THE BROMINATION OF 2-PYRIMIDONE

AND ITS N-METHYL DERIVATIVES

Sujit Banerjee

A THESIS

in

The Department

of

Chemistry

Presented in Partial Fulfillment of the Requirements for
the Degree of Master of Science at
Sir George Williams University
Montreal, Canada

July, 1972

ABSTRACT

SUJIT BANERJEE

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

TABLE OF CONTENTS

PART 1 - INTRODUCTION   Page

PART 2 - EXPERIMENTAL

PART 3 - RESULTS
PART 4 - DISCUSSION

INDEX TO TABLES

INDEX TO FIGURES

Page

PART 1 - INTRODUCTION

GENERAL INTRODUCTION

The role of the pyrimidines in biological processes is well established[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[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-pyrimidones suggested that the covalent hydrates of these compounds were the reactive intermediates involved in hydrogen-deuterium exchange[3]. The object of this work was to determine the mechanism of bromination[4] of a number of pyrimidones, 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[36]. 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[6].

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[5].
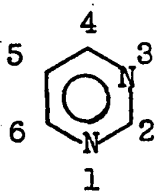
1

---

* 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 (5)[8].

Pyrimidones may undergo both protonation ($pK_1 = 2.24$)[9] and deprotonation ($pK_2 = 9.14$)[10].

2   3   4
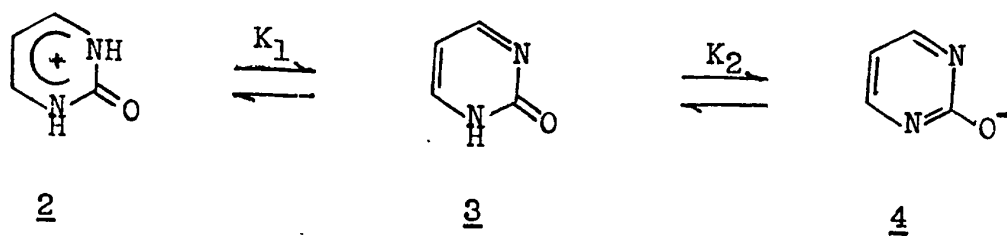
Protonation occurs on the aza-nitrogen rather than on oxygen[7]. Further confirmation of the structure of cation (2) is afforded by the similarity of its U.V. and N.M.R. spectra to those of the quaternary ion (6), ($R_1 = R_2 = Me$)[3c].

5   6   7
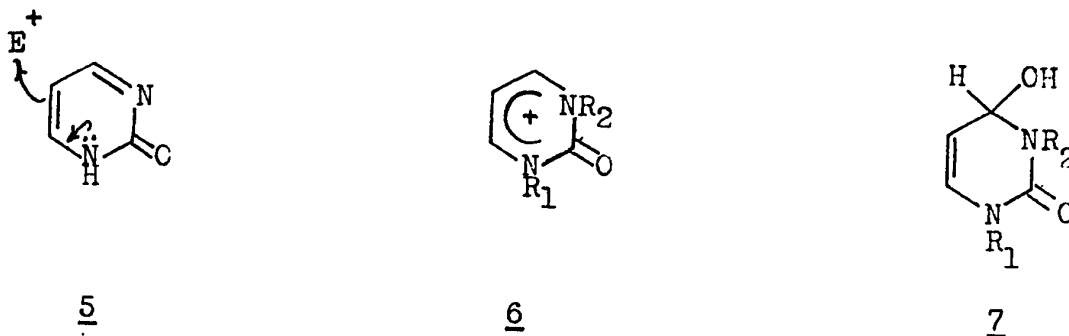
2-Pyrimidone undergoes acid-catalysed hydrogen-deuterium exchange[3] at the 5-position at a much faster rate than anticipated by comparison with 2-pyridone[12]. In explanation it has been suggested that reaction occurs via a covalent hydrate (7), ($R_1 = R_2 = H$) in equilibrium with the parent molecule (3), but only present to the extent of 0.1-1% of the mixture[3]. In support of this it was shown that (6), ($R_1 = R_2 = Me$) also undergoes exchange almost certainly via its pseudo-base (7), ($R_1 = R_2 = Me$).

Amino-pyrimidines

Amino-substitution of a pyrimidine ring increases its reactivity towards electrophilic substitution[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[3,14].

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

Nitro-pyrimidines

The nitration of pyrimidines was previously believed to

occur only in the presence of at least two electron-releasing groups[5]. This has now been proved to be unnecessary, and monosubstituted pyrimidines may be nitrated under very vigorous conditions[5].

The kinetics of nitration of 2-pyrimidones has been studied[17], 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-nitro-pyrimidinium cation (8) is known to be hydrated[18].

Halogeno-pyrimidines

Pyrimidines may be halogenated either by direct halogenation, or by the action of halogenating agents such as phosphoryl chloride[5]. Since bromination is of importance in the context of this work, the chemistry of bromo-pyrimidines is discussed in detail.

Pyrimidine is brominated by molecular bromine at a temperature of $160°$ [19]. 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[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[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[23,37,38].
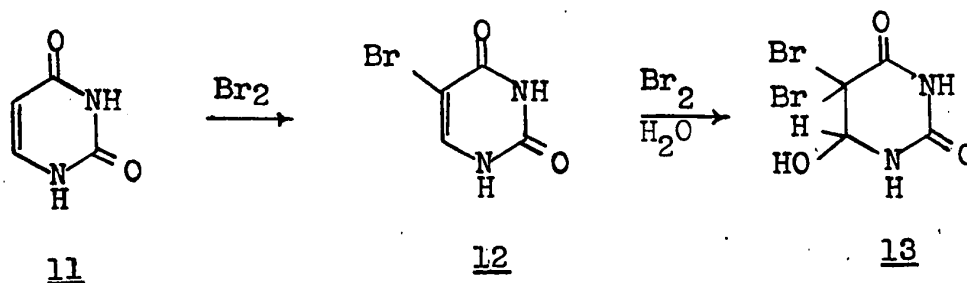
The mechanism postulated involves the addition of HOBr,

and subsequent dehydration. The 5-bromo-uracil (12) then

adds a second molecule of HOBr[37] to give the tetrahydro-

pyrimidine (13).

Dibrominated products may also be obtained from cytosine

(14)[23], isocytosine (15)[5], barbituric acid (16)[5] and other

compounds.

