THE BROMINATION OF 2-PYRIMIDONE
AND ITS N-METHYL DERIVATIVES

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ABSTRACT

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THE BROMINATION OF 2-PYRIMIDONE AND ITS N-METHYL DERIVATIVES

The bromination of the salts of 2-pyrimidone, its N-methyl and N,N'-dimethyl derivatives has been investigated. Initial reaction of bromine with substrate (as covalent hydrate or pseudo-base) is rapid and irreversible, leading to the formation of a 5-bromo-4,6-dihydroxy-hexahydro-2-oxo-pyrimidine. This undergoes slow acid-catalysed conversion to the aromatic 5-bromo-product, the process being of the first-order at constant acid concentration. The 5-bromo-pyrimidone once formed reacts further with an excess of bromine to form a 5,5-dibromo-4,6-dihydroxy-hexahydro-2-oxo-pyrimidine. On treatment with strong acid, the latter reverts to the 5-bromo-compound. A mechanistic scheme for the entire bromination sequence has been proposed.
"... it is more important to have beauty in one's equations than to have them fit experiment."

P.A.M. Dirac

(Sci. Am. 208 (5) 45, (1963))
ACKNOWLEDGEMENTS

The author wishes to express his gratitude to Dr. O. S. Tee for initiating the project, and for his guidance and understanding throughout the course of this work. He would also like to thank the Department of Chemistry for financial assistance.
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PART 1 – INTRODUCTION
GENERAL INTRODUCTION

The role of the pyrimidines in biological processes is well established\textsuperscript{1}, and interest in the pyrimidine ring system has continued since its discovery. Earlier research however, centred more on the synthetic aspects of pyrimidine chemistry, mechanistic implications being largely ignored. Consequently, a general pattern of N-heteroaromatic behaviour has not yet emerged, and quantitative correlations with benzenoid systems have still to be established.

Katritzky and Johnson\textsuperscript{2} surveyed the limited amount of quantitative data available on the electrophilic substitution of N-heterocycles, and stressed the need for systematic mechanistic investigations. Subsequent kinetic work on 2-pyrimidinones suggested that the covalent hydrates of these compounds were the reactive intermediates involved in hydrogen-deuterium exchange\textsuperscript{3}. The object of this work was to determine the mechanism of bromination\textsuperscript{4} of a number of pyrimidinones, in order to enable comparison with other electrophilic substitution reactions in this series.

The acid-catalysed bromination of 1,2-dihydro-2-oxo-pyrimidinium chloride and its N-methyl derivatives were
studied, the rate of appearance of the brominated product being monitored spectrophotometrically.

It was found that the addition of bromine caused a rapid disappearance of the substrate leading to the formation of some non-absorbing intermediate. This subsequently converted to the 5-bromo-product, the reaction being of the first order both with respect to the intermediate and to acid. The 5-bromo-pyrimidine was found to undergo further bromination to form a 5,5-dibrominated product, which reverted back to 5-bromo-pyrimidine upon addition of strong acid. Successive introduction of methyl groups on the ring nitrogen atoms was found to increase the reaction rate.
INTRODUCTION TO THE PYRIMIDINES

Electron withdrawal by a ring nitrogen atom is similar to that of a nitro-group in a benzenoid system. Consequently the 5-position of pyrimidine (1) is the most susceptible to attack by electrophiles*, since it is the least influenced by the electron-withdrawing effects of the aza-substituents. This is borne out by the results of molecular orbital calculations.

Facile electrophilic substitution requires electron-releasing groups in the 2,4 or 6-positions. Conversely, nucleophilic substitution is favored at these positions. In general, the 2-position is found to be the most easily substituted, owing to the adjacency of the two ring nitrogen atoms.

* In many heterocyclic systems electrophiles preferentially attack a nitrogen lone pair. This attack, however, is usually reversible and of no overall consequence.
Hydroxy-pyrimidine and Pyrimidones

2,4 or 6-hydroxy-pyrimidines are known to exist in their tautomeric keto-forms\(^7\). Tautomerism of this type has led to confusion in the nomenclature of these compounds, and the terms 'hydroxy-pyrimidine' and 'pyrimidone' are often used interchangeably. In this thesis the latter term will be used throughout. In the keto form of 2-pyrimidone, the lone pair on nitrogen-1 facilitates electrophilic attack at the 5-position (6)\(^8\).

Pyrimidones may undergo both protonation (\(pK_1=2.24\))\(^9\) and deprotonation (\(pK_2=9.14\))\(^10\).

\[
\begin{align*}
\text{2} & \quad \overset{K_1}{\rightleftharpoons} & \quad \text{3} & \quad \overset{K_2}{\rightleftharpoons} & \quad \text{4}
\end{align*}
\]

Protonation occurs on the aza-nitrogen rather than on oxygen\(^7\). Further confirmation of the structure of cation (2) is afforded by the similarity of its U.V. and N.M.R. spectra to those of the quaternary ion (6), (\(R_1=R_2=\text{Me}\))\(^3c\).

\[
\begin{align*}
\text{5} & \quad \text{6} & \quad \text{7}
\end{align*}
\]
2-Pyrimidone undergoes acid-catalysed hydrogen-deuterium exchange\textsuperscript{3} at the 5-position at a much faster rate than anticipated by comparison with 2-pyridone\textsuperscript{12}. In explanation it has been suggested that reaction occurs via a covalent hydrate (7), (R\textsubscript{1}=R\textsubscript{2}=H) in equilibrium with the parent molecule (2), but only present to the extent of 0.1-1\% of the mixture\textsuperscript{3}. In support of this it was shown that (6), (R\textsubscript{1}=R\textsubscript{2}=Me) also undergoes exchange almost certainly via its pseudo-base (7), (R\textsubscript{1}=R\textsubscript{2}=Me).

**Amino-pyrimidines**

Amino-substitution of a pyrimidine ring increases its reactivity towards electrophilic substitution\textsuperscript{5}. The kinetics of hydrogen-deuterium exchange at the 5-position of 2-amino-pyrimidine and 6-amino-2,4-dimethyl-pyrimidine indicate that the influence of two aza-substituents is roughly twice the effect of a single substituent\textsuperscript{3,14}.

The study of these compounds is hindered by their tendency to hydrolyse in both acidic and basic media\textsuperscript{3,15,16}. Amino-pyrimidines find extensive application as starting materials in the synthesis of bicyclic heterocycles\textsuperscript{5}.

**Nitro-pyrimidines**

The nitration of pyrimidines was previously believed to
occur only in the presence of at least two electron-releasing groups. This has now been proved to be unnecessary, and monosubstituted pyrimidines may be nitrated under very vigorous conditions.

The kinetics of nitration of 2-pyrimidones has been studied, and the reactive species was shown to be the free base. The electron-withdrawing effect of the nitro-group facilitates nucleophilic addition, and the 5-nitropyrimidinium cation (9) is known to be hydrated.

**Halogeno-pyrimidines**

Pyrimidines may be halogenated either by direct halogenation, or by the action of halogenating agents such as phosphoryl chloride. Since bromination is of importance in the context of this work, the chemistry of bromopyrimidines is discussed in detail.

Pyrimidine is brominated by molecular bromine at a temperature of 160°. The presence of electron-releasing groups facilitates the reaction, and 2,4 or 6-substituted pyrimidines are easily brominated by bromine in water,
acetic acid, methanol\textsuperscript{24,5} or other media to form 5-brominated products. 2-Pyrimidone and its N-methyl derivatives readily form the 5-brominated compounds by reaction with molecular bromine\textsuperscript{20,21,22}.

The 5-bromo-compound once formed may undergo further bromination to a 5,5-dibromo-tetrahydro-pyrimidine. For example, uracil (11), is known to be brominated in two stages\textsuperscript{23,37,38}.

\[
\begin{align*}
\text{11} & \quad \text{Br}_2 \quad \text{Br} \quad \text{H}2O \\
\text{12} & \quad \text{Br} \\
\text{13} & \quad \text{Br} \quad \text{H}2O \\
\end{align*}
\]

The mechanism postulated involves the addition of HOBr, and subsequent dehydration. The 5-bromo-uracil (12) then adds a second molecule of HOBr\textsuperscript{37} to give the tetrahydro-pyrimidine (13).

