H, 5.6; N, 12.0%); n.m.r. 1.37 (d, J 6, \( \text{Me}_2 \)); 3.23 (sep., J 6, CH of \( \text{Pr}^1 \)); 7.50 (m, H5+H3′+H4′+H5′); 8.03 (m, H2′+H6′).
2-Isopropyl-4-phenylpyrimidine

The above chlorophenylpyrimidine (9.5 g) was hydrogenated (5 h) at 1 atm. in methanol (200 ml) containing sodium hydrogen carbonate (3.5 g) and palladium-on-charcoal (10%; 0.9 g). The filtered solution was evaporated to small bulk and diluted with ether. Salts were removed and subsequent distillation gave the isopropylphenylpyrimidine (80%), b.p. 139-140°/4 mm (Found: C, 78.6; H, 7.4. \( \text{C}_{13}\text{H}_{14}\text{N}_{2} \) requires C, 78.8; H, 7.1%); n.m.r. 1.37 (d, \( J = 6 \), Me); 3.23 (sep., \( J = 6 \), CH of Pr); 7.27 (m, H5+H3'+H4'+H5'); 7.87 (m, H2'+H6'); 8.40 (d, \( J = 6 \), H6).

2-(1'-Bromo-1'-methylethyl)-4-phenylpyrimidine

The isopropylphenylpyrimidine (1.0 g) was brominated by \( N \)-bromosuccinimide (0.9 g) as for 2-isopropylpyrimidine above. The yellow brominated phenylpyrimidine (>95% yield) had m.p. 86-87° (Found: C, 56.9; H, 4.7; Br, 28.6. \( \text{C}_{13}\text{H}_{13}\text{BrN}_{2} \) requires C, 56.3; H, 4.7; Br, 28.8%); n.m.r. 2.30 (s, Me); 7.40 (m, H5+H3'+H4'+H5'); 8.00 (m, H2'+H6'); 8.67 (d, \( J = 6 \), H6).

4-Chloro-2-isopropyl-6-methoxypyrimidine

The dichloropyrimidine (4g) was stirred in methanolic sodium methoxide (40 ml; sodium 0.49 g) at 0° for 1 h. The resulting suspension was evaporated in a vacuum at 10° to c. 5 ml and then diluted with ether (30 ml). Distillation of the filtrate gave the chloroisopropylmethoxy­pyrimidine (77%), b.p. 59-61°/0.6 mm (Found: C, 51.8;
H, 6.0; N, 15.1. $C_8H_{11}ClN_2O$ requires C, 51.5; H, 5.9; N, 15.0%; n.m.r. 1.30 (d, $\downarrow 6$, $Me_2$ of Pr); 3.10 (sep., $\downarrow 6$, CH of Pr); 3.93 (s, OMe); 6.57 (s, H5).

2-Isopropyl-4-methoxypyrimidine

The foregoing chloropyrimidine (1.5 g) was dechlorinated as its phenyl analogue to give the isopropylmethoxypyrimidine (73%), b.p. 42-43°/0.3mm (Found: C, 63.3; H, 7.7; N, 18.6. $C_8H_{12}N_2O$ requires C, 63.1; H, 7.9; N, 18.4%); n.m.r. 1.30 (d, $\downarrow 6$, Me$_2$ of Pr); 3.10 (sep., $\downarrow 6$, CH of Pr); 3.93 (s, OMe); 6.57 (d, $\downarrow 6$, H5); 8.43 (d, $\downarrow 6$, H6).

2-(1'-Bromo-1'-methylethyl)-4-methoxypyrimidine

The above isopropylmethoxypyrimidine was brominated as for its demethoxy analogue but refluxing was continued for 18 h. The brominated methoxypyrimidine (60%) had b.p. 72-74°/0.3mm (Found: C, 42.0; H, 4.9; N, 12.1. $C_8H_{11}BrN_2O$ requires C, 41.6; H, 4.8; N, 12.1%); n.m.r. 2.23 (s, CMe$_2$); 4.00 (s, OMe); 6.67 (d, $\downarrow 6$, H5); 8.53 (d, $\downarrow 6$, H6).

2-(1'-Methoxy-1'-methylethyl)pyrimidine

2-(1'-Bromo-1'-methylethyl)pyrimidine (0.67 g) and anhydrous methanol (15 ml) were boiled under reflux for 45 h. Sodium hydrogen carbonate (0.28 g) was added to the cooled solution which was then evaporated to a small volume
and diluted with ether. The precipitated salts were removed and distillation of the dehydrated filtrate gave the methoxymethylethylpyrimidine (80%), b.p. 41-43°/0.1mm (Found: C, 62.6; H, 8.1; N, 18.1. C₈H₁₂N₂O requires C, 63.1; H, 8.0; N, 18.4%); n.m.r. 1.63 (s, CMe₂); 3.23 (s, OMe); 7.27 (t, J 6, H5); 8.70 (d, J 6, H4+H6).

2-(1'-Methoxy-1'-methylethyl)-4-phenylpyrimidine

2-(1'-Bromo-1'-methylethyl)-4-phenylpyrimidine (0.2 g) and methanol (100 ml) were stirred at 53° for 3 days with apparent pH maintained at 6.8-7.0 by automatic addition of 1.02N-potassium hydroxide. The methanol was removed at 40° in a vacuum and the residue was diluted with ether to precipitate salt. Evaporation of the ethereal filtrate gave the methoxymethylethylphenylpyrimidine (87%), m.p. 49-50° (from light petroleum)(Found: C, 73.4; H, 7.0. C₁₄H₁₆N₂O requires C, 73.7; H, 7.1%); n.m.r. 1.73 (s, CMe₂); 3.30 (s, OMe); 7.60 (m, H₃"+H₄"+H₅"+H₅); 8.27 (m, H₂"+H₆"); 8.94 (d, J 6, H6).

4-Methoxy-2-(1'-methoxy-1'-methylethyl)pyrimidine

(a) 2-(1'-Bromo-1'-methylethyl)-4-methoxypyrimidine (0.53 g), methanol (20 ml), and sodium hydrogen carbonate (0.2 g) were boiled under reflux for 48 h. The residue from evaporation was diluted with ether. The filtrate was loaded on to a silica column (40 x 1.5 cm) and subsequently eluted with ethyl acetate to give the methoxymethoxymethyl-ethylpyrimidine (51%), b.p. 52-54°/0.2mm (Found: C, 59.2;
H, 8.0; N, 15.5. \( \text{C}_9\text{H}_{14}\text{N}_2\text{O}_2 \) requires C, 59.3; H, 7.7; N, 15.4\%; n.m.r. 1.60 (s, CMe\(_2\)); 3.27 (s, 1'-OMe); 4.03 (s, 4-OMe); 6.67 (d, \( \sim 6\), H5); 8.53 (d, \( \sim 6\), H6).

The olefin, described below, was present (c. 30\%) in the crude reaction product (n.m.r.).