The question of covalent halogen adducts has been raised
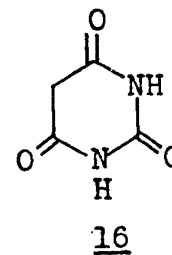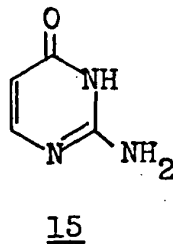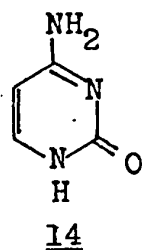
by Eisch[4] who commented on the possibility of a stable adduct
forming the aromatic product through an elimination step.
This has been shown to be the case in the bromination of
2-sulfonamido-pyrimidine (17)[24]. The stable adduct (18)
is initially formed, and converts to the 5-bromo-pyrimidine
(20) on treatment with anhydrous alkali. A second product
(19) is also formed to some extent, but its mechanism of
formation is as yet unknown.
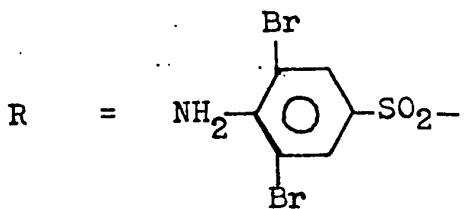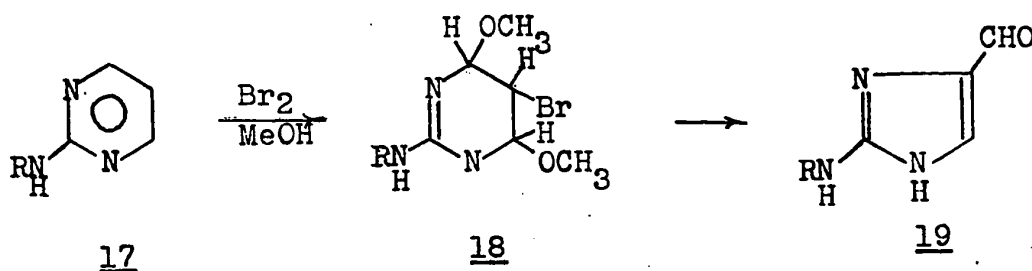
COVALENT HYDRATION

The reactivity of electron-deficient aromatic systems
towards nucleophiles is well known, and has been
demonstrated in substituted benzenes[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[27,28,36]. The 5-nitro-
pyrimidinium cation (8) is extensively hydrated in acid
solution[18], as is the 5-methyl-sulphonyl-pyrimidine cation[18].
The acid-catalysed hydrogen-deuterium exchange of
2-pyrimidone has been suggested as occurring via a hydrated
intermediate according to the following scheme[3]:
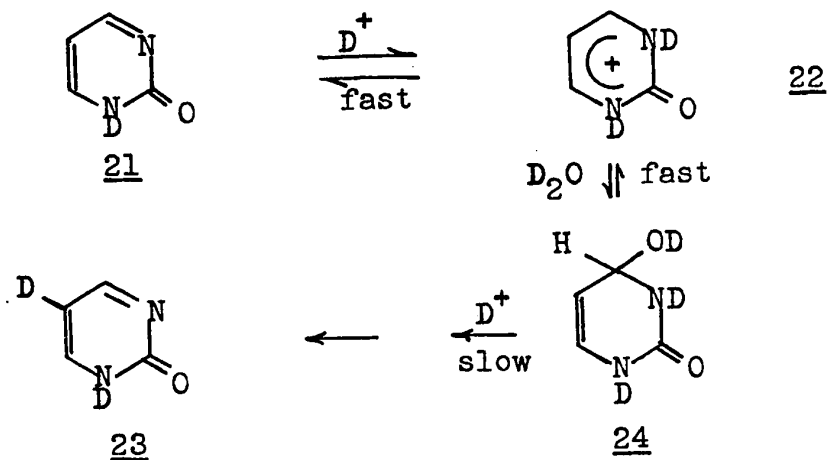
Quaternization of the ring nitrogen atoms as in 1,2-dihydro-
1,3-dimethyl-2-oxo-pyrimidinium bisulfate allows formation
of the pseudo-base (26). This is entirely analogous to
covalent hydration, and involves the attack of water on the

cation (25)[3].

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

$$H_2O \quad + \quad \underset{25}{[\text{structure}]} \quad \rightleftharpoons \quad \underset{26}{[\text{structure}]} \quad + \quad H^+$$
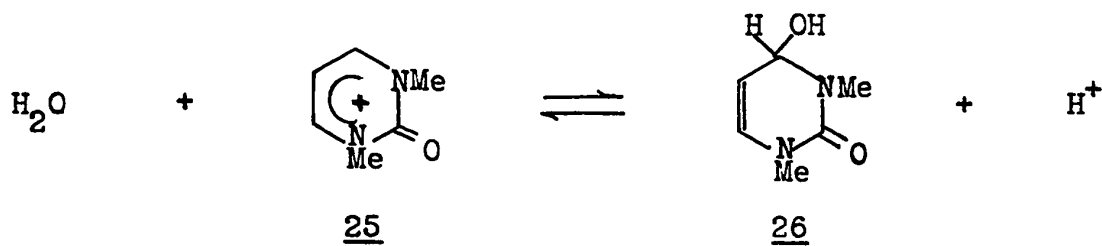
ACIDITY FUNCTIONS

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 'H_o', although not universally applicable[29], provides a fairly accurate estimate of acid strength at high acid concentration.

For the dissociation of a protonated base 'B',
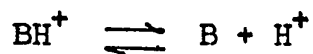
$$BH^+ \rightleftharpoons B + H^+$$

the thermodynamic dissociation constant may be represented by

$$K = \frac{a_{H^+} \cdot a_B}{a_{BH^+}} = \frac{a_{H^+} \cdot f_B \cdot [B]}{f_{BH^+} \cdot [BH]^+} \qquad \ldots(1)$$

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

The function 'H_o' is defined as

$$H_o = -\log_{10} h_o = -\log_{10} \frac{a_{H^+} \cdot f_B}{f_{BH^+}} \qquad \ldots(2)$$

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[30].