Dibrominated products may also be obtained from cytosine (14)\textsuperscript{23}, isocytosine (15)\textsuperscript{5}, barbituric acid (16)\textsuperscript{5} and other compounds.

The question of covalent halogen adducts has been raised
by Eisch who commented on the possibility of a stable adduct forming the aromatic product through an elimination step. This has been shown to be the case in the bromination of 2-sulfonamido-pyrimidine (17). The stable adduct (18) is initially formed, and converts to the 5-bromo-pyrimidine (20) on treatment with anhydrous alkali. A second product (19) is also formed to some extent, but its mechanism of formation is as yet unknown.

\[
\begin{align*}
&\text{17} \quad \text{Br}_2 \quad \text{MeOH} \quad \text{18} \\
&\text{19} \\
\end{align*}
\]
COVALENT HYDRATION

The reactivity of electron-deficient aromatic systems towards nucleophiles is well known, and has been demonstrated in substituted benzenes\textsuperscript{25,26}. The inductive effect of an aza-substituent is comparable to that of a nitro group, and polyaza substituted aromatic rings are known to undergo solvent addition\textsuperscript{27,28,36}. The 5-nitropyrimidinium cation (8) is extensively hydrated in acid solution\textsuperscript{18}, as is the 5-methyl-sulphonyl-pyrimidine cation\textsuperscript{18}. The acid-catalysed hydrogen-deuterium exchange of 2-pyrimidone has been suggested as occurring via a hydrated intermediate according to the following scheme\textsuperscript{3}:

Quaternization of the ring nitrogen atoms as in 1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium bisulfate allows formation of the pseudo-base (26). This is entirely analogous to covalent hydration, and involves the attack of water on the
cation (25)$^3$. 

The intermediary of covalent hydrates in bromination reactions will be postulated in this investigation, and discussed at length in a later section.

$$H_2O + \text{25} \xrightleftharpoons{} \text{26} + H^+$$
ACIDITY FUNCTIONS

The measurement of rate constants for acid-catalysed reactions below the pH range is complicated by the non-linear variation of acid strength with acid concentration. Recourse must therefore be made to a reference scale, and the Hammett Acidity Function \( \text{H}_0 \), although not universally applicable\(^{29} \), provides a fairly accurate estimate of acid strength at high acid concentration.

For the dissociation of a protonated base \( \text{B} \),

\[
\text{BH}^+ \rightleftharpoons \text{B} + \text{H}^+
\]

the thermodynamic dissociation constant may be represented by

\[
K = \frac{a_{\text{H}^+} \cdot a_\text{B}}{a_{\text{BH}^+} \cdot f_{\text{BH}^+} \cdot [\text{BH}^+]} \quad \ldots(1)
\]

where \( 'a' \) and \( 'f' \) denote activity and activity coefficient respectively, the subscripts referring to the species involved.

The function \( \text{H}_0 \) is defined as

\[
\text{H}_0 = -\log_{10} a_\text{H}^+ \cdot f_\text{B} = -\log_{10} a_{\text{H}^+} \cdot f_{\text{BH}^+} \quad \ldots(2)
\]
The ratio $f_B / f_{BH^+}$ was found to be constant and independent of the nature of the base for a particular set of neutral bases\textsuperscript{30}.

From equations (1) and (2),

\[
H_o = pK_a - \log_{10} \frac{[BH^+]}{[B]} \quad ... \ (3)
\]

At low acidity, $f_B / f_{BH^+}$ equals unity, and $H_o$ converts to pH. Equation (3) may then be written as

\[
pH = pK_a - \log_{10} \frac{[BH^+]}{[B]} \quad ... \ (4)
\]

The ratio $f_B / f_{BH^+}$ has recently been found to be not completely independent of $B_0$\textsuperscript{31-33}, and more sophisticated methods of calculation have been devised\textsuperscript{34,35}. However, since an exact treatment has yet to be found, Hammett acidity functions were used in this investigation.
PART 2 - EXPERIMENTAL
INTRODUCTION

The objective of this work was to study the bromination of 2-pyrimidones and derive a mechanism consistent with the kinetics of the reaction.

The systems studied were the salts (6):

\[ \text{6 (a)}: R_1=R_2=\text{Me} \quad \text{(as HSO}_4^-) \]
\[ \text{6 (b)}: R_1=\text{Me}; R_2=\text{H} \quad \text{(as Cl}^-) \]
\[ \text{6 (c)}: R_1=R_2=\text{H} \quad \text{(as Cl}^-) \]

The N,N'-dimethyl derivative was studied in some detail since it represents the 'fixed form' of the parent cation (6c).

The U.V. absorption maxima, extinction coefficients and ionization constants of these compounds as well as those of their 5-bromo-derivatives are listed in Table 1 (p.14). In the case of the N,N'-dimethyl derivative, pseudo-base formation to (26) is possible\textsuperscript{3}, and measurements were made in 0.5M sulfuric acid to suppress this equilibrium.

Addition of bromine water to an aqueous solution of substrate (6 a,b or c), resulted in a rapid disappearance of all peaks above 220 nm. On addition of acid, slow formation
Table 1

Ionization constants and U.V. parameters of the substrates

<table>
<thead>
<tr>
<th></th>
<th>pH in H2O</th>
<th>pK_a</th>
<th>$\lambda_{\text{Max}}$ (logε)$^{\text{ref}}$</th>
</tr>
</thead>
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<tr>
<td>1,2-dihydro-2-oxo-pyrimidinium chloride</td>
<td>6.21</td>
<td>2.24±0.04</td>
<td>298(3.67), 215(&gt;4.0)$^{11}$</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>2.24±0.04</td>
<td>309(3.75), 215(&gt;3.2)$^{11}$</td>
</tr>
<tr>
<td>1,2-dihydro-1-methyl-2-oxo-pyrimidinium chloride</td>
<td>6.0</td>
<td>2.5±0.04</td>
<td>302(3.73), 215(4.0)$^{11}$</td>
</tr>
<tr>
<td></td>
<td>0.3</td>
<td>2.5±0.04</td>
<td>313(3.85), 215(3.80)$^{11}$</td>
</tr>
<tr>
<td>1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium hydrogen sulfate</td>
<td>0.29</td>
<td></td>
<td>316(3.93), 215(&gt;4.0)$^{3c}$</td>
</tr>
<tr>
<td>5-bromo-2-pyrimidone</td>
<td>4.0</td>
<td>0.44±0.02</td>
<td>322(3.54), 222(4.16)$^{49}$</td>
</tr>
<tr>
<td></td>
<td>0.22</td>
<td>0.44±0.02</td>
<td>343(3.65), 220(4.19)$^{49}$</td>
</tr>
<tr>
<td>5-bromo-1-methyl-2-pyrimidone</td>
<td>4.0</td>
<td>0.55±0.03</td>
<td>326(3.43), 225(4.0)$^{49}$</td>
</tr>
<tr>
<td></td>
<td>-2.0</td>
<td>0.55±0.03</td>
<td>346(3.55), 224(3.96)$^{49}$</td>
</tr>
<tr>
<td>5-bromo-1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium hydrogen sulfate</td>
<td>0.29</td>
<td></td>
<td>346(3.85), 222(4.10)$^{22}$</td>
</tr>
</tbody>
</table>
of the product was observed as indicated by an increase in the long-wavelength absorption band of the 5-bromo-compound. It therefore appears that the reaction involves at least two steps, the first resulting in the rapid formation of a non-absorbing intermediate, the second corresponding to slow acid-catalysed product formation. The spectral changes accompanying the bromination of 1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium hydrogen sulfate are shown in Fig.6(p.43).