(b) When the sodium hydrogen carbonate was added only after solvolysis above, the result was different: preparative t.l.c. of the crude material gave the product (c. 25\%) and 2-(1'-methoxy-1'-methylethyl)pyrimidin-4(3H)-one (c. 10\%), m.p. 98-100\(^\circ\), \( M^+ \) 168, and \( \nu_{\text{max}} \) 1680 (C=O); n.m.r. 1.47 (s, CMe\(_2\)); 3.27 (s, 1'-OMe); 6.27 (d, \( \sim 6\), HS); 7.87 (d, \( \sim 6\), H6).

2-(1'-Acetoxy-1'-methylethyl)-4-phenylpyrimidine

2-(1'-Bromo-1'-methylethyl)-4-phenylpyrimidine (0.50 g) was added during 20 minutes to a stirred solution of silver acetate (0.37 g) in acetic acid (150 ml) at c. 100\(^\circ\); heating was continued for 10 minutes prior to cooling and subsequent filtration (kieselguhr). The residue from evaporation of the filtrate was diluted with water (10 ml) and neutralized with 1\% sodium hydrogen carbonate solution. The aqueous solution was chloroform extracted (6 x 20 ml). Evaporation gave a mixture of two products (t.l.c.), separated by chromatography on a silica column (40 x 1 cm) using ethyl acetate for elution. The first was the acetoxyprymidine (50\%), m.p. 75-76\(^\circ\) (Found: C, 70.1; H, 6.3; N, 11.0. \( \text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_2 \) requires C, 70.3; H, 6.3; N, 10.9\%); n.m.r. 1.83 (s, CMe\(_2\)); 2.10 (s, Ac); 7.57 (m, H3"+H4"+H5"+H5); 8.17 (m, H2"+H6"); 8.77 (d, \( \sim 6\), H6).

The second product (c. 20\%) was the olefin.
2-(1'-Hydroxy-1'-methylethyl)-4-phenylpyrimidine

2-(1'-Acetoxy-1'-methylethyl)-4-phenylpyrimidine (50 mg) was heated with sodium hydroxide (1 mole) in water (10 ml) at 90-95° for 24 h. The solution was cooled and extracted with diethyl ether (6 x 20 ml). The ether was dried over calcium sulphate and evaporated to yield the alcohol (25 mg) as a viscous liquid. N.m.r.

\[
\begin{align*}
\text{\text{1.70 (s, CMe}_2\text{) ; 7.63 (m, H3"+H4"+H5"+H5) ; 8.23 (m, H2"+H6") ; 8.86 (d, J 6, H6); v\text{max.} 3480 (OH str.); M}^+ 214.}
\end{align*}
\]

2-Isopropenylpyrimidine

2-(1'-Bromo-1'-methylethyl)pyrimidine (1.0 g) and methanolic sodium methoxide (50 ml; sodium, 125 mg) were warmed at 60° for 24 h. The residue from evaporation was triturated with anhydrous ether (55 ml). The salts were filtered off and washed with ether. The combined ethereal solutions were again dehydrated over magnesium sulphate and then distilled to give 2-isopropenylpyrimidine (84%), b.p. 35-37°/0.05mm (Found: C, 69.9; H, 6.7. N, 23.9. C\text{7H}_8\text{N}_2 requires C, 70.0; H, 6.7; N, 23.3%); n.m.r. 2.27 (m, Me); 5.60 (m, H\text{B}); 6.53 (m, H\text{G}); 7.17 (t, J 6, H5); 8.14 (d, J 6, H4+H6). The n. m.r. spectrum of the undistilled material indicated the presence of 5-10% of 2-(1'-methoxy-1'-methylethyl)pyrimidine.
2-Isopropenyl-4-phenyl- and 2-Isopropenyl-4-methoxy-pyrimidine

2-(1'-Bromo-1'-methylethyl)-4-phenylpyrimidine (1.38 g) or its 4-methoxy analogue (1.16 g) were treated with methanolic sodium methoxide as above to give the isopropenylphenylpyrimidine (85%), b.p. 128-130°/0.5mm

(Found: C, 79.8; H, 6.4; N, 14.1. C_{13}H_{12}N_{2} requires C, 79.6; H, 6.2; N, 14.3%); n.m.r. 2.30 (m, Me); 5.53 (m, H_β); 6.50 (m, H_α); 7.40 (m, H_5+H_3 ‚ H_4 ‚ H_5 ‚ H_6); 8.07 (m, H_2 ‚ H_6); 8.67 (d, J 6, H_6) and the isopropenylmethoxypyrimidine (70%), b.p. 85-87°/18mm

(Treated: C, 63.7; H, 6.9. C_{8}H_{10}N_{2}O requires C, 64.0; H, 6.7%); n.m.r. 2.17 (m, Me of propenyl); 3.93 (s, OMe); 5.47 (m, H_β); 6.40 (m, H_α); 6.53 (d, J H5);
8.37 (d, J 6, H6), respectively. Before distillation, the latter contained almost 20% of 4-methoxy-2-(1'-methoxy-1'-methylethyl)pyrimidine, as indicated by n.m.r. Treatment of 2-(1'-bromo-1'-methylethyl)-4-phenylpyrimidine (200 mg) with 18-crown-6 (190 mg, 1 mole) in dry acetonitrile (10 ml) in the presence of potassium fluoride (50 mg, 1 mole) for 5 h at 70° gave the olefin in high yield in the absence of any solvolysis product.

2-(1',2'-Epoxy-1'-methylethyl)-4-phenylpyrimidine

2-Isopropenyl-4-phenylpyrimidine (0.30 g), m-chloroperoxybenzoic acid (84%; 0.31 g), and anhydrous chloroform (30 ml) were stirred under reflux for 16 h. The cooled solution was extracted sequentially with (i) 20% aqueous sodium hydrogen sulphite (3 x 20 ml); (ii) 10% aqueous
sodium carbonate (3 x 20 ml); and (iii) water (3 x 20 ml). The chloroform layer was dehydrated and evaporated to give the epoxypyrimidine (85%), b.p. 158-160°/0.5mm (Found: C, 73.1; H, 5.3. \( \text{C}_{13}\text{H}_{12}\text{N}_{2}\text{O} \) requires C, 73.6; H, 5.7%); n.m.r. 1.93 (s, br, Me); 3.03 (d, \( J = 6 \), \( H_{\alpha} \) or \( H_{\beta} \)); 3.57 (d, \( J = 6 \), \( H_{\beta} \) or \( H_{\alpha} \)); 7.50 (s, br, \( H_{3}''+H_{4}''+H_{5}''+H_{5}'' \)); 8.10 (s, br, \( H_{2}''+H_{6}'' \)); 8.65 (d, \( J = 6 \), \( H_{6} \)).