From equations (1) and (2),

$$H_o = pK_a - \log_{10} \frac{[BH^+]}{[B]} \qquad \ldots(3)$$

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

$$pH = pK_a - \log_{10} \frac{[BH^+]}{[B]} \qquad \ldots(4)$$

The ratio f_B/f_{BH}^+ has recently found to be not completely independent of 'B'[31-33], and more sophisticated methods of calculation have been devised[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):
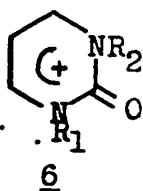
6 (a) $R_1=R_2=Me$ (as HSO_4^-)

(b) $R_1=Me; R_2=H$ (as Cl^-)

(c) $R_1=R_2=H$ (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[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

	pHorH$_0$	pK$_a$	λMax(logϵ)^{ref}
1,2-dihydro-2-oxo-pyrimidinium chloride	6.21		298(3.67), 215(>4.0)[11]
	0	2.24±0.04	309(3.75), 215(>3.2)[11]
1,2-dihydro-1-methyl-2-oxo-pyrimidinium chloride	6.0		302(3.73),215(4.0)[11]
	0.3	2.5±0.04	313(3.85), 215(3.80)[11]
1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium hydrogen sulfate	0.29		316(3.93), 215(>4.0)[3c]
5-bromo-2-pyrimidone	4.0		322(3.54),222(4.16)[49]
	0.22	0.44±0.02	343(3.65),220(4.19)[49]
5-bromo-1-methyl-2-pyrimidone	4.0		326(3.43),225(4.0)[49]
	-2.0	0.55±0.03	346(3.55),224(3.96)[49]
5-bromo-1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium hydrogen sulfate	0.29		346(3.85),222(4.10)[22]

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[39], and rapid reaction methods[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

<u>2-Pyrimidone hydrochloride</u> 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:

<u>5-bromo-2-pyrimidone</u>[22]

<u>1,2-dihydro-1-methyl-2-oxo-pyrimidinium chloride</u>[3]

<u>1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium hydrogen sulfate</u>[22]
1,3-dimethyl-urea (8.8g.,0.1moles)in 40 mls. of absolute ethanol was added to 1,1,3,3-tetraethoxy-propane (22g., 0.1moles). The resulting solution was cooled in ice water, and 95% sulfuric acid (20g.,0.2moles) 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. $204-206^{\circ}$. Wt.=18.4g.Yield=83%.

<u>N.M.R.</u> (in D_2O) compared favorably with literature values.
<u>Analysis</u> $C_6H_{10}N_2O_5S$ 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.,0.01moles)in 10mls. of D_2O was sealed in a thick-walled glass tube and heated at $10C^o$ for ten days. After cooling to 0°, 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 D_2O) 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., 0.0034moles) 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^o(after darkening at 180°),lit.210-211° [21].

N.M.R.(in D_2O with DSS as reference) 6.03τ(singlet,area 3), 0.51τ,0.67τ(AB quartet, J=3Hz,area 2).

Analysis $C_5H_5N_2OBr$ 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[22]

1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium chloride
(0.17g.,0.001moles) 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 D_2O with DSS as reference) 6.12τ(singlet,area 6),
0.95τ(singlet, area 2).

Analysis $C_6H_8N_2OBr_2$ 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.,0.0035moles) 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-d_6 with TMS as reference) 7.13τ(singlet,
area 3), 5.00τ(singlet, area 1).

Analysis $C_6H_{10}N_2O_3Br_2$ 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:

$$A = ecl \qquad \qquad ...(5)$$

where 'A' is the absorbance, 'c' the molar concentration,
'e' the molar extinction coefficient, and 'l' the path
length of the cell in cm.[41]. 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 $\longrightarrow$ C

$$[B] = [B]_0 - [C] = [B]_0 \, e^{-kt}$$

and
$$kt = \ln \frac{[B]_0}{[B]_0 - [C]} \qquad \qquad ...(6)$$

where $[B]_0$ 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 λ the following relationships pertain:

Initially, $\qquad A_0 = e_B^{\lambda}[B]_0 l$

At time 't' $\qquad A_t = e_B^{\lambda}([B]_0 - [C])l + e_C^{\lambda}[C]l$

At $t = \infty$ $\qquad A_{\infty} = e_C^{\lambda}[C]_{\infty}l = e_C^{\lambda}[B]_0 l$

Hence $\qquad (A_{\infty} - A_0) = (e_C^{\lambda} - e_B^{\lambda})[B]_0 l$

$\qquad (A_{\infty} - A_t) = (e_C^{\lambda} - e_B^{\lambda})([B]_0 - [C])l$

and $\qquad \dfrac{(A_{\infty} - A_0)}{(A_{\infty} - A_t)} = \dfrac{[B]_0}{[B]_0 - [C]} = \exp(kt)$

Rearranging, $\qquad \ln(A_{\infty} - A_t) = \ln(A_{\infty} - A_0) - kt \;\ldots(7)$

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

When $t = t_{\frac{1}{2}}$ (the half life of the reaction), $[C] = \frac{1}{2}[B]_0$
and from eqn. (6), $t_{\frac{1}{2}} = \frac{1}{k}\ln 2$

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

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

Substituting for 'k' in eqn.(8) gives

$$t_{99.9\%} = \frac{\ln 1000}{\ln 2} \, t_{\frac{1}{2}} = 9.966 t_{\frac{1}{2}} \qquad \ldots(9)$$

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_∞' 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-oxo-
pyrimidinium 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°C by circulating water from a Neslab Model
TE9 constant temperature bath through the thermostatted

cell holder.

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: $0.3M \ H_2SO_4$

Wavelength: $3750 \ \text{Å}$

Temperature: $30^\circ C$

A_∞: 0.9

Time (mins.)	A_t	$-\ln(A_\infty - A_t)$
7	.012	.1188
48	.121	.2497
53	.132	.2639
58	.145	.2810
63	.156	.2957
68	.169	.3133
73	.18	.3285
78	.191	.3439
83	.201	.3581

Time (mins.)	A_t	$-\ln(A_\infty - A_t)$
88	.211	.3725
93	.222	.3886
98	.235	.4079
103	.245	.4277
108	.254	.4369
193	.405	.7032
198	.412	.7174
203	.421	.7361
208	.429	.7529
213	.436	.7679
218	.442	.7809
223	.45	.7985
228	.457	.8142
233	.464	.8301
238	.47	.8439
243	,478	.8628
248	.482	.8723
283	.528	.9889
288	.532	.9997
293	.54	1.0217
298	.542	1.0272
303	.55	1.0498
313	.558	1.0729
318	.564	1.0906
323	.569	1.1056
365	.605	1.2208

Rate Constant: -3.12×10^{-3} mins^{-1}

Standard Deviation: 1×10^{-5} mins^{-1}

Half-life: 222 mins.