The initial formation of the intermediate was too rapid to be followed by the conventional spectrophotometric technique\textsuperscript{39}, and rapid reaction methods\textsuperscript{40} will have to be used for its study. The second slow step was amenable to observation and a large number of kinetic runs were carried out to determine the effect of varying the concentrations of substrate, bromine and acid.
PREPARATION OF COMPOUNDS

2-Pyrimidone hydrochloride was a commercial sample which was recrystallised from ethanol-water before use. M.P.: darkened over 130°.

The following compounds were obtained from Dr. O. S. Tee:

5-bromo-2-pyrimidone

1,2-dihydro-1-methyl-2-oxo-pyrimidinium chloride

1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium hydrogen sulfate

1,3-dimethyl-urea (8.8g., 0.1 moles) in 40 mls. of absolute ethanol was added to 1,1,3,3-tetraethoxy-propane (22g., 0.1 moles). The resulting solution was cooled in ice water, and 95% sulfuric acid (20g., 0.2 moles) was added with stirring. The solution turned yellow and deposited a yellow-orange precipitate. The reaction mixture was then heated gradually to 50°, and was maintained there for thirty minutes. Cooling to room temperature and filtration gave pale yellow crystals. Recrystallisation from ethanol-methanol-water afforded long colorless needles m.p. 204-206°. Wt. = 18.4g. Yield = 83%.

N.M.R. (in D₂O) compared favorably with literature values.

**Analysis** C₆H₁₀N₂O₅S requires C, 32.43%; H, 4.54%; N, 12.61%.

found 32.54  4.59  12.72
5-deuterio-1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium hydrogen sulfate
1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium hydrogen sulfate (2.2g., 0.01 moles) in 10mls. of D₂O was sealed in a thick-walled glass tube and heated at 100°C for ten days. After cooling to 0°C, the tube was opened and the contents decolorised by filtering through 'Norite'. Solvent removal by a rotary evaporator afforded a white material which recrystallised from ethanol-water to form long white needles similar in appearance to the starting material. Wt.=1.82g. Yield=81%.

N.M.R. (in D₂O) showed a trace (<3%) of the starting material.

5-bromo-1-methyl-2-pyrimidone
1,2-dihydro-1-methyl-2-oxo-pyrimidinium chloride (0.5g., 0.0034 moles) was dissolved in 5mls. of distilled water. Saturated bromine water was added dropwise with stirring till the colour persisted. The solution was taken to dryness on a rotary evaporator to yield a yellow material which recrystallised from ethanol to give white flakes m.p. 237-239°C (after darkening at 180°C), lit. 210-211°C. N.M.R. (in D₂O with DSS as reference) 6.03τ (singlet, area 3), 0.51τ, 0.67τ (AB quartet, J=3Hz, area 2).

Analysis C₉H₅N₂OBr requires C, 31.78%, H, 2.65%; N, 14.83%; Br, 42.28%.

found 31.80  2.75  14.85  42.17
5-bromo-1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium bromide

(0.17g., 0.001 moles) was weighed into a flask. To this was added 10mls. of 0.1M bromine water. The solid dissolved and the bromine was decolorised almost instantly. The resulting solution was taken to dryness on a rotary evaporator to yield a pale yellow solid. Recrystallisation from ethanol gave bright yellow crystals M.p. 267-268° (dec.).

Wt. = 0.189g., Yield = 67%.

N.M.R. (in D₂O with DSS as reference) 6.12σ(singlet, area 6), 0.95σ(singlet, area 2).

Analysis C₆H₈N₂OBr₂ requires C, 25.38%; H, 2.84%; N, 9.87%; Br, 56.28%.

found  25.59  2.82  9.76  56.06

5,5-dibromo-4,6-dihydroxy-1,3-dimethyl-hexahydro-2-oxo-pyrimidine

5-bromo-1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium bromide (1g., 0.0035 moles) was weighed into a flask. To this was added saturated bromine water till the colour persisted. A white material immediately precipitated out of solution. Wt. = 0.97g., Yield = 87%. M.p. darkened over 135°.

N.M.R. (in DMSO-d₆ with TMS as reference) 7.13σ(singlet, area 3), 5.00σ(singlet, area 1).

Analysis C₆H₁₀N₂O₃Br₂ requires C, 22.67%; H, 3.15%; N, 8.81%; Br, 50.27%.

found  22.63  3.05  8.86  50.13

Mass spectrum (m/e for parent ion): 316, 318, 320 (intensity 1:2:1)
Volumetric solutions

Sulfuric acid, hydrochloric acid and sodium thiosulfate solutions were prepared from commercially available standard volumetric concentrates.
KINETIC PROCEDURE

Theory

For those compounds which obey Beer-Lambert's law, concentration is linearly proportional to absorbance according to the relation:

\[ A = ecl \] \ ...(5)

where 'A' is the absorbance, 'c' the molar concentration, 'e' the molar extinction coefficient, and 'l' the path length of the cell in cm. The rate and extent of a reaction can therefore be measured spectrophotometrically if the reaction involves a well defined spectral change.

For a first order process \( B \rightarrow C \)

\[ [B] = [B]_o - [C] = [B]_o e^{-kt} \]

and \[ kt = \ln \frac{[B]_o}{[B]_o - [C]} \] \ ...(6)

where \([B]_o\) is the initial concentration of B, \([C]\) the concentration of C at time 't', and 'k' the first-order rate constant.

If the reaction is followed spectrophotometrically at
some wavelength \( \lambda \) the following relationships pertain:

Initially, \[ A_0 = e^\lambda B_0 \]

At time 't' \[ A_t = e^\lambda (B_0 - C) + e^\lambda C \]

At \( t = \infty \) \[ A_\infty = e^\lambda C = e^\lambda B_0 \]

Hence \[ (A_\infty - A_0) = (e^\lambda - e^\lambda B) B_0 \]

\[ (A_\infty - A_t) = (e^\lambda - e^\lambda B)(B_0 - C) \]

and \[ \frac{(A_\infty - A_0)}{(A_\infty - A_t)} = \frac{B_0}{B_0 - C} = \exp(kt) \]

Rearranging, \[ \ln(A_\infty - A_t) = \ln(A_\infty - A_0) - kt \ldots (7) \]

Hence a plot of \( \ln(A_\infty - A_t) \) vs. 't' should give a straight line with slope 'k'.

When \( t = t_{1/2} \) (the half life of the reaction), \( [C] = \frac{1}{2} [B]_0 \)

and from eqn. (6), \( t_{1/2} = \frac{1}{k} \ln 2 \)

For 99.9% reaction, \( [C] = 0.999 [B]_0 \), and again from eqn. (6),

\[ t_{99.9\%} = \frac{1}{k} \ln 1000 \ldots (8) \]

Substituting for 'k' in eqn. (8) gives
\[ t_{99.9\%} = \frac{\ln 1000}{\ln 2} \quad t_H = 9.966t_H \quad \ldots(9) \]

ie. for most purposes the reaction is complete after ten half-lives.

In the present study the reactions were followed by measuring the increase in U.V. absorption due to the particular 5-bromo-product for periods ranging from 1 to 3 half-lives. Bearing in mind eqn. (9), values of \( A_{\infty} \) were measured after at least ten half-lives.

Experimental Measurements

All absorbance values and spectra were measured on a Cary Model 14 recording spectrophotometer with the following instrumental parameters:

- Dynode: 3
- Slit Control: Variable (20-40)
- Slit: On
- Slit Height: 20 mm.
- Selector: Vis.
- Chart Speed: 3 div./min.

The visible lamp was used for all kinetic runs.