2-Isopropylpyrimidin-4(3H)-one

2-Isopropyl-4-methoxypyrimidine (2.8 g) was stirred in a 5% benzene solution of hydrobromic acid (100 ml) for 24 h at 50°. The solution was cooled in ice and the white crystalline precipitate filtered and dissolved in methanol (100 ml) The solution was neutralized with sodium bicarbonate and evaporated to dryness. Extraction with boiling ethyl acetate (2 x 100 ml) filtration and removal of the organic solvent produced 2.8 g (80%) of the isopropylpyrimidinone, m.p. 143-144° (Found: C, 60.5, H, 7.3; N, 20.1. \( \text{C}_{7}\text{H}_{10}\text{N}_{2}\text{O} \) requires C, 60.9; H, 7.3; N, 20.3%).

4-Chloro-2-isopropylpyrimidine

The above isopropylpyrimidinone (2.0 g) was refluxed with phosphorus oxychloride (40 ml) and diethylaniline (2.2 g) for 45 mins. The solution was cooled, evaporated to a small volume and poured onto crushed ice. The aqueous solution was extracted with ether (6 x 20 ml) washed with 5% sodium bicarbonate (2 x 10 ml) dehydrated over calcium sulphate and
evaporated to yield the chloropyrimidine (1.7 g), b.p. 39-41°/1mm (Found: C, 54.0; H, 6.2; N, 18.4. 
\(\text{C}_7\text{H}_9\text{ClN}_2\) requires C, 53.7; H, 5.8; N, 17.9%); n.m.r. 1.30 (d, \(J\ 6\), Me\(_2\)); 3.17 (sep., \(J\ 6\), CH of Pr\(^i\)); 7.10 (d, \(J\ 6\), H5); 8.47 (d, \(J\ 6\), H6).

2-(1'-Bromo-1'-methylethyl)-4-chloropyrimidine

4-Chloro-2-isopropylpyrimidine (500 mg) was refluxed in carbon tetrachloride for 45 minutes with N-bromosuccinimide (580 mg) and a trace of dibenzoyl peroxide. The solution was cooled, filtered and evaporated to a small volume. Diethyl ether was added and the precipitated succinimide filtered off. The ether was removed to yield the (bromomethylethyl)chloropyrimidine (550 mg), b.p. 80-82°/1.5mm (Found: C, 36.1; H, 3.5; N, 12.2. \(\text{C}_7\text{H}_8\text{BrClN}_2\) requires C, 35.7; H, 3.4; N, 11.9%); n.m.r. 2.27 (s, Me\(_2\)); 7.33 (d, \(J\ 6\), H5); 8.76 (d, \(J\ 6\), H6).

2-Isopropylpyrimidin-4-yltrimethylammonium chloride

4-Chloro-2-isopropylpyrimidine (900 mg) was dissolved in benzene (20 ml) and added to a 15% solution of trimethylamine in benzene (40 ml). The solution was stoppered and stored at room temperature for 3 days after which time the white amorphous precipitate was filtered off, washed with diethyl ether and dried at 20° over \(\text{P}_2\text{O}_5\) in a vacuum (950 mg); m.p. 124-125° (dec.)(Found: C, 55.4; H, 8.8. \(\text{C}_{10}\text{H}_{18}\text{ClN}_3\) requires C, 55.6; H, 8.4%).
**4-Fluoro-2-isopropylpyrimidine**

2-Isopropylpyrimidin-4-yltrimethylammonium chloride (690 mg) was added to an aqueous solution of potassium hydrogen difluoride (2.5 g; 10 ml water) at 5°C. Diethyl ether was added (30 ml) and the mixture stirred so that the two phases were thoroughly mixed. Stirring was continued for 20 minutes after which time the ether was removed, washed with 1% sodium bicarbonate (3 x 10 ml) and water (3 x 10 ml) and dried over calcium sulphate. A further portion of ether was added and the process continued for about 2 h after which time no further organic material passes into the ether (as judged by t.l.c.).

The combined ether extracts were evaporated to yield the fluoropyrimidine (350 mg, 80%), b.p. 141-142°C/719 mm (Found: C, 60.4; H, 6.6. C7H9FN2 requires C, 60.0; H, 6.5%). n.m.r. 1.37 (d, J 6, Me2); 3.57 (sep., J 6, CH of Pr); 6.90 (q, J5,6 6, J5,F 3, H5); 8.80 (q, J5,6 6, J6,F 12, H6).

**2-(1'-Bromo-1'-methyllethyl)-4-fluoropyrimidine**

4-Fluoro-2-isopropylpyrimidine (200 mg) was refluxed with N-bromosuccinimide (255 mg) in carbontetrachloride (20 ml) in the presence of a trace of dibenzoyl peroxide for 30 minutes. The solution was cooled, evaporated to a small volume, diluted with ether and the precipitated succinimide removed by filtration. Dehydration of the ether over calcium sulphate and evaporation in vacuo at 20°C
gave the \((\text{bromomethylethyl})\text{fluoropyrimidine}\) (250 mg), b.p. 65-68°/22mm (Found: C, 38.9; H, 3.5. \(\text{C}_7\text{H}_8\text{BrFN}_2\) requires C, 38.4; H, 3.7%); n.m.r. 2.27 (s, \(\text{Me}_2\)); 6.97 (q, \(\text{J}_{5,6} 6, \text{J}_{5,F} 3, \text{H}5\)); 8.97 (q, \(\text{J}_{5,6} 6, \text{J}_{6,F} 12, \text{H}6\)).

\textbf{6-Chloro-2-isopropyl-4-piperidinopyrimidine}

\(4,6\)-\text{Dichloro-2-isopropylpyrimidine} (1.5 g) was treated with piperidine (1 mole) in methanol (35 ml) at 20° for 2 h. At the end of this period the mixture was briefly refluxed and then evaporated to a small volume. Diethyl ether (100 ml) was added and precipitated salts filtered off. The methanol was removed \textit{in vacuo} and the remaining solid recrystallized from ethanol giving the \textit{chloroisopropylpiperidinopyrimidine} (1.35 g, 76%), m.p. 61-63° (Found: C, 60.1; H, 7.4; N, 17.7. \(\text{C}_{12}\text{H}_{18}\text{ClN}_3\) requires C, 60.1; H, 7.7; N, 17.5%); n.m.r. 1.23 (d, \(\text{J} 6, \text{Me}_2\)); 1.63 (br, \(\text{H}3'\text{+H}4'\text{+H}5'\)); 2.93 (sep., \(\text{J} 6, \text{CH of Pr}^1\)); 3.60 (br, \(\text{H}2'\text{+H}6'\)); 6.27 (s, \(\text{H}5\)).