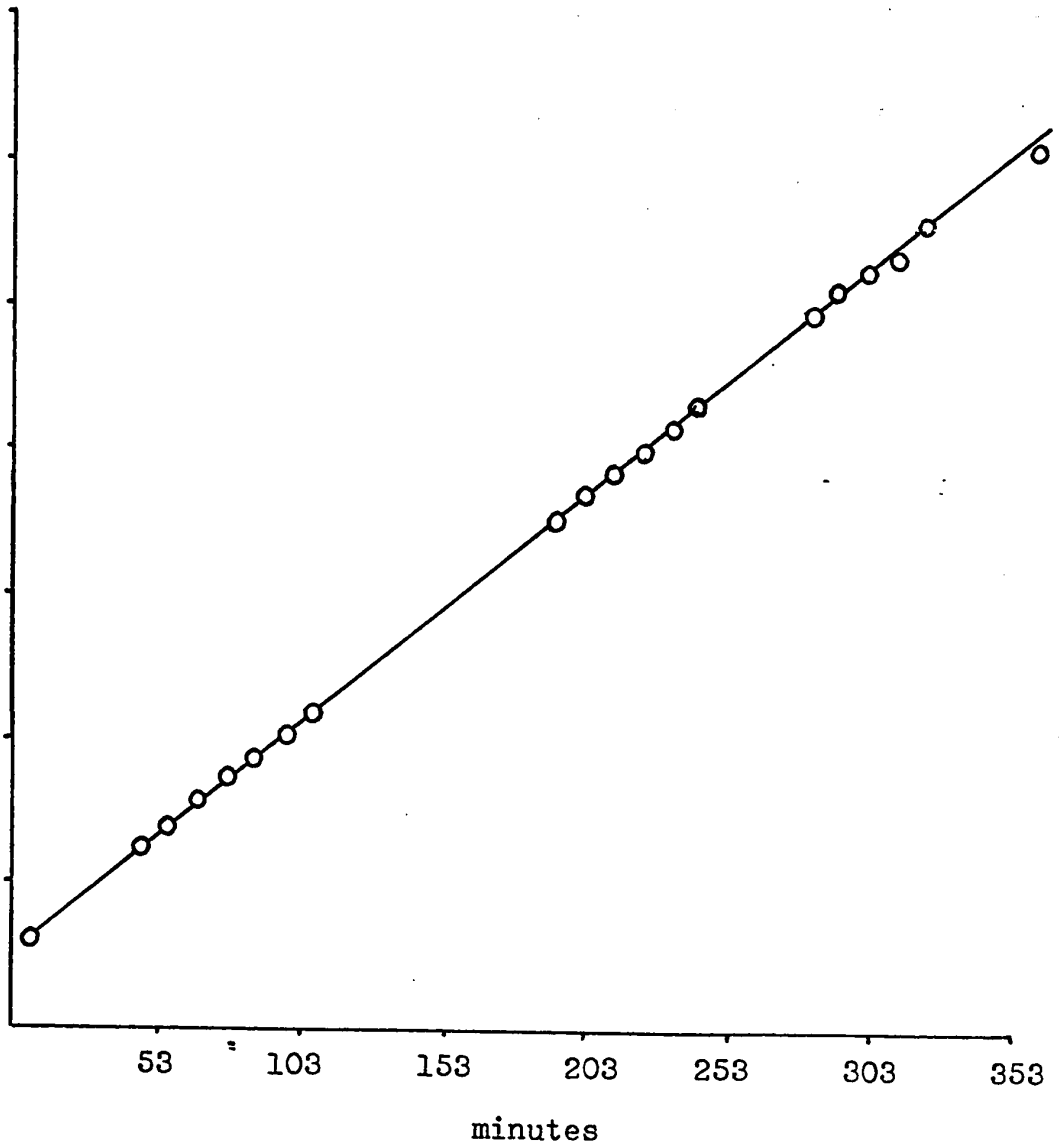Correlation Coefficient: .999915

Fig.1

Illustration of a rate plot

$-\ln(A_\infty - A_t)$ Run No. 24A

minutes

Rate constants were calculated by applying the method of least-squares[42] to eqn.(7), (p.21), and using a computer program written in BASIC[22] for the Hewlett Packard 2114A. In cases where 'A_∞' could not be experimentally determined, the absorbance at 'infinity' was obtained by varying 'A_∞' using an iterative computer program written in BASIC. The value of 'A_∞' was estimated and the rate constant and correlation coefficient calculated from the least squares corrected line. The 'A_∞' 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_∞' used, since it is involved in each datum point ($\ln(A_\infty - A_t)$). Collins[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_∞' values.

CALCULATION OF ACID STRENGTH

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

$$H_2SO_4 \;\; \overset{K_1}{\underset{\longleftarrow}{\longrightarrow}} \;\; H_3O^+ \; + \; HSO_4^-$$
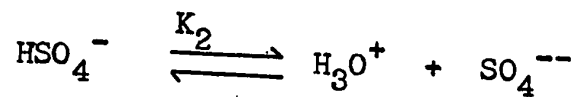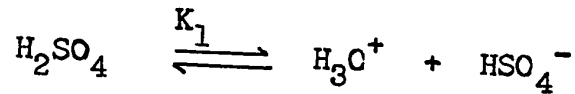
$$HSO_4^- \;\; \overset{K_2}{\underset{\longleftarrow}{\longrightarrow}} \;\; H_3O^+ \; + \; SO_4^{--}$$

where

$$K_2 = \frac{[H_3O^+] \, [SO_4^{--}]}{[HSO_4^-]} \qquad \ldots(10)$$

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

$$[H_2SO_4]_0 = c = [HSO_4^-] + [SO_4^{--}]$$

and

$$[H_3O^+] = b = [HSO_4^-] + 2[SO_4^{--}]$$

therefore

$$[SO_4^{--}] = b-c$$

and

$$[HSO_4^{--}] = c-(b-c) = 2c-b$$

On substituting in equation (10),

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

Solving for 'b' gives

$$[H_3O^+] = b = \frac{(c-K_2) \pm \sqrt{(K_2^2 + 6cK_2 + c^2)}}{2} \qquad \ldots(11)$$

of which only the positive root is meaningful. Values for $[H_3O^+]$ were calculated using $K_2 = 1.2 \times 10^{-2}$ [45].