The brominated product, by virtue of its aromaticity, has
a high molar extinction coefficient (Table 1;p.14), and solutions with concentrations of the order of $10^{-5}$M would have to be used if the reaction were to be followed at the absorption maxima. This would necessitate the use of low bromine concentrations. However, since the estimation of bromine is complicated by its volatility, relatively high concentrations of bromine are required for accurate determination. Hence, in the reactions where substrate concentration exceeded that of bromine, the reaction was followed at the long-wavelength side of the peak, in order to minimise the absorption, due to excess substrate. For the bromination of the 1,2-dihydro-1,3-dimethyl-2-oxopyrimidinium salt, the wavelength was set between 365 nm. and 380 nm., the product maxima occurring at 345 nm. It was shown that the rate constant was independent of the observation wavelength, proving that the increase of absorbance was caused by the formation of a single product.

Prior to a kinetic run, the baseline of the instrument was set with the solvent placed in both sample and reference compartments, matched 1cm. cells being used in all cases. Aliquots of substrate and bromine were rapidly mixed, and the mixture introduced into the cell, the absorbance being measured with respect to the solvent in the reference cell. Temperature control was maintained to within $\pm 0.02^\circ$C by circulating water from a Neslab Model TE9 constant temperature bath through the thermostatted
Data for a typical run are given below and plotted in Fig.1 (p.26). The latter illustrates the linear dependence of \( \ln(A_\infty - A_t) \) with time. In the processes studied, the concentration of acid far exceeded that of the substrate, and therefore pseudo-first-order behaviour was usually observed.

**Run No. 24AO.6**

1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium hydrogen sulfate (25): 3.71 \( \times \) \( 10^{-3} \) M  
Bromine: 1.38 \( \times \) \( 10^{-3} \) M  
Solvent: 0.3 M \( \text{H}_2\text{SO}_4 \)  
Wavelength: 3750 Å  
Temperature: 30°C  
\( A_\infty \): 0.9

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<th>(-\ln(A_\infty - A_t))</th>
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<tr>
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</table>

Rate Constant: $-3.12 \times 10^{-3}$ mins$^{-1}$

Standard Deviation: $1 \times 10^{-5}$ mins$^{-1}$

Half-life: 222 mins.

Correlation Coefficient: .999915
Illustration of a rate plot

\[-\ln(A_\infty - A_t)\]

Run No. 24A
Rate constants were calculated by applying the method of least-squares\textsuperscript{42} to eqn.(7), (p.21), and using a computer program written in BASIC\textsuperscript{22} for the Hewlett Packard 2114A. In cases where '\(A_\infty\)' could not be experimentally determined, the absorbance at 'infinity' was obtained by varying '\(A_\infty\)' using an iterative computer program written in BASIC. The value of '\(A_\infty\)' was estimated and the rate constant and correlation coefficient calculated from the least squares corrected line. The '\(A_\infty\)' was then successively increased or decreased by 0.001 absorbance units, and the correlation coefficients calculated for each value. These were compared with preceding values, and iteration was continued till the correlation coefficient registered a maximum.

The value of a calculated rate constant is particularly sensitive to the value of '\(A_\infty\)' used, since it is involved in each datum point (\(\ln(A_\infty - A_t)\)). Collins\textsuperscript{44} has shown that an error of one part in the infinity value may be magnified up to fourteen times in the rate constant. Therefore particular care was taken in measuring '\(A_\infty\)' values.
CALCULATION OF ACID STRENGTH

The dissociation of sulfuric acid in water may be represented by the equilibria:

\[
\begin{align*}
\text{H}_2\text{SO}_4 & \rightleftharpoons \text{H}_3\text{O}^+ + \text{HSO}_4^- \\
\text{HSO}_4^- & \rightleftharpoons \text{H}_3\text{O}^+ + \text{SO}_4^{2-}
\end{align*}
\]

where \[ K_2 = \frac{[\text{H}_3\text{O}^+][\text{SO}_4^{2-}]}{[\text{HSO}_4^-]} \] ....(10)

In dilute solutions, the first dissociation \((K_1)\) is far to the right, and may be assumed to be complete. Hence, if

\[
\begin{align*}
[\text{H}_2\text{SO}_4]_0 &= c = [\text{HSO}_4^-] + [\text{SO}_4^{2-}] \\
[\text{H}_3\text{O}^+] &= b = [\text{HSO}_4^-] + 2[\text{SO}_4^{2-}]
\end{align*}
\]

therefore \([\text{SO}_4^{2-}] = b - c\)

and \([\text{HSO}_4^-] = c - (b - c) = 2c - b\)

On substituting in equation (10),

\[
K_2 = \frac{b(b - c)}{(2c - b)}
\]

Solving for 'b' gives

\[
[\text{H}_3\text{O}^+] = b = \frac{(c - K_2) \pm \sqrt{(K_2^2 + 6cK_2 + c^2)}}{2} \] ....(11)
of which only the positive root is meaningful. Values for $[H_3O^+]$ were calculated using $K_2 = 1.2 \times 10^{-2}$.

In the high acid region, the pH scale is no longer valid and the use of acidity functions is necessary. Since $H_o$ is usually available in terms of 'Wt. % acid', an expression relating the latter term to molarity ($M$) was required. For sulfuric acid,

$$M = \frac{\text{conc.}(g./\text{lit.})}{M.W. H_2SO_4}$$

$$= \frac{\text{conc.}(g./\text{lit.})}{98}$$

therefore

$$W(\text{Wt. } % H_2SO_4) = \frac{\text{Wt. } H_2SO_4(g.) \times 100}{\text{Wt. soln.}(g.)}$$

$$= \frac{\text{conc.}(g./\text{lit.})}{10 \times \text{density}(g./\text{ml.})}$$

$$= \frac{98M}{10d} \cdots(12)$$

where 'M', 'W' and 'd' represent molarity, 'Wt. % $H_2SO_4$' and density respectively. The density of sulfuric acid-water solutions at $30^\circ C$ were used to calculate 'Wt. % $H_2SO_4$' from molarity. This was then converted to $H_o$ using the data of Johnson, Katritzky and Shapiro.
ESTIMATION OF BROMINE

Bromine was estimated by the addition of excess potassium iodide to the bromine solution, and titrating the liberated iodine with sodium thiosulfate.48

$\text{Br}_2 + 2\text{KI} \rightarrow 2\text{KBr} + \text{I}_2$

$\text{I}_2 + 2\text{Na}_2\text{S}_2\text{O}_3 \rightarrow \text{Na}_2\text{S}_4\text{O}_6 + 2\text{NaI}$

Quantitative determination of bromine is complicated by its tendency to volatilise, and solutions of bromine were freshly prepared before each kinetic run.
PART 3 - RESULTS
### Table 2
Variation of the rate of product-appearance with acidity

Substrate: \[
\begin{array}{c}
\text{NMe} \\
\text{N} \\
\text{Me} \\
\text{0}
\end{array}
\quad \text{HSO}_4^- \\
\text{Temperature: } 25^\circ\text{C}
\]

<table>
<thead>
<tr>
<th>Run No.</th>
<th>Py (x10^{-2}M)</th>
<th>Br(_2) (x10^{-3}M)</th>
<th>k x 10^3 (mins(^{-1}))</th>
<th>(\lambda) (nm)</th>
<th>H(_2)SO(_4) (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>2.27</td>
<td>1.65</td>
<td>3.10</td>
<td>375</td>
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* The rate constant refers to the kinetics of bromine decrease
Table 3

Variation of the rate of product-appearance with acidity

Substrate: \[
\begin{align*}
\text{NMe} & \quad \text{HSO}_4^- \\
\text{Me} & \quad \text{NMe}
\end{align*}
\]

Temperature: 30°C

<table>
<thead>
<tr>
<th>Run No.</th>
<th>(Py \times 10^{-3} \text{M})</th>
<th>(Br_2 \times 10^{-3} \text{M})</th>
<th>(k \times 10^3 \text{(mins}^{-1}\text{)})</th>
<th>(\lambda \text{(nm.)})</th>
<th>(H_2SO_4 \text{(M)})</th>
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*The rate constant refers to the kinetics of bromine decrease.*
Fig. 2