The above material (1.35 g) was hydrogenated in methanol (40 ml) with 10\% Pd/C (100 mg) in the presence of sodium bicarbonate (500 mg) to give \textit{2-isopropyl-4-}
\textit{piperidinopyrimidine} as a liquid (1.1 g); n.m.r. 1.23 (d, \(\text{J} 6, \text{Me}_2\)); 1.60 (br, \(\text{H}3'\text{+H}4'\text{+H}5'\)); 2.92 (sep., \(\text{J} 6, \text{CH of Pr}^1\)); 3.60 (br, \(\text{H}2'\text{+H}6'\)); 6.33 (d, \(\text{J} 6, \text{H}5\)); 8.17 (d, \(\text{J} 6, \text{H}6\)).
This material (1.1 g) was then treated, without further purification, with N-bromosuccinimide (1.05 g) in dry carbon tetrachloride (20 ml) in the presence of a trace of dibenzoyl peroxide for 16 h. at 20°. Evaporation of the carbon tetrachloride gave a liquid, b.p. 105-106°/1mm identified as 5-bromo-2-isopropyl-4-piperidinopyrimidine (Found: C, 51.0; H, 6.2.
\[\text{C}_{12}\text{H}_{18}\text{BrN}_3\] requires C, 50.7; H, 6.4%); n.m.r.
1.27 (d, J 6, Me2); 3.70 (br, H2'+H6'); 2.93 (sep., J 6, CH of Pr'); 1.70 (br, H3'+H4'+H5'); 8.43 (s, H6).
(a) Ionization Constants

The acidic ionization constants were determined potentiometrically according to the method of Albert and Serjeant (1971). The sodium salts of the acids were weighed out to give accurately known concentrations (ca. $6.7 \times 10^{-3}$ M). The solutions were titrated with 0.200 M hydrochloric acid and changes in pH monitored on a Pye Unicam model 290 pH meter connected to a Philips CA 14/02 combination glass/calomel electrode. The apparatus was calibrated using a 0.05 M-potassium hydrogen phthalate solution (pH 4.00) and a 0.01 M sodium borate solution (pH 9.23). Standardized acid was added in 0.05 or 0.025 ml quantities from an 'Alga' all glass syringe. The solutions were stirred with a slow stream of nitrogen gas which was stopped during readings. Values for $pK_a$ were calculated using a standard computer program written in focal and using a P.D.P.-8 computer. A typical print out is shown in Fig.27. Total volumes were always 15 ml except for the 4-ethylsulphonyl and 4-fluoro acids for which they were 5 ml because of the small quantities of pure material available. In these cases calculations were performed by hand and volume corrections were made.

Some overlapping occurred, particularly with the 4-methoxy and 4-ethylthio acids. This was allowed for by using a computer program designed to correct for the presence of the overlapping species during the titration. An example of this is shown in Fig.28.
**FIG. 27**

![Chemical Structure](image)

Calculation of $pK_a^2$ from potentiometric titration.

**CALCULATION OF PK FROM POTENTIOMETRIC TITRATION USING STANDARD ACID**

**VOL: 15 ACID:** 0.26% $pKW$: 14.16 $F = 0.98$ FREE BASE: 0

**CONC OF SPECIES TITRATED:** 0.00647 NO. OF PTS: 6

<table>
<thead>
<tr>
<th>$X$</th>
<th>PH</th>
<th>PK</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.14</td>
<td>4.29</td>
<td>3.6666</td>
</tr>
<tr>
<td>0.15</td>
<td>4.57</td>
<td>3.6743</td>
</tr>
<tr>
<td>0.20</td>
<td>3.66</td>
<td>3.6445</td>
</tr>
<tr>
<td>0.25</td>
<td>3.71</td>
<td>3.6569</td>
</tr>
<tr>
<td>0.30</td>
<td>3.55</td>
<td>3.6473</td>
</tr>
<tr>
<td>0.35</td>
<td>3.49</td>
<td>3.6456</td>
</tr>
<tr>
<td>0.40</td>
<td>3.26</td>
<td>3.6566</td>
</tr>
<tr>
<td>0.45</td>
<td>3.11</td>
<td>3.6538</td>
</tr>
</tbody>
</table>

**AVERAGE VALUE OF PKCALC** 3.6554
Calculation of $pK_a^2$ from potentiometric titration

$pK_a^1$ is 1.81

**FIG. 28**

**TWG PK VALUES. TITRATION WITH ACID**

VOL: 15 ACID: 0.2 M PKW: 14.26-14.16 $F = 0.986$ FREE BASE: 0
ONCN OF SPECIES TITRATED: 0.0067 NO. OF PTS, 1ST HALF: 8
NO. OF PTS, 2ND HALF: 1

**ESTIMATE OF PK2: 1.81**

<table>
<thead>
<tr>
<th>X</th>
<th>PH</th>
<th>PK1</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>4.24</td>
<td>4.2318</td>
</tr>
<tr>
<td>0.05</td>
<td>4.41</td>
<td>4.2020</td>
</tr>
<tr>
<td>0.25</td>
<td>4.23</td>
<td>4.1995</td>
</tr>
<tr>
<td>0.30</td>
<td>4.16</td>
<td>4.1906</td>
</tr>
<tr>
<td>0.35</td>
<td>3.69</td>
<td>4.1417</td>
</tr>
<tr>
<td>0.40</td>
<td>3.71</td>
<td>4.2041</td>
</tr>
<tr>
<td>0.45</td>
<td>3.52</td>
<td>4.2198</td>
</tr>
</tbody>
</table>

**ESTIMATE OF PK1:**
For the basic pKₐ values, the spectrophotometric method described by Albert and Serjeant (1971) was used. This employed solutions of hydrochloric acid of known Hammett acidity function, Hₒ, (Paul and Long, 1957). This involved measuring the optical density of the cationic species d_c, the molecular species d_m and values (usually seven) of the optical density d of the molecule at Hₒ values close to that of the pKₐ. The value of pKₐ was then given by

\[
pKₐ = Hₒ + \log \left( \frac{d - d_m}{d_c - d} \right).
\]

In many cases, the value of d_m (and hence ε_m) was obtained by extrapolation from the values in solutions of known Hₒ and using d_c. This was achieved using the expression

\[
d = d_m + [H^+](d_c - d)/K
\]

where K was the equilibrium constant. Values of d plotted against [H⁺](d_c - d) gave a straight line of intercept ([H⁺] = 0) d_m. The absorbance in strong acid for the 4-halogeno acids were similarly obtained.

(b) Zwitterionic Ratios

In the instances where zwitterions were present, the value for ε_m was calculated using the above extrapolation procedure. This is illustrated with reference to sodium 2-(4'-ethylthiopyrimidin-2'-yl)acetate. The value of ε at 306 nm for the cationic species of the acid (ε_CAT.) was 16,250 (the value for the ester was 16,160). The value of ε for the ester in water was 811. This was
assumed equal to the value of the non-zwitterionic neutral acid. The value of "$\varepsilon_m$" extrapolated to zero hydrogen ion concentration was 5860.

$$K_z = \frac{\varepsilon_{\text{ESTER}} - \varepsilon_m}{\varepsilon_m - \varepsilon_{\text{CAT}}} = \frac{811 - 5860}{5860 - 16,250} = 0.49$$

For this value of $K_z$, a change of ±10% produces a change of ±0.02 units in the microscopic $pK_a$ values.