In the high acid region, the pH scale is no longer valid and the use of acidity functions is necessary. Since 'H_0' is usually available in terms of 'Wt. % acid', an expression relating the latter term to molarity (M) was required. For sulfuric acid,

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

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

therefore

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

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

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

where 'M','W' and 'd' represent molarity, 'Wt. % H_2SO_4' and density respectively. The density of sulfuric acid-water solutions at $30^\circ C$ [46] were used to calculate 'Wt. % H_2SO_4' from molarity. This was then converted to 'H_0' using the data of Johnson, Katritzky and Shapiro[47].

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].

$$Br_2 + 2KI \longrightarrow 2KBr + I_2$$

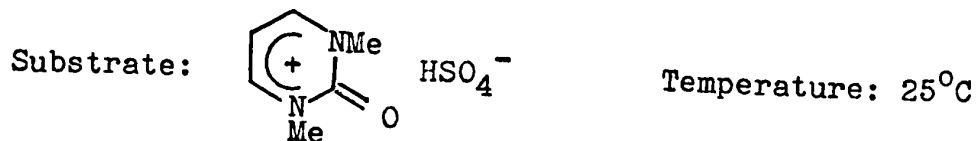$$I_2 + 2Na_2S_2O_3 \longrightarrow Na_2S_4O_6 + 2NaI$$
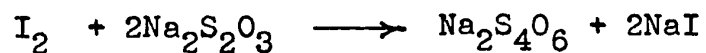
Quantitative determination of bromine is complicated by
its tendency to volatilise, and solutions of bromine were
freshly prepared before each kinetic run.

PART 3 - RESULTS

Table 2

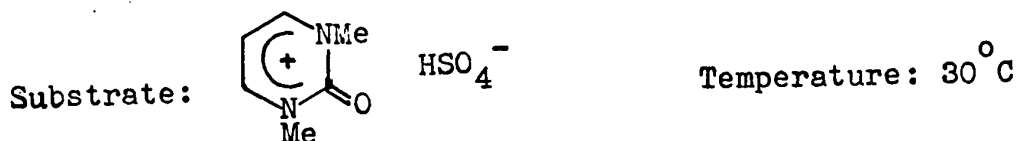Variation of the rate of product-appearance with acidity

Substrate: [structure: pyridinium ring with NMe, N-Me, =O] HSO$_4^-$ Temperature: 25°C

Run No.	Py(x10^{-3}M)	Br$_2$(x10^{-3}M)	kx10^3(mins^{-1})	λ(nm.)	H$_2$SO$_4$(M)
H1	2.27	1.65	3.10	375	0.500
H2	"	0.73	3.51	365	"
H3	"	2.10	3.83	375	"
H4	"	1.11	3.70	370	"
H5*	"	4.30	3.67	375	"
H6	"	1.87	3.75	"	"
H7	"	2.74	3.48	"	"
H8	"	3.60	3.66	"	"
H11*	"	3.30	3.44	"	"
H12	"	5.40	3.18	"	"
H13	"	3.70	3.20	"	"
H14	"	4.80	3.09	"	"
H14*	"	4.80	3.75	"	"
O1	2.27	0.77	7.23	375	0.750
O2	"	0.87	7.28	"	"
N1	2.27	3.00	9.50	375	1.00
N2	"	3.15	9.67	"	"
N3	"	3.38	10.01	"	"
N4	"	2.38	9.73	"	"
N5	"	2.38	9.65	"	"

* The rate constant refers to the kinetics of bromine decrease

Table 3

Variation of the rate of product-appearance with acidity

Substrate: [structure with NMe, +, N, O, Me] HSO_4^- Temperature: $30\,^\circ C$

Run No.	$Py(x10^{-3}M)$	$Br_2(x10^{-3}M)$	$kx10^3(mins^{-1})$	$\lambda(nm.)$	$H_2SO_4(M)$
8A	5.17	1.80	0.593	375	0.0500
30A	3.55	3.60	0.605	"	"
31A	4.73	1.80	0.575	"	"
44A	4.67	1.57	1.05	375	0.100
45A	4.29	2.88	1.11	"	"
36A	3.87	0.60	2.67	375	0.250
37A	4.98	1.63	2.69	"	"
38A	4.94	1.75	2.81	"	"
42A	3.87	4.88	3.08	"	"
43A	3.92	4.14	2.92	"	"
24A	3.71	1.38	3.12	375	0.300
25A	2.89	4.14	3.13	"	"
34A	2.06	1.63	3.31	"	"
35A	2.89	0.98	3.47	"	"
48A	5.25	1.35	3.52	"	"
49A	5.25	1.27	3.64	"	"
50A	4.67	2.54	3.70	"	"
20A	4.43	2.78	5.26	375	0.430
21A	3.32	5.56	5.39	"	"
4A	2.07	1.80	6.57	375	0.500
5A	1.84	2.00	6.30	"	"
9A	1.91	1.84	6.52	"	"
11A	3.72	4.94	6.05	"	"
12A	2.48	3.03	6.31	"	"
13A	4.46	0.60	6.06	"	"
29A*	1.42	3.93	6.09	"	"
32A	3.54	1.57	6.43	"	"
33A	3.89	1.46	6.66	"	"
26A	5.27	2.22	7.95	375	0.665
27A	5.36	1.97	8.17	"	"
10A	3.27	3.90	8.40	375	0.690

*The rate constant refers to the kinetics of bromine decrease.