Variation of the rate of appearance of 5-bromo-1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium bromide with acidity
Table 4

Variation of the rate of product-appearance with acidity (H<sub>0</sub> region)

Substrate:

\[
\begin{array}{c}
\text{Me} \\
\text{N}\text{Me} \\
\text{C} \\
\text{C} \\
\text{+} \\
\text{HSO}_4^- \\
\end{array}
\]

Temperature: 30° C

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<tr>
<th>Run No.</th>
<th>Py (x10&lt;sup&gt;-3&lt;/sup&gt; M)</th>
<th>Br&lt;sub&gt;2&lt;/sub&gt; (x10&lt;sup&gt;-3&lt;/sup&gt; M)</th>
<th>k x 10&lt;sup&gt;3&lt;/sup&gt; (min&lt;sup&gt;-1&lt;/sup&gt;)</th>
<th>λ (nm&lt;sub&gt;s&lt;/sub&gt;)</th>
<th>H&lt;sub&gt;2&lt;/sub&gt;SO&lt;sub&gt;4&lt;/sub&gt; (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>51A</td>
<td>5.91</td>
<td>1.25</td>
<td>16.9</td>
<td>375</td>
<td>1.00</td>
</tr>
<tr>
<td>52A</td>
<td>5.42</td>
<td>2.13</td>
<td>18.1</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>3A</td>
<td>5.63</td>
<td>2.42</td>
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</tr>
<tr>
<td>6A</td>
<td>5.84</td>
<td>0.75</td>
<td>24.5</td>
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<td>&quot;</td>
</tr>
<tr>
<td>59A</td>
<td>3.75</td>
<td>2.46</td>
<td>37.2</td>
<td>375</td>
<td>1.50</td>
</tr>
<tr>
<td>60A</td>
<td>3.93</td>
<td>2.88</td>
<td>36.3</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>53A</td>
<td>4.68</td>
<td>2.04</td>
<td>59.7</td>
<td>375</td>
<td>2.00</td>
</tr>
<tr>
<td>54A</td>
<td>4.13</td>
<td>1.17</td>
<td>59.5</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>1A</td>
<td>3.57</td>
<td>2.14</td>
<td>84.7</td>
<td>375</td>
<td>2.19</td>
</tr>
<tr>
<td>7A</td>
<td>5.18</td>
<td>0.80</td>
<td>82.8</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>2A</td>
<td>3.99</td>
<td>1.65</td>
<td>86.6</td>
<td>370</td>
<td>&quot;</td>
</tr>
</tbody>
</table>
Variation of the rate of appearance of 5-bromo-1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium bromide with acidity ($H_o$ region)

$-\log k$ (mins$^{-1}$)

$H_o$

$-0.3$ $-0.4$ $-0.5$ $-0.6$ $-0.7$ $-0.8$ $-0.9$ $-1.0$
Table 5

Variation of the rate of product-appearance with acidity

Substrate: \[
\begin{array}{c}
\begin{array}{c}
\text{NMe} \\
\text{Cl}^- \\
\text{H} \\
\end{array}
\end{array}
\]

Temperature: 30°C

<table>
<thead>
<tr>
<th>Run No.</th>
<th>Py(x10^{-3}\text{M})</th>
<th>Br(_2)(x10(^{-3}\text{M}))</th>
<th>k(x10^3\text{(mins}^{-1}\text{)})</th>
<th>(\lambda\text{(nm.)})</th>
<th>H(_2\text{SO}_4)(\text{M})</th>
</tr>
</thead>
<tbody>
<tr>
<td>4B</td>
<td>4.50</td>
<td>1.07</td>
<td>0.603</td>
<td>370</td>
<td>0.250</td>
</tr>
<tr>
<td>5B</td>
<td>6.64</td>
<td>1.07</td>
<td>0.616</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>8B</td>
<td>3.62</td>
<td>3.33</td>
<td>0.803</td>
<td>370</td>
<td>0.350</td>
</tr>
<tr>
<td>10B</td>
<td>6.47</td>
<td>2.17</td>
<td>0.822</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>11B</td>
<td>5.07</td>
<td>1.94</td>
<td>0.760</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>6B</td>
<td>5.00</td>
<td>2.68</td>
<td>0.88</td>
<td>370</td>
<td>0.400</td>
</tr>
<tr>
<td>7B</td>
<td>4.86</td>
<td>2.03</td>
<td>1.02</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>1B</td>
<td>3.29</td>
<td>2.65</td>
<td>1.24</td>
<td>375</td>
<td>0.500</td>
</tr>
<tr>
<td>2B</td>
<td>3.29</td>
<td>1.55</td>
<td>1.23</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>3B</td>
<td>3.81</td>
<td>1.96</td>
<td>1.14</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
</tbody>
</table>
Fig. 4

Variation of the rate of appearance of 5-bromo-1-methyl-2-pyrimidone with acidity

\[ k \times 10^4 \text{ (mins}^{-1}) \]
Table 6

Variation of the rate of product-appearance with acidity

Substrate: \[
\begin{array}{ccc}
\text{NH} & \text{S} \\
\end{array}
\]

Temperature: 30°C

<table>
<thead>
<tr>
<th>Run No.</th>
<th>Py (10^{-3})M</th>
<th>Br(_2) (10^{-3})M</th>
<th>(k \times 10^4) mins(^{-1})</th>
<th>(\lambda) (nm)</th>
<th>H(_2)SO(_4) (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5C</td>
<td>3.85</td>
<td>2.78</td>
<td>1.89</td>
<td>365</td>
<td>0.250</td>
</tr>
<tr>
<td>6C</td>
<td>5.55</td>
<td>1.92</td>
<td>1.86</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>3C</td>
<td>2.91</td>
<td>1.36</td>
<td>2.18</td>
<td>375</td>
<td>0.300</td>
</tr>
<tr>
<td>7C</td>
<td>5.83</td>
<td>2.19</td>
<td>2.19</td>
<td>365</td>
<td>&quot;</td>
</tr>
<tr>
<td>4C</td>
<td>4.80</td>
<td>3.80</td>
<td>3.19</td>
<td>365</td>
<td>0.400</td>
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<tr>
<td>8C</td>
<td>3.89</td>
<td>2.70</td>
<td>3.18</td>
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<td>&quot;</td>
</tr>
<tr>
<td>1C</td>
<td>3.53</td>
<td>4.00</td>
<td>4.02</td>
<td>375</td>
<td>0.500</td>
</tr>
<tr>
<td>2C</td>
<td>3.33</td>
<td>1.50</td>
<td>4.21</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>9C</td>
<td>4.21</td>
<td>2.05</td>
<td>16.5</td>
<td>365</td>
<td>2.00</td>
</tr>
</tbody>
</table>
Fig. 5