(c) Solvolysis Rates

The rates of solvolysis of the 2-(1'-bromo-1'-methylethyl)pyrimidines were measured at a constant pH of 6.8 to 7.0. Each bromo compound (10-12 mg) dissolved in methanol (~30 ml) was thermostatted at the required temperature. This solution (25 mls) was mixed with an equal volume of water similarly thermostatted. The rate of liberation of $H^+$ was followed by the addition of 0.15N potassium hydroxide from an 'Alga' all-glass syringe controlled by a Radiometer automatic titration recorder set in the pH-stat. mode at apparent pH 7.0. The electrodes were standardized at the temperature of the reaction using borax buffer (pH 8.99 at 55°C). First-order rate constants were calculated from the standard equation

$$k = t^{-1} \ln \left[ \frac{V}{(V-X)} \right]$$

in which $t$ = time in seconds, $V$ = final volume of titre, $X$ = titre at time $t$. Each reaction was followed to at least 87% completion with standard deviations ≤ 2%.
Rate constants were calculated using a program written in focal on a P.D.P.-8 computer using the above expression. A typical print out is shown in Fig.29. Fig.30 shows the type of trace obtained during titrations. For the 4-fluoro- and 4-chloro-pyrimidines the possibility of concomitant solvolysis of the potentially labile 4-substituent existed. This was shown not to occur to any significant extent by performing a blank run using the 4-halogeno-2-isopropylpyrimidine. No solvolysis was observed (as judged by a drop in pH) over a period of 2 h. For very slow reactions, in particular the 4-halogeno-α-bromopyrimidines at low temperature, the value for the infinity volume \( V \) was difficult to determine and Guggenheim's method (Guggenheim, 1926) was used to determine rate constants.

In the case of the 4-phenylpyrimidine, the products of the reaction were examined by t.l.c. after about 10 half-lives. Comparison with authentic material showed only the alcohol and methoxy ether present. No olefin was observable although a minute amount could be detected from the n.m.r. of the products. No attempt was made to determine product ratios.
In 50% v/v aqueous methanol
t=61.2°

**FIRST ORDER KINETIC EQUATION**

**EQU IS**

\[
K = \frac{(1/T) \cdot \ln(V/(V-X))}{(V/(V-X))}
\]

**FROM TITRATION AT CONSTANT PH**

<table>
<thead>
<tr>
<th>T</th>
<th>X</th>
<th>K</th>
<th>% REACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>6346</td>
<td>22</td>
<td>6.60685E-03</td>
<td>21.755</td>
</tr>
<tr>
<td>6586</td>
<td>34</td>
<td>6.47777E-03</td>
<td>38.875</td>
</tr>
<tr>
<td>6626</td>
<td>44</td>
<td>6.47711E-03</td>
<td>41.569</td>
</tr>
<tr>
<td>1468</td>
<td>53</td>
<td>6.49414E-03</td>
<td>56.482</td>
</tr>
<tr>
<td>1368</td>
<td>61</td>
<td>6.55288E-03</td>
<td>57.547</td>
</tr>
<tr>
<td>1548</td>
<td>67</td>
<td>6.45915E-03</td>
<td>63.206</td>
</tr>
<tr>
<td>1768</td>
<td>73</td>
<td>6.52646E-03</td>
<td>68.868</td>
</tr>
<tr>
<td>2628</td>
<td>78</td>
<td>6.56487E-03</td>
<td>73.585</td>
</tr>
<tr>
<td>2248</td>
<td>82</td>
<td>6.54931E-03</td>
<td>77.358</td>
</tr>
<tr>
<td>2580</td>
<td>85</td>
<td>6.45601E-03</td>
<td>81.189</td>
</tr>
<tr>
<td>2740</td>
<td>88</td>
<td>6.45240E-03</td>
<td>83.919</td>
</tr>
<tr>
<td>3220</td>
<td>93</td>
<td>6.50089E-03</td>
<td>87.736</td>
</tr>
<tr>
<td>3720</td>
<td>96</td>
<td>6.36692E-03</td>
<td>90.566</td>
</tr>
<tr>
<td>4180</td>
<td>99</td>
<td>6.48804E-03</td>
<td>93.396</td>
</tr>
</tbody>
</table>

**AVERAGE VALUE OF K**

6.51826E-03

**STANDARD DEVIATION** = 75.1855E-05

\( (= 1.15\%) \)