Fig.2

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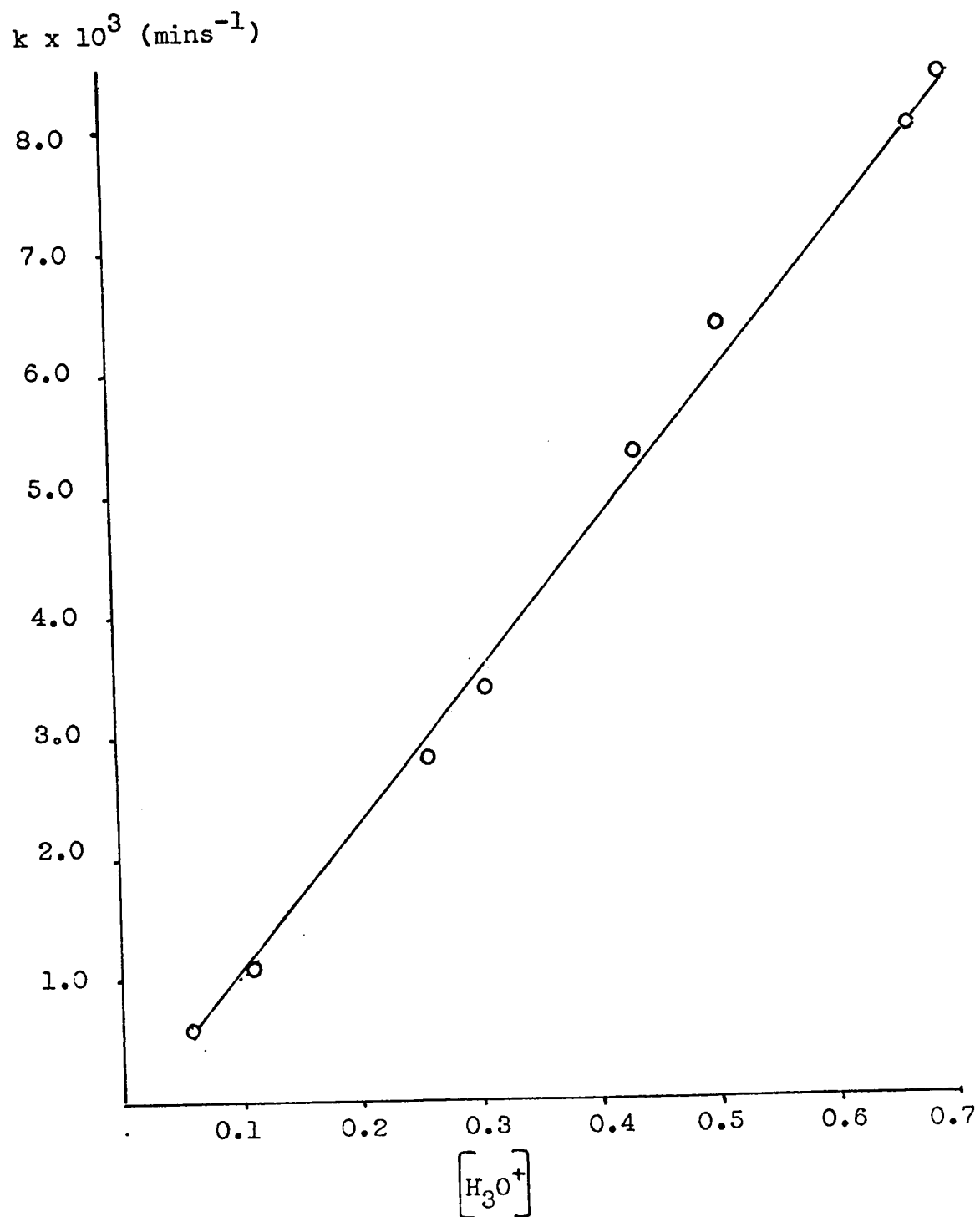1,3-dimethyl-2-oxo-pyrimidinium bromide with acidity

Table 4

Variation of the rate of product-appearance with acidity
(H_0 region)

Substrate:

HSO_4^-

Temperature: $30^\circ C$

Run No.	Py($\times 10^{-3}$M)	Br$_2$($\times 10^{-3}$M)	$k \times 10^3$(mins^{-1})	λ(nm.)	H$_2$SO$_4$(M)
51A	5.91	1.25	16.9	375	1.00
52A	5.42	2.13	18.1	"	"
3A	5.63	2.42	28.6	375	1.28
6A	5.84	0.75	24.5	"	"
59A	3.75	2.46	37.2	375	1.50
60A	3.93	2.88	36.3	"	"
53A	4.68	2.04	59.7	375	2.00
54A	4.13	1.17	59.5	"	"
1A	3.57	2.14	84.7	375	2.19
7A	5.18	0.80	82.8	"	"
2A	3.99	1.65	86.6	370	"

Fig. 3

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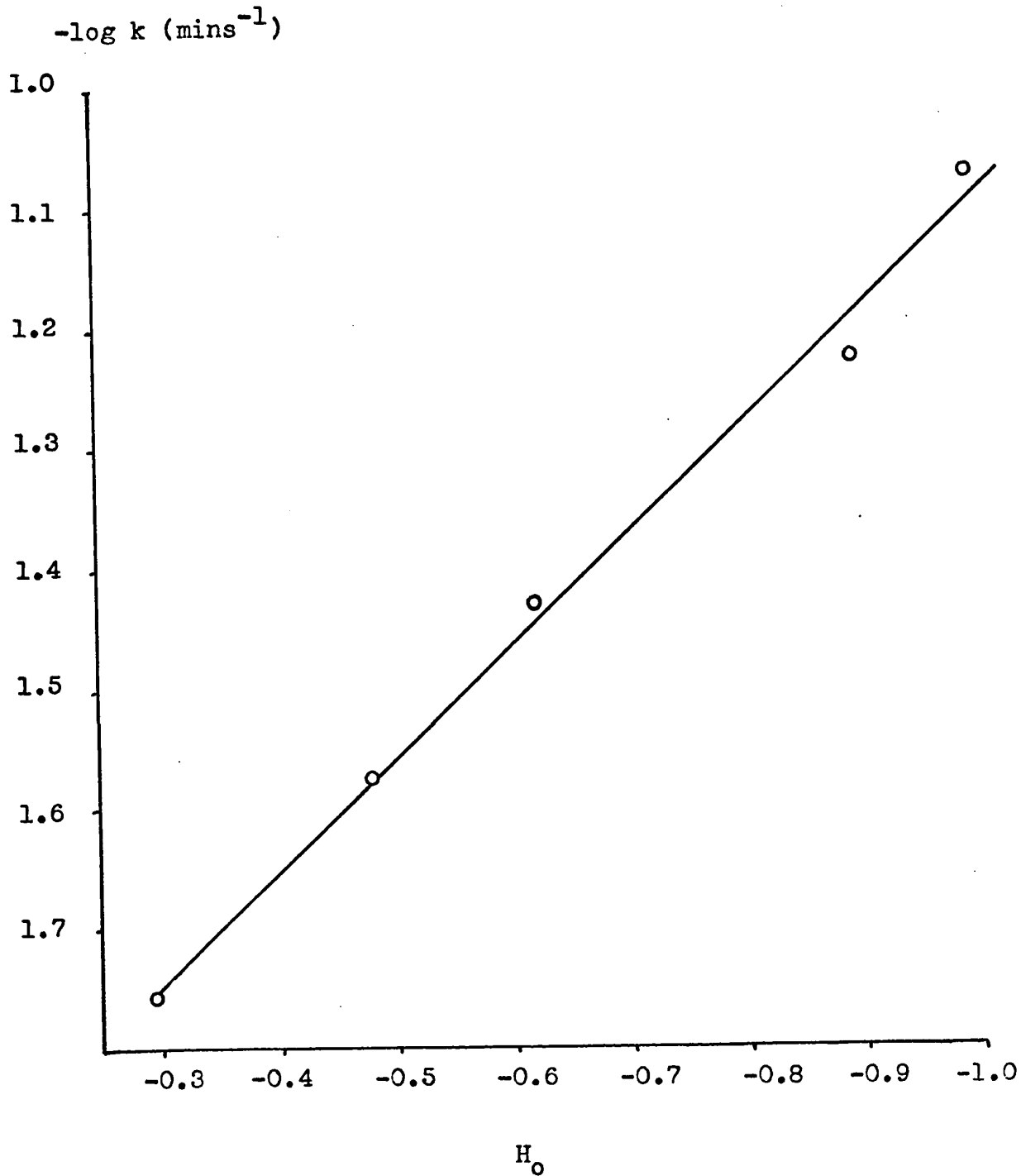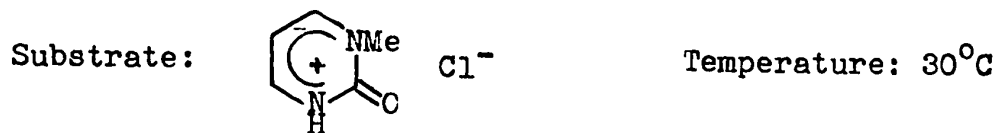
Table 5