Variation of the rate of appearance of 5-bromo-2-pyrimidone with acidity

\[ k \times 10^4 \text{ (mins}^{-1}\text{)} \]
### Table 7

Comparison of the rates of product-appearance of 2-pyrimidones

<table>
<thead>
<tr>
<th>R&lt;sub&gt;1&lt;/sub&gt; R&lt;sub&gt;2&lt;/sub&gt; X</th>
<th>k x 10&lt;sup&gt;3&lt;/sup&gt; (min&lt;sup&gt;-1&lt;/sup&gt;)</th>
<th>H&lt;sub&gt;2&lt;/sub&gt;SO&lt;sub&gt;4&lt;/sub&gt; (M)</th>
<th>Temp. (°C)</th>
<th>Av. Dev.</th>
<th>[H&lt;sub&gt;2&lt;/sub&gt;O&lt;sup&gt;+&lt;/sup&gt;] (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me Me HSO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>84.(7)</td>
<td>2.19</td>
<td>30</td>
<td>1.(3)</td>
<td>0.702</td>
</tr>
<tr>
<td></td>
<td>59.6</td>
<td>2.00</td>
<td>**</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>36.8</td>
<td>1.50</td>
<td>**</td>
<td>0.4(5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>26.(6)</td>
<td>1.28</td>
<td>**</td>
<td>2.(0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17.5</td>
<td>1.00</td>
<td>**</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.40</td>
<td>0.690</td>
<td>**</td>
<td></td>
<td>0.702</td>
</tr>
<tr>
<td></td>
<td>8.0(6)</td>
<td>0.665</td>
<td>**</td>
<td>0.1(1)</td>
<td>0.677</td>
</tr>
<tr>
<td></td>
<td>6.3(3)</td>
<td>0.500</td>
<td>**</td>
<td>0.2(3)@</td>
<td>0.511</td>
</tr>
<tr>
<td></td>
<td>5.33</td>
<td>0.430</td>
<td>**</td>
<td>0.07</td>
<td>0.441</td>
</tr>
<tr>
<td></td>
<td>3.4(1)</td>
<td>0.300</td>
<td>**</td>
<td>0.2(3)@</td>
<td>0.311</td>
</tr>
<tr>
<td></td>
<td>2.8(3)</td>
<td>0.250</td>
<td>**</td>
<td>0.1(7)@</td>
<td>0.261</td>
</tr>
<tr>
<td></td>
<td>1.08</td>
<td>0.100</td>
<td>**</td>
<td>0.03</td>
<td>0.110</td>
</tr>
<tr>
<td></td>
<td>0.59(1)</td>
<td>0.050</td>
<td>25</td>
<td>0.01(1)</td>
<td>0.059</td>
</tr>
<tr>
<td></td>
<td>3.4(5)</td>
<td>0.500</td>
<td>**</td>
<td>0.2(9)@</td>
<td>0.511</td>
</tr>
<tr>
<td></td>
<td>7.26</td>
<td>0.750</td>
<td>**</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9.7(1)</td>
<td>1.00</td>
<td>**</td>
<td>0.1(9)@</td>
<td></td>
</tr>
<tr>
<td>Me H Cl</td>
<td>1.20</td>
<td>0.500</td>
<td>30</td>
<td>0.04</td>
<td>0.511</td>
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<tr>
<td></td>
<td>0.95</td>
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<td>0.07</td>
<td>0.411</td>
</tr>
<tr>
<td></td>
<td>0.79(5)</td>
<td>0.350</td>
<td>**</td>
<td>0.02(3)</td>
<td>0.361</td>
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<tr>
<td></td>
<td>0.610</td>
<td>0.250</td>
<td>**</td>
<td>0.007</td>
<td>0.261</td>
</tr>
<tr>
<td>H H Cl</td>
<td>1.65</td>
<td>2.00</td>
<td>30</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.412</td>
<td>0.500</td>
<td>**</td>
<td>0.009</td>
<td>0.511</td>
</tr>
<tr>
<td></td>
<td>0.319</td>
<td>0.400</td>
<td>**</td>
<td>0.411</td>
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<td>0.219</td>
<td>0.350</td>
<td>**</td>
<td>0.311</td>
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<td>0.188</td>
<td>0.250</td>
<td>**</td>
<td>0.002</td>
<td>0.261</td>
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</tbody>
</table>

** Single value determination  
@ Standard Deviation
Table 8

Rate constants for the bromination of 5-deuterio-1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium deuterium sulfate

<table>
<thead>
<tr>
<th>Run No.</th>
<th>Py (x10^{-3}M)</th>
<th>Br\textsubscript{2} (x10^{-3}M)</th>
<th>k x 10^3 (mins^{-1})</th>
<th>\lambda (nm)</th>
<th>H\textsubscript{2}SO\textsubscript{4} (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4A'</td>
<td>2.89</td>
<td>2.30</td>
<td>1.08</td>
<td>375</td>
<td>0.500</td>
</tr>
<tr>
<td>5A'</td>
<td>3.66</td>
<td>2.33</td>
<td>1.10</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>6A'</td>
<td>2.53</td>
<td>1.59</td>
<td>1.05</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

\[ k_D = 1.08 \times 10^{-3} \text{ mins}^{-1} \]
\[ k_H = 6.38 \times 10^{-3} \text{ mins}^{-1} \]
\[ k_H/k_D = 5.91 \]
PART 4 - DISCUSSION
1,2-DIHYDRO-1,3-DIMETHYL-2-OXO-PYRIDINIUM HYDROGEN SULFATE (25)

(i) Results for the pH region

The addition of bromine to a neutral solution of the substrate (25) results in rapid disappearance of the long-wavelength absorption band, with no subsequent increase of the product peak (Fig. 6, p. 43). The introduction of a few drops of concentrated sulfuric acid induces the gradual appearance of the product π-π* maxima. This suggests the intermediacy of some stable non-absorbing substance. The reaction therefore consists of at least two steps, the first leading to rapid formation of an intermediate, the second corresponding to relatively slow, acid-catalysed conversion of the intermediate to the product.

Intermediate formation during the bromination of pyrimidines has been established in a number of systems\textsuperscript{24}. The bromination of a 2-sulfonamido-pyrimidine in methanol has been proved to proceed via a tetrahydro-pyrimidine intermediate\textsuperscript{24} (18).

\begin{align*}
\text{25} & \quad \text{18}
\end{align*}
Fig. 6

Initial spectral changes accompanying the bromination of 1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium hydrogen sulfate

Curves 1-4 represent spectra obtained after addition of 0, 0.25, 0.5, 0.8 moles of Br₂ per mole of substrate.
The work of Baev et al. provides further examples of intermediate formation. Addition of bromine to a solution of uracil (11) resulted in the disappearance of the long-wavelength band. On repeating the reaction on a synthetic scale, 5,5-dibromo-6-hydroxy-uracil (13) was isolated.

Guanine (27) and cytosine (14) exhibited similar behaviour towards bromination. In both cases, rapid disappearance of the $\pi - \pi^*$ band followed the addition of bromine. Cytosine bromination in aqueous media is accompanied by hydrolysis, and 5,5-dibromo-6-hydroxy-uracil (13) has been shown to be present.

For the title compound (25) the rate of appearance of 5-bromo-product was measured in acidic media. The observed pseudo-first-order rate constants were independent of initial pyrimidine and bromine concentrations at constant acid strength (Tables 2,3; p.31,32). This indicates that the first step of the reaction, the addition of bromine is rapid and irreversible. Over the

![Chemical structures](image-url)
range 0.05-0.69M H$_2$SO$_4$ the observed rate constants vary linearly with acidity (Table 3; p.32; Fig. 2 p.33) confirming the earlier assertion that the breakdown of the intermediate is acid-catalysed. The reaction measured kinetically is then the conversion of the intermediate to the 5-bromo-product. The initial concentration of the intermediate can therefore be assumed to be equal to the initial concentration of bromine or pyrimidine (whichever is the lesser), and the kinetics of product-formation be considered as a single-step first-order process, within this particular range of acid concentration.

**Case (1) Py$\supset$Br**

In all cases where Py$\supset$Br, the bromine color was rapidly discharged on addition. Kinetic runs with varying substrate to bromine ratios, with the substrate concentration always exceeding that of bromine yielded the same rate constant at constant temperature and acidity. Fig. 2 (p.33) shows the linear relationship between rate constant and [H$_3$O$^+$] typical of first-order acid catalysis. The bimolecular rate constant can be calculated to be 1.24x10$^{-2}$M$^{-1}$ sec$^{-1}$ from the least-squares corrected line (Corr.Coeff.=.9987).