**TIME FOR 51% REACTION** = 1164.71 secs.
INDEX TO PREPARATIONS

Compounds in italics have not been described previously; those in roman involve a new or improved preparation of a compound which has been described previously.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-(1'-Acetoxy-1'-methylethyl)-4-phenylpyrimidine</td>
<td>113</td>
</tr>
<tr>
<td>2-Amino-1,6-dihydro-4-methyl-6-oxopyridine-3-carboxamide</td>
<td>87</td>
</tr>
<tr>
<td>2-Amino-1,6-dihydro-6-oxo-4-phenylpyridine-3-carboxamide</td>
<td>84</td>
</tr>
<tr>
<td>2-(4',6'-Bisethylthiopyrimidin-2'-yl)acetic acid</td>
<td>100</td>
</tr>
<tr>
<td>5-Bromo-2-fluoropyrimidine</td>
<td>104</td>
</tr>
<tr>
<td>5-Bromo-2-isopropyl-4-piperidinopyrimidine</td>
<td>120</td>
</tr>
<tr>
<td>2-(1'-Bromo-1'-methylethyl)-4-chloropyrimidine</td>
<td>117</td>
</tr>
<tr>
<td>2-(1'-Bromo-1'-methylethyl)-4-fluoropyrimidine</td>
<td>118</td>
</tr>
<tr>
<td>2-(1'-Bromo-1'-methylethyl)-4-methoxypyrimidine</td>
<td>111</td>
</tr>
<tr>
<td>2-(1'-Bromo-1'-methylethyl)-4-phenylpyrimidine</td>
<td>110</td>
</tr>
<tr>
<td>2-(1'-Bromo-1'-methylethyl)pyrimidine</td>
<td>108</td>
</tr>
<tr>
<td>2-(4'-Bromopyrimidin-2'-yl)acetic acid</td>
<td>98</td>
</tr>
<tr>
<td>2-(4'-t-Butyl-6'-chloropyrimidin-2'-yl)acetonitrile</td>
<td>89</td>
</tr>
<tr>
<td>2-(4'-t-Butyl-1',6'-dihydro-6'-oxopyrimidin-2'-yl)acetamide</td>
<td>88</td>
</tr>
<tr>
<td>4-t-Butyl-2-methylpyrimidine</td>
<td>105</td>
</tr>
<tr>
<td>2-(4'-t-Butylpyrimidin-2'-yl)acetic acid</td>
<td>89</td>
</tr>
<tr>
<td>2-Carbamoylmethyl-1,6-dihydro-6-oxopyrimidine-4-carboxylic acid</td>
<td>102</td>
</tr>
<tr>
<td>4-Chloro-2-isopropyl-6-methoxy pyrimidine</td>
<td>110</td>
</tr>
<tr>
<td>4-Chloro-2-isopropyl-6-phenylpyrimidine</td>
<td>109</td>
</tr>
<tr>
<td>6-Chloro-2-isopropyl-4-piperidinopyrimidine</td>
<td>119</td>
</tr>
<tr>
<td>Chemical Name</td>
<td>Page</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>4-Chloro-2-isopropylpyrimidine</td>
<td>116</td>
</tr>
<tr>
<td>2-(4'-Chloro-6'-isopropylpyrimidin-2'-yl)acetonitrile</td>
<td>90</td>
</tr>
<tr>
<td>2-(4'-Chloro-6'-methoxypyrimidin-2'-yl)acetic acid</td>
<td>100</td>
</tr>
<tr>
<td>2-(4'-Chloro-6'-methylpyrimidin-2'-yl)acetic acid</td>
<td>103</td>
</tr>
<tr>
<td>2-(4'-Chloro-6'-methylpyrimidin-2'-yl)acetonitrile</td>
<td>87</td>
</tr>
<tr>
<td>2-(4'-Chloro-6'-phenylpyrimidin-2'-yl)acetonitrile</td>
<td>85</td>
</tr>
<tr>
<td>2-(4'-Chloropyrimidin-2'-yl)acetic acid</td>
<td>93</td>
</tr>
<tr>
<td>4,6-Dichloro-2-isopropylpyrimidine</td>
<td>108</td>
</tr>
<tr>
<td>2-(4',6'-Dichloropyrimidin-2'-yl)acetic acid</td>
<td>83</td>
</tr>
<tr>
<td>Diethyl 2-(5'-bromopyrimidin-2'-yl)malonate</td>
<td>104</td>
</tr>
<tr>
<td>2-(1',6'-Dihydro-4'-isopropyl-6'-oxopyrimidin-2'-yl)acetamide</td>
<td>89</td>
</tr>
<tr>
<td>2-(1',6'-Dihydro-4'-methyl-6'-oxopyrimidin-2'-yl)acetamide</td>
<td>87</td>
</tr>
<tr>
<td>2-(1',6'-Dihydro-6'-oxo-4'-phenylpyrimidin-2'-yl)acetamide</td>
<td>84</td>
</tr>
<tr>
<td>2-(4',6'-Dimethoxypyrimidin-2'-yl)acetic acid</td>
<td>99</td>
</tr>
<tr>
<td>2-(1',2'-Epoxy-1'-methyl-ethyl)-4-phenylpyrimidine</td>
<td>115</td>
</tr>
<tr>
<td>Ethyl 2-(4'-chloro-6'-methylpyrimidin-2'-yl)acetate</td>
<td>88</td>
</tr>
<tr>
<td>Ethyl 2-(4'-chloro-6'-methylpyrimidin-2'-yl)acetimidate hydrochloride</td>
<td>88</td>
</tr>
<tr>
<td>Ethyl 2-(4',6'-dichloropyrimidin-2'-yl)acetate</td>
<td>80</td>
</tr>
<tr>
<td>Ethyl 2-(4',6'-dichloropyrimidin-2'-yl)acetimidate hydrochloride</td>
<td>79</td>
</tr>
<tr>
<td>2-(4'-Ethyl-1',6'-dihydro-6'-oxopyrimidin-2'-yl)acetamide</td>
<td>91</td>
</tr>
<tr>
<td>Ethyl methoxyformimidoylacacetate hydrochloride</td>
<td>84</td>
</tr>
<tr>
<td>Name</td>
<td>Page</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Ethyl 2-((4'-methylpyrimidin-2'-yl)acetate</td>
<td>88</td>
</tr>
<tr>
<td>Ethyl 2-(pyrimidin-2'-yl)acetate</td>
<td>81</td>
</tr>
<tr>
<td>2-(4'-Ethylsulphonylpyrimidin-2'-yl)acetic acid</td>
<td>94</td>
</tr>
<tr>
<td>Ethyl 2-((1',4',5',6'-tetrahydropyrimidin-2'-yl)acetate hydrochloride</td>
<td>81</td>
</tr>
<tr>
<td>2-(4'-Ethylthiopyrimidin-2'-yl)acetic acid</td>
<td>94</td>
</tr>
<tr>
<td>4-Fluoro-2-isopropylpyrimidine</td>
<td>118</td>
</tr>
<tr>
<td>2-(4'-Fluoropyrimidin-2'-yl)acetic acid</td>
<td>96</td>
</tr>
<tr>
<td>6-Hydroxy-2-isopropylpyrimidin-4(3H)-one</td>
<td>107</td>
</tr>
<tr>
<td>2-((1'-Hydroxy-1'-methylethyl)-4-phenylpyrimidine</td>
<td>114</td>
</tr>
<tr>
<td>2-((4'-Iodopyrimidin-2'-yl)acetic acid</td>
<td>98</td>
</tr>
<tr>
<td>Isobutyramidine hydrochloride</td>
<td>107</td>
</tr>
<tr>
<td>2-Isopropenyl-4-methoxypyrimidine</td>
<td>115</td>
</tr>
<tr>
<td>2-Isopropenyl-4-phenylpyrimidine</td>
<td>115</td>
</tr>
<tr>
<td>2-Isopropenylpyrimidine</td>
<td>114</td>
</tr>
<tr>
<td>2-Isopropyl-4-methoxypyrimidine</td>
<td>111</td>
</tr>
<tr>
<td>2-Isopropyl-4-phenylpyrimidine</td>
<td>110</td>
</tr>
<tr>
<td>2-Isopropyl-6-phenylpyrimidin-4(3H)-one</td>
<td>109</td>
</tr>
<tr>
<td>2-Isopropylpyrimidine</td>
<td>108</td>
</tr>
<tr>
<td>2-Isopropylpyrimidin-4(3H)-one</td>
<td>116</td>
</tr>
<tr>
<td>2-((4'-Isopropylpyrimidin-2'-yl)acetic acid</td>
<td>90</td>
</tr>
<tr>
<td>2-Isopropylpyrimidin-4-yltrimethylammonium chloride</td>
<td>117</td>
</tr>
<tr>
<td>Chemical Structure</td>
<td>Page</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>2-Methoxy carbonylmethyl-6-methylpyrimidin-4-yltrimethylammonium chloride</td>
<td>102</td>
</tr>
<tr>
<td>2-Methoxy carbonylpymimidin-4-yltrimethylammonium chloride</td>
<td>95</td>
</tr>
<tr>
<td>4-Methoxy-2-(1'-methoxy-1'-methylthethyl)pyrimidine</td>
<td>112</td>
</tr>
<tr>
<td>2-(1'-Methoxy-1'-methylthethyl)-4-phenylpyrimidine</td>
<td>112</td>
</tr>
<tr>
<td>2-(1'-Methoxy-1'-methylthethyl)pyrimidine</td>
<td>111</td>
</tr>
<tr>
<td>2-(1'-Methoxy-1'-methylthethyl)pyrimidin-4(3H)-one</td>
<td>113</td>
</tr>
<tr>
<td>2-(4'-Methoxypyrimidin-2'-yl)acetic acid</td>
<td>83</td>
</tr>
<tr>
<td>Methyl 2-(4',6'-bisethylthiopyrimidin-2'-yl)acetate</td>
<td>99</td>
</tr>
<tr>
<td>Methyl 2-(4'-bromopyrimidin-2'-yl)acetate</td>
<td>97</td>
</tr>
<tr>
<td>Methyl 2-(4'-t-buty1-6'-chloropyrimidin-2'-yl)acetate</td>
<td>89</td>
</tr>
<tr>
<td>Methyl 2-(4'-t-buty1-6'-chloropyrimidin-2'-yl)acetate acetimidate hydrochloride</td>
<td>89</td>
</tr>
<tr>
<td>Methyl 2-(4'-t-buty1pyrimidin-2'-yl)acetate</td>
<td>89</td>
</tr>
<tr>
<td>Methyl 2-(4'-chloro-6'-ethylthiopyrimidin-2'-yl)acetate</td>
<td>100</td>
</tr>
<tr>
<td>Methyl 2-(4'-chloro-6'-isopropylpyrimidin-2'-yl)acetate</td>
<td>90</td>
</tr>
<tr>
<td>Methyl 2-(4'-chloro-6'-isopropylpyrimidin-2'-yl)acetate acetimidate hydrochloride</td>
<td>90</td>
</tr>
<tr>
<td>Methyl 2-(4'-chloro-6'-methoxypyrimidin-2'-yl)acetate</td>
<td>82</td>
</tr>
<tr>
<td>Methyl 2-(4'-chloro-6'-methoxypyrimidin-2'-yl)acetate acetimidate hydrochloride</td>
<td>88</td>
</tr>
<tr>
<td>Methyl 2-(4'-chloro-6'-phenylpyrimidin-2'-yl)acetate</td>
<td>85</td>
</tr>
<tr>
<td>Methyl 2-(4'-chloro-6'-phenylpyrimidin-2'-yl)acetate acetimidate hydrochloride</td>
<td>85</td>
</tr>
<tr>
<td>Methyl 2-(4'-chloropyrimidin-2'-yl)acetate</td>
<td>92</td>
</tr>
<tr>
<td>Methyl 2-(4'-cyano-6'-methylpyrimidin-2'-yl)acetate</td>
<td>103</td>
</tr>
<tr>
<td>Methyl 2-(4'-cyanopyrimidin-2'-yl)acetate</td>
<td>97</td>
</tr>
<tr>
<td>Methyl 2-(4',6'-dichloropyrimidin-2'-yl)acetate</td>
<td>80</td>
</tr>
<tr>
<td>Methyl 2-(4'-dimethylamino-6'-methylpyrimidin-2'-yl)acetate</td>
<td>103</td>
</tr>
<tr>
<td>Chemical Name</td>
<td>Page</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Methyl 2-(4',6'-dichloropyrimidin-2'-yl)acetimidate hydrochloride</td>
<td>79</td>
</tr>
<tr>
<td>Methyl 2-(1',6'-dihydro-6'-oxopyrimidin-2'-yl)acetate</td>
<td>91</td>
</tr>
<tr>
<td>Methyl 2-(4',6'-dimethoxypyrimidin-2'-yl)acetate</td>
<td>99</td>
</tr>
<tr>
<td>Methyl 2-(4'-dimethylamino-6'-methylpyrimidin-2'-yl)acetate</td>
<td>103</td>
</tr>
<tr>
<td>Methyl 2-(4'-dimethylaminopyrimidin-2'-yl)acetate</td>
<td>97</td>
</tr>
<tr>
<td>Methyl 2-(4'-ethylsulphonylpyrimidin-2'-yl)acetate</td>
<td>94</td>
</tr>
<tr>
<td>Methyl 2-(4'-ethylthiopyrimidin-2'-yl)acetate</td>
<td>93</td>
</tr>
<tr>
<td>Methyl 2-(4'-fluoropyrimidin-2'-yl)acetate</td>
<td>95</td>
</tr>
<tr>
<td>Methyl 2-(4'-iodopyrimidin-2'-yl)acetate</td>
<td>98</td>
</tr>
<tr>
<td>Methyl 2-(4'-isopropylpyrimidin-2'-yl)acetate</td>
<td>90</td>
</tr>
<tr>
<td>Methyl 2-(4'-methoxypyrimidin-2'-yl)acetate</td>
<td>82</td>
</tr>
<tr>
<td>Methyl 2-(4'-phenylpyrimidin-2'-yl)acetate</td>
<td>86</td>
</tr>
<tr>
<td>Methyl 2-(pyrimidin-2'-yl)acetate</td>
<td>106</td>
</tr>
<tr>
<td>2-(4'-Methylpyrimidin-2'-yl)acetic acid</td>
<td>88</td>
</tr>
<tr>
<td>2-(4'-Phenylpyrimidin-2'-yl)acetic acid</td>
<td>86</td>
</tr>
<tr>
<td>2-(pyrimidin-2'-yl)acetic acid</td>
<td>81</td>
</tr>
<tr>
<td>Sodium 2-(1',6'-dihydro-6'-oxopyrimidin-2'-yl)acetate</td>
<td>101</td>
</tr>
</tbody>
</table>
REFERENCES