Variation of the rate of product-appearance with acidity

Substrate: (structure) Cl^- Temperature: $30^\circ C$

Run No.	$Py(\times10^{-3}M)$	$Br_2(\times10^{-3}M)$	$k\times10^3(mins^{-1})$	$\lambda(nm.)$	$H_2SO_4(M)$
4B	4.50	1.07	0.603	370	0.250
5B	6.64	1.07	0.616	"	"
8B	3.62	3.33	0.803	370	0.350
10B	6.47	2.17	0.822	"	"
11B	5.07	1.94	0.760	"	"
6B	5.00	2.68	0.88	370	0.400
7B	4.36	2.03	1.02	"	"
1B	3.29	2.65	1.24	375	0.500
2B	3.29	1.55	1.23	"	"
3B	3.81	1.96	1.14	"	"

Fig. 4

Variation of the rate of appearance of 5-bromo-1-methyl-2-pyrimidone with acidity
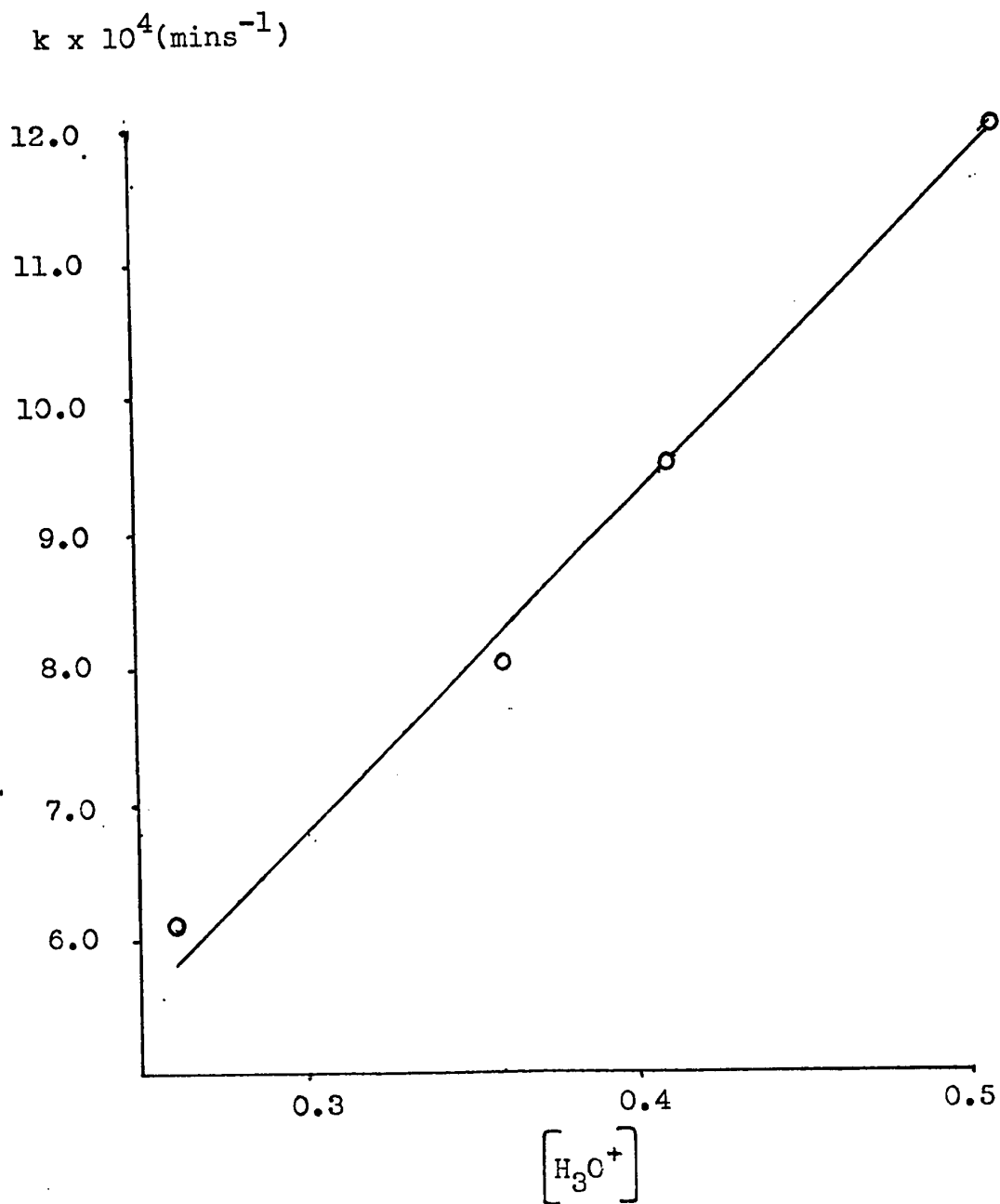
Table 6