* 'Py' and 'Br' represent starting pyrimidine and bromine concentration respectively.*
The rapid addition of bromine to the substrate seems unlikely if the latter undergoes reaction in its cationic form (25)#, since the positive charge on the pyrimidine ring would be expected to hinder electrophilic attack.* A possible explanation is that the substrate reacts not in the form (25), but rather as some neutral species in equilibrium with (25). Previous work\(^3\) has shown that the reactive entity in the hydrogen-deuterium exchange of (25) is the pseudo-base (26) in equilibrium with its parent ion. The pseudo-base would be expected to be reactive towards bromine since it contains an isolated double bond. However, since the proportion of (26) decreases with increasing acidity\(^2\), an increase in the decolorisation time of bromine would be expected if the reaction were to be carried out in highly acidic media. This was observed to be the case and will be discussed later.

The intermediate formed from the initial reaction of bromine with substrate is non-aromatic, and converts to (32) on treatment with acid. If reaction occurs on the isolated double bond of the pseudo-base, the intermediate could

* However Bell and Marshall\(^{58}\) have demonstrated that the bromination of 2,3-dihydro-4,7-dimethyl-1,4-diazepinium perchlorate in the 6-position in aqueous perchloric acid is a bimolecular reaction between the cation and bromine.

# Structures overleaf
have the structure (28) or (29). The former is unlikely, since the reaction of bromine with (32) gives a product that has been identified as (33). Recent work on the bromination of 2-sulfonamido-pyrimidines\textsuperscript{50-52} has shown that (30), \((R_1=\text{Me}; R_2=R_3=\text{H})\) and (30), \((R_1=R_2=R_3=\text{H})\) may be isolated from methanolic and acetic acid-water solutions respectively\textsuperscript{50}. The bromination of 2-sulfonamido-5-methyl-pyrimidine\textsuperscript{51} yields (30), \((R_1=R_2=\text{H}; R_3=\text{Me})\) in aqueous solution, and (30), \((R_1=R_3=\text{Me}; R_2=\text{H})\) in methanol, while 2-sulfonamido-4-methyl-pyrimidine\textsuperscript{52} is brominated to (30) \((R_1=R_2=\text{Me}; R_3=\text{H})\) by bromine in methanol.
Thymine is known to be brominated to (31), (R=Me)\(^{53}\), and the bromination of uracil has been postulated to occur via (31), (R=H)\(^{37}\). In the case of uracil, the intermediate (31), (R=H) converts to 5-bromo-uracil in the presence of acid.

Bromination involving an addition-elimination mechanism has also been demonstrated in quinolines. The N-cyanoquinolinium ion (34) is brominated via its pseudo-base (35) to form an adduct (36)\(^{54}\).

On the basis of the above evidence it is reasonable to assume that (29) is the structure of the intermediate formed in the present study. Attempts to isolate the intermediate (29) were unsuccessful, and yielded white labile materials which readily transformed to the 5-bromo-compound (32). The kinetic results (Table 3; p.32) support a two-step mechanism, the rate constant exhibiting a linear dependence on acid concentration. The following sequence may therefore be suggested, the step under observation corresponding to acid-catalysed dehydration of (29) to (32).
The pseudo-base formation of (32) has been observed by Tee\textsuperscript{22}, and it is probable that (32) is formed through the intermediacy of (37).

Case (2) Br>2Py

On adding bromine water in slight excess to an acidified solution of 1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium hydrogen sulfate (25), some residual coloration corresponding to unreacted bromine was observed. The coloration faded with time, suggesting the possibility of
a further slow bromination step. The experiment was repeated with the bromine concentration being twice that of the pyrimidone. The absorption spectrum of the reaction mixture showed the absence of any 5-bromo-product (32), the only significant spectral feature above the 220 nm. region being the peak due to excess bromine. The intensity of this absorption however, gradually decreased to a final measurable value. Analysis of the kinetics of the decrease yielded a rate constant, identical within the limits of experimental error, to that derived from the kinetics of formation of the 5-bromo-product (32) from the intermediate (29) as in the previous case (Table 3;p.32).

It is apparent that the rate-controlling step in this reaction is the formation of the 5-bromo-pyrimidone (32) which then undergoes rapid reaction with bromine to form a non-absorbing product.

To test this hypothesis, bromine was added to an aqueous solution of the 5-bromo-cation (32). The bromine color was rapidly discharged, and on repeating the reaction on a synthetic scale, a white material was obtained which gave spectra and elemental analysis consistent with the structure (33).
Case (3) Py<Br<2Py

Under the conditions where Py<Br<2Py, the 5-bromo-compound (32) initially formed, would be expected to react with the excess bromine till a point where all the unreacted bromine was completely consumed.

The reaction was monitored spectrophotometrically, the absorbance at 375 nm. being recorded with time. However since bromine and the 5-bromo-product (32) have maxima at 390 nm. and 346 nm. respectively, both absorb in the region of observation at the concentrations used in the experiment. An absorbance-time plot is shown in Fig.7 (p.52).

The initial decreasing absorbance may be attributed to unreacted bromine, since all the substrate would have been converted into the non-absorbing form (29). The subsequent increase of absorbance would then correspond to simple formation of the aromatic product (32).

Analysis of the increasing portion of the kinetic run yielded a rate constant essentially the same as those obtained for the previous cases (Table2 ;p.31).

The calculation of a rate constant from the kinetics of the decreasing region is complicated, since although the
Fig. 7

Absorbance-time plot for the case where \( \text{Py} < \text{Br} < 2\text{Py} \)

Absorbance

Run No.: H14

(minutes)
changes in bromine absorbance are measured, the rate-determining step represents the formation of the 5-bromo-compound (32) and an 'A∞' for the reaction is not available. The final bromine concentration is undoubtedly zero, but this cannot be taken as 'A∞' since the formation of the 5-bromo-product does not cease with the disappearance of bromine, and thus a first-order plot with 'A∞'=0 is significantly curved (Fig.8A; p.54). A value of 'A∞' must be selected such that it represents the final concentration of bromine had it been present, and in the present case this would necessarily be negative. Fig.7 (p.52) illustrates the above reasoning. If 'e₁' and 'e₂' be the extinction coefficients of the 5-bromo-product (32) and bromine respectively, then \( A₁/e₁ = A₂/e₂ \). The equation was not verified owing to the difficulty in obtaining an accurate extinction coefficient for bromine in aqueous solution.

Appropriate values of 'A∞' were calculated from the best least-squares fit of a first-order plot (Fig.8B; p.54). The rate constants so derived were found to agree closely with those obtained for the previous case (Table2; p.31; Run No.H14*).
Rate plot for the case where Py < Br < 2Py

\[-\ln(A_\infty - A_t)\]
(ii) Results for the $H_0$ region

The reaction time of bromine with substrate tends to increase with the acidity of the medium, and in the 1.0-2.19M region, the decolorisation of bromine by substrate is no longer as rapid as in the previous case. In the equilibrium (25) to (26), the proportion of the pseudo-base (26) decreases with increase of acid strength, and if (26) is indeed the species undergoing bromination, the time of decolorisation would increase with increasing acidity. The dehydration rate of the brominated intermediate would, however, be expected to increase with acidity if a first-order dependence on acid strength is valid in this region.

\[
\begin{align*}
25 & \quad \text{H}_2\text{O} & \quad 26 \\
32 & \quad \text{H}_2\text{O} & \quad 37
\end{align*}
\]

A first-order plot for the rate of product formation is significantly curved. This apparent deviation from simple first-order behaviour may be explained by considering the sequence in Table 9 (p.56), ($R_1=R_2=\text{Me}$).

The higher acidity involved would tend to reduce the proportion of the pseudo-base (7) and consequently decrease the rate of formation of the intermediate (38).
Table 9

Mechanism of bromination of 2-pyrimidones

\[ \text{45} \xrightarrow{\text{H}^+} \text{6} \xrightarrow{\text{H}_2\text{O},-\text{H}^+} \text{7} \xrightarrow{\text{Br}_2, \text{fast}} \]

\[ \text{38} \xrightarrow{\text{H}^+,-\text{H}_2\text{O}} \text{39} \xrightarrow{\text{H}_2\text{O},-\text{H}^+} \]

\[ \text{46} \xrightarrow{\text{H}^+} \text{40} \xrightarrow{\text{H}_2\text{O},-\text{H}^+} \text{41} \xrightarrow{\text{Br}_2, \text{fast}} \]

\[ \text{42} \xrightarrow{\text{H}^+,-\text{H}_2\text{O}} \text{43} \xrightarrow{\text{H}_2\text{O},-\text{H}^+} \]
On the other hand, since the rate of dehydration of (38) increases with acidity, the small amount of the brominated product (40) formed would compete with the substrate (6) for the remaining bromine, and a portion of (40) would be converted to the dibrominated product (42).