Albert, A., and Barlin, G. B., 1959:


Albert, A., and Serjeant, E. P., 1972:

'Ionization Constants of Acids and Bases'


Armarego, W. L. F., 1977:

'Stereochemistry of Heterocyclic Compounds'


Bachmann, G. B., and Micucci, D. D., 1948:


Baker, F. W., Parish, R. C., and Stock, L. M., 1967:


Barlin, G. B., and Perrin, D. D., 1966:


Beavan, G. H., 1958:

'Steric Effects in Conjugated Systems' Chap. 3,


Biemann, K., 1962:

'Mass Spectrometry: Organic Chemical Applications'


Chapman, N. B., and Shorter, J., 1972:

'Advances in Linear Free Energy Relationships'


Clark, J., and Perrin, D. D., 1964:


Clementi, S., Linda, P., and Vergoni, M., 1971:


Cookson, R. F., and Cheeseman, G. W. H., 1972:


Daniels, R., Grady, L. T., and Bauer, L., 1965:


Davies, W. H., and Piggott, H. A., 1945:


Deady, L. W., and Shanks, R. A., 1972:


Dean, E. B., and Eaborn, C., 1959:


Deno, N. C., Richey, H. G., Liu, J. S., Lincoln, D. N., and Turner, J. O., 1965:


Dewar, M. J. S., and Grisdale, P. J., 1962:

Dornow, A., and Neuse, E., 1954:
Dornow, A., and Siebrecht, M., 1960:
Chem. Ber., 93, 1106.
Drozdov, N. S., and Bekhli, A. F., 1944:
Zh. obshch. Khim., 14, 280
(through C.A., 1945, 39, 3784).
Dunn, G. E., and Thimm, H. F., 1977:
Dyson, P., and Hammick, D. L., 1937:

Eaborn, C., Eastmond, R., and Walton, D. R. M., 1971:
Ehrenson, S., Brownlee, R. T. C., and Taft, R. W., 1973:
Ellam, G. B., and Johnson, C. D., 1971:
English, J. P., Clark, J. H., Clapp, J. W.,
Seeger, D., and Ebel, R. H., 1946:
Everard, K. B., and Sutton, L. E., 1951:
Exner, O., 1972: 'Advances in Linear Free Energy
Relationships' Ch.1, Plenum Press, London.
Exner, O., and Simon, W., 1964:
(through C.A., 82, 171,040K).