It was observed that the absorbance measured after approximately ten half-lives did not remain constant, but increased very slowly well after the reaction should have theoretically gone to completion if it was limited to the simple conversion of (38) to (40). A first-order plot of a kinetic run in 1.28M sulfuric acid is shown in Fig. 9 (p. 53). The gradual increase of the final absorbance reading cannot be explained on the basis of a single-step reaction, and suggests a further slow reaction leading to the formation of the 5-bromo-pyrimidone (40).

In a separate experiment bromine was added to an acidified solution (2M \( \text{H}_2\text{SO}_4 \)) of 5-bromo-1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium bromide (40). It was found that the absorbance due to the 5-bromo-cation (40) increased very gradually over the period of a month. Finally when the dibrominated product (42) was dissolved in 2M \( \text{H}_2\text{SO}_4 \), a gradual conversion to the 5-bromo-product (40) was observed.

If the above reasoning is correct, the slow increase of the absorbance after ten half-lives corresponds to the conversion of the dibrominated product (42) to the 5-bromo-pyrimidone (40). Therefore, although this reaction does not occur to
Fig. 9

Rate plot for the high-acid region (uncorrected for $A_\infty$)

$-\ln(A_\infty - A_t)$

Run No.: 3A
any significant extent during the time of measurement, it influences the $A_{\infty}$ to some small extent. Hence on lowering $A_{\infty}$ slightly to correct for this reaction, a simple first-order plot should be obtained for the rate of appearance of the 5-bromo-product (40). A first-order plot using a corrected $A_{\infty}$ is shown in Fig.10,(p.60). Rate constants obtained in this manner showed a linear dependence on acidity i.e. $\log k$ vs. $H_0$ gave a straight line (Fig. 3, p.35, Table 4, p.34).
Rate plot for the high-acid region (corrected for $A_\infty$)

$-\ln(A_\infty - A_t)$

Run No.: 3A
(iii) Effect of Isotopic Substitution of the 5-Hydrogen Atom

Isotopic substitution of the 5-hydrogen atom in the 1,3-dimethyl-pyrimidone (25) would be expected to decrease the rate constant appreciably, if the rate-determining step involves the breaking of the 5-carbon-hydrogen bond\(^{55}\). To test this hypothesis, (25) was deuterated at the 5-position\(^3\), and the bromination of the deuterated derivative was followed kinetically. However quantitative deuteration was not achieved, and a first-order plot for the appearance of the 5-bromo-product showed an initial curvature (Fig. 11 p.62). This reflects the simultaneous conversion of the undeuterated pyrimidone (25) and its deuterated derivative to (32), the former reaction being the more rapid. The linear portion of the plot corresponds to the formation of (32) from the deuterated compound alone, the more reactive intermediate having been consumed. Rate constants for the slower reaction were obtained by the method of Brown and Fletcher\(^{56}\), the results being given in Table 8 (p.41). The large isotope effect obtained confirms that the rate-determining step for the formation of the 5-bromo-product (32) is indeed the loss of the 5-H from the intermediate (29) (ie. (39) to (41) in Table 9, p.56).
Fig. 11

Rate plot for the bromination of 5-deuterio-1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium hydrogen sulfate

\[-\ln(A_\infty - A_t)\]

Run No.: 6A'
1,2-DIHYDRO-1-METHYL-2-OXO-PYRIMIDINIUM CHLORIDE (6)\( (R_1=H,R_2=Me) \)

The bromination pattern of 1,2-dihydro-1-methyl-2-oxo-pyrimidinium chloride (6),\( (R_1=H,R_2=Me) \) was found to closely parallel that of its \( N,N' \)-dimethyl-derivative (6),\( (R_1=R_2=Me) \). The rate-determining step, ie. the formation of the 5-bromo-pyrimidone (40),\( (R_1=H,R_2=Me) \) was independent of both bromine and substrate concentrations. Initial addition of bromine to a solution of substrate resulted in rapid decolorisation, and in the disappearance of all peaks above 220 nm. The formation of the 5-brominated product (40),\( (R_1=Me,R_2=H) \) was acid-catalysed and corresponded to pseudo-first-order kinetics, the rate constant being linearly variant with acid concentration (Table 5, p.36), (Fig.4, p.37).

The 5-bromo-product rapidly lost its long-wavelength absorption band on further reaction with bromine. This reaction was not pursued at either kinetic or synthetic levels, although comparison with the \( N,N' \)-dimethyl-derivative suggests a product with structure (42),\( (R_1=Me,R_2=H) \). On the basis of the above evidence, the mechanism postulated for the \( N,N' \)-dimethyl-derivative also seems appropriate for this particular case (Table 9, p.56)\( (R_1=Me,R_2=H) \).
2-PYRIMIDONE HYDROCHLORIDE (6)(R₁=R₂=H)

The mechanism of bromination of 2-pyrimidone hydrochloride (6), (R₁=R₂=H) strongly resembled that of its N-quaternised derivatives. On treatment with bromine, an aqueous solution of substrate lost all U.V. absorption over the 220 nm. region (Fig. 12, p. 65) to form a stable non-aromatic intermediate which underwent acid-catalysed conversion to the 5-bromo-product (40), (R₁=R₂=H). The latter step exhibited pseudo-first-order kinetics, being linearly dependent on acid concentration (Table 6, p. 38), (Fig. 5, p. 39), and independent of bromine and substrate concentrations. The 5-bromo-product was found to react further with bromine (Fig. 13, p. 66). The product of this second bromination step, although not isolated or identified, is expected to be the 5,5-dibromo-derivative (42), (R₁=R₂=H).

The quaternary ion (6), (R₁=R₂=Me) represents the fixed form of the parent cation (6), (R₁=R₂=H), and the similarity in behaviour towards bromination suggests a close correspondence in mechanism. Thus 2-pyrimidone may be said to undergo reaction as its covalent hydrate via the mechanism outlined in Table 9 (p. 56), (R₁=R₂=H).
Fig. 12

Initial spectral changes accompanying the bromination of 1,2-dihydro-2-oxo-pyrimidinium chloride

Curves 1-3 represent spectra obtained after addition of 0, 0.4, 0.8 moles of Br₂ per mole of substrate.

Absorbance

0.6 0.4 0.2

Wavelength (Å)

3500 3250 3000 2750 2500
Fig. 13

Initial spectral changes accompanying the bromination of 5-bromo-2-pyrimidone

Curves 1-3 represent spectra obtained after addition of 0, 0.3, 0.7 moles of Br$_2$ per mole of substrate.
GENERAL SUMMARY

The evidence cited in previous sections and summarized in Table 7, (p. 40) indicates that the bromination of 2-pyrimidone (3) proceeds via an adduct formed by the reaction of bromine with the covalent hydrate (44). Recent work on similar systems\textsuperscript{24,50-52} has provided further examples of the addition-elimination mechanism in bromination reactions. It now appears that pyrimidines with electron-releasing substituents in the 2-position tend to react through the intermediacy of relatively stable hexahydropyrimidines.

Previous work on the uracils has shown that 5-bromo-uracil is formed through a covalent adduct\textsuperscript{37}. Although the lack of published kinetic data precludes further definition, preliminary kinetic runs on this system by the author suggest that uracils may well undergo reaction in a manner analogous to 2-pyrimidone.

\[
\begin{align*}
&\text{3} \\
&\text{44}
\end{align*}
\]
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