Gutowsky, H. S., and Holm, C. H., 1956:

Hall, G. G., Hardisson, A., and Jackman, L. M., 1962:
Haller, A., and Bauer, E., 1913:
Harvey, K. B., and Porter, G. B., 1963:
  'Physical Inorganic Chemistry'
  Addison-Wesley, Massachusetts.
Hepworth, W., and Thomson, T. W., 1971:
  Br. Pat. 1,121,922
  (through C.A. 75, 151831).
Holtz, H. D., and Stock, L. M., 1964:

Imbach, J. L., Jacquier, R., and Vidal, J.-L., 1970:

Jaffé, H. H., and Jones, H. L., 1964:
Janda, M., Šrogl, J., Němec, M., and Kalfus, K., 1976:
Johnson, C. D., and Tomasik, P., 1976:

Katritzky, A. R., and Topsom, R. D., 1971:

Kemula, W., and Krygowski, T. M., 1968:

Khromov-Borisov, N. V., 1968:
_(through C.A. 69, 61946 ).


Kirkwood, J. G., and Westheimer, F. H., 1938:

Krutosikova, A., Sura, J., Kováč, J., and Kalfus, K.,

Laidler, K. J., 1963:

McDaniel, D. H., and Brown, H. C., 1958:

McElvain, S. M., and Nelson, J. W., 1942:

McElvain, S. M., and Schroeder, J. P., 1949:

McElvain, S. M., and Tate, B., 1951:
Matyushecheva, G. I., Tolmachev, A. I.,
    Shulezhko, A. A., Shulezhko, L. M.,
    and Yagupol’skii, L. M., 1976:
    Zh. obsch. Khim., 46, 162.
Mizukami, S., and Hirai, E., 1966:
Moroney, M. J., 1953:
Murrell, J. N., Gil, V. M. S., and Van Duijneveldt, F.B.,
Nakanishi, K., 1962: 'Infra-Red Spectroscopy'
    Holden-Day, San Francisco.
Nelson, J. H., Garvey, R. G., and Ragsdale, R. O.,
Němec, M., Janda, M., Šcrogl, J., and Stibor, I., 1974:
Newman, M. S., 1963:
    'Steric Effects in Organic Chemistry'
    Wiley, New York.
Noyce, D. S., and Stowe, G. T., 1973:
Noyce, D. S., and Virgilio, J. A., 1973:
Noyce, D. S., Virgilio, J. A., and Bartman, B., 1973:
Olah, G. A., and Calvin, M., 1968:

Omura, I., Baba, H., Higashi, K., and Kanaoka, Y., 1957:


Bases in Aqueous Solution', Butterworths, London.
Pinner, A., 1892:
'Die Imidoäther und ihre Derivate', Berlin, 231.
Pinner, A., and Oppenheimer, C., 1895:
Pitman, C. U., and Olah, G. A., 1965:
Pople, J. A., Schneider, W. G., and Bernstein, H. J.,
1959: 'High Resolution Nuclear Magnetic Resonance'

Reynolds, W. F., Peat, I. R., Freedman, M. H., and
Rice, J. M., Dudek, G.O., and Barber, M., 1965:
Ritchie, C. D., and Sager, W. F., 1964:
Rogers, M. T., and Woodbrey, J. C., 1962:  

Roth, B., and Strelitz, J. Z., 1969:  


Schaleger, L. L., and Long, F. A., 1963:  

Schleyer, P. von R., Fort, R. C., Watts, W. E.,  
Comisarow, M. B., and Olah, G. A., 1964:  

Schleyer, P. von R., and Nicholas, R. D., 1961:  


Shatenshtein, A. I., 1963:  

Short, L. N., and Thomson, H. W., 1952:  


Smith, V. H., and Christensen, B. E., 1955:  

Spinelli, D., Consiglio, G., and Noto, R., 1976:  

Spinelli, D., Guanti, G., and Dell'ebra, C., 1972:  


Spotswood, T. McL., and Tanzer, C. I., 1967:  
Stirling, C. J. M., 1965:
'Radicals in Organic Chemistry'
Oldbourne Press, London.


Swain, C. G., and Lupton, E. C., 1968:

Taagepera, M., Henderson, W. G., Brownlee, R. T. C.,
Beauchamp, J. L., Holtz, D., and Taft, R. W., 1972:

Taft, R. W., 1956:
'Steric Effects in Organic Chemistry' Ch. 13
Wiley, New York.


Taft, R. W., and Lewis, I. C., 1958:

Taft, R. W., and Lewis, I. C., 1959:


Thornton, E. R., 1964:

Tomasik, P., 1973:
Wroclaw Technic. Univ. No.16 Monograph 4.

Topsom, R. D., 1976:

Longmans and Green, London.

Vratny, F., Rao, C. N. R., and Dilling, M., 1961:


Wells, P. R., Ehrenson, S., and Taft, R. W., 1968:

Winstein, S., and Fainberg, A. H., 1957:

Winstein, S., Grunwald, E., and Jones, H. W., 1951:

Winterfeld, K., and Flick, K., 1956:
*Arch. Pharm.*, 26, 448
(through *C.A.* 51, 11346c, 1957).


Yukawa, Y., and Tsuno, Y., 1959:

Zagulyaeva, O. A., Saikovich, E. G., and Mamaev, V. P.
PUBLICATIONS

BASED ON THE WORK DESCRIBED IN THIS THESIS

D.J. Brown and P. Waring
"Simple Pyrimidines. XVI.
A Synthetic Route to Some
2-(Pyrimidin-2'-yl)acetic Acids and Esters"

D.J. Brown and P. Waring
"Pyrimidine Reactions. XXVI.
2-(1'-Bromo-1'-methylethyl)pyrimidines.
Synthesis, Solvolysis and Dehydrobromination
to 2-Isopropenylpyrimidines"

D.J. Brown and P. Waring
"Simple Pyrimidines. XVII.
(in preparation).