Variation of the rate of product-appearance with acidity

Substrate: Cl$^-$ Temperature: 30°C
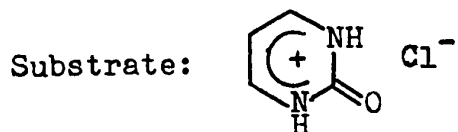
Run No.	Py($\times 10^{-3}$M)	Br$_2$($\times 10^{-3}$M)	k$\times 10^4$(mins^{-1})	λ(nm.)	H$_2$SO$_4$(M)
5C	3.85	2.78	1.89	365	0.250
6C	5.55	1.92	1.86	"	"
3C	2.91	1.36	2.18	375	0.300
7C	5.83	2.19	2.19	365·	"
4C	4.80	3.80	3.19	365	0.400
8C	3.89	2.70	3.18	"	"
1C	3.53	4.00	4.02	375	0.500
2C	3.33	1.50	4.21	"	"
9C	4.21	2.05	16.5	365	2.00

Fig. 5

Variation of the rate of appearance of 5-bromo-2-pyrimidone with acidity
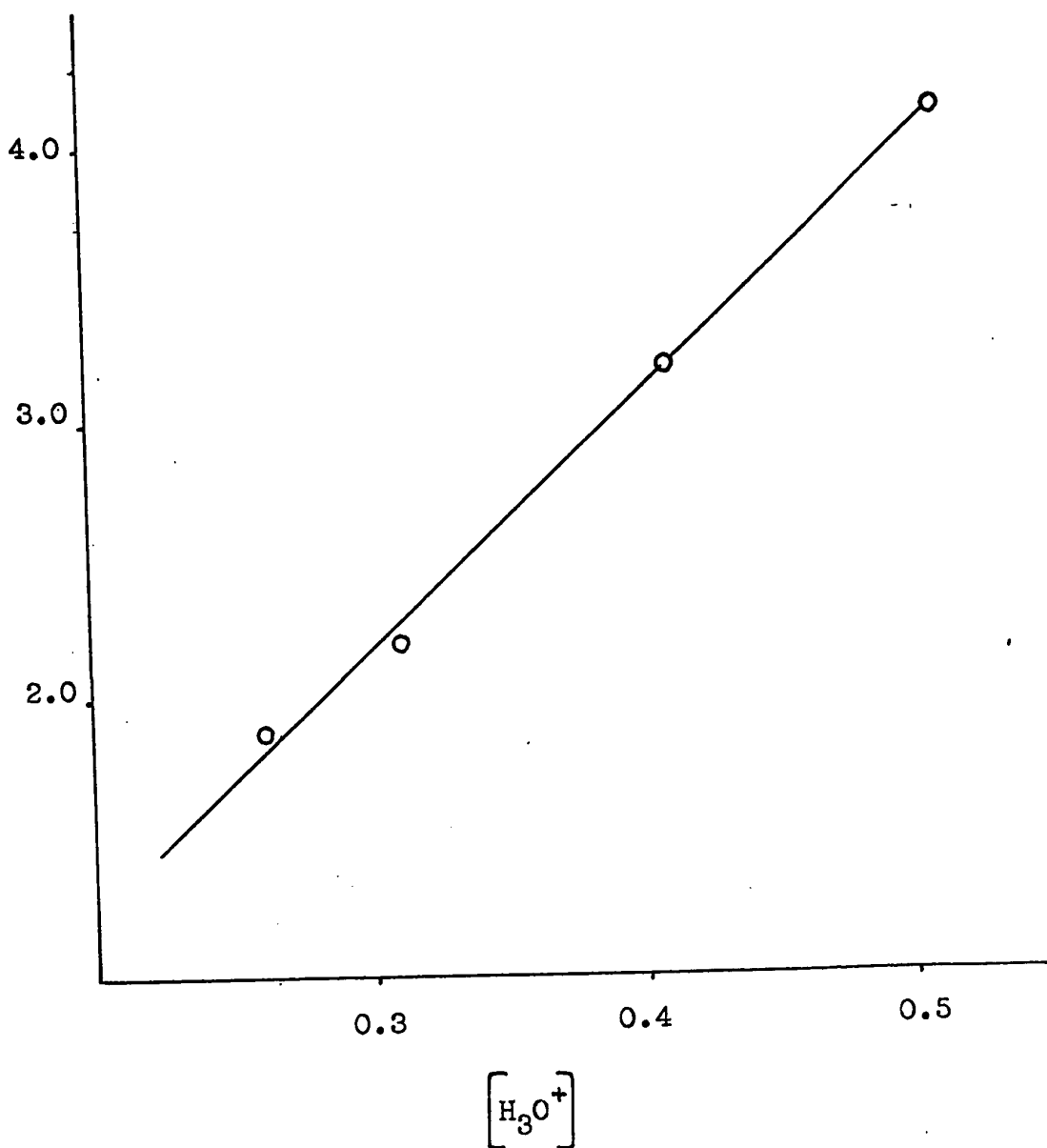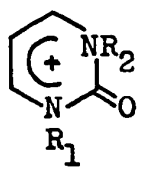
Table 7

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

Substrate

[structure: pyrimidinium cation with NR$_2$ and =O substituents, N-R$_1$, X$^-$]

R$_1$ R$_2$ X	k x 10^3 (mins^{-1})	H$_2$SO$_4$ (M)	Temp. (°C)	Av.Dev.	[H$_3$O$^+$] (M)
Me Me HSO$_4$	84.(7)	2.19	30	1.(3)	
	59.6	2.00	"	0.0	
	36.8	1.50	"	0.4(5)	
	26.(6)	1.28	"	2.(0)	
	17.5	1.00	"	0.6	
	8.40	0.690	"	**	0.702
	8.0(6)	0.665	"	0.1(1)	0.677
	6.3(3)	0.500	"	0.2(3)@	0.511
	5.33	0.430	"	0.07	0.441
	3.4(1)	0.300	"	0.2(3)@	0.311
	2.8(3)	0.250	"	0.1(7)@	0.261
	1.08	0.100	"	0.03	0.110
	0.59(1)	0.050	"	0.01(1)	0.059
	3.4(5)	0.500	25	0.2(9)@	0.511
	7.26	0.750	"	0.03	
	9.7(1)	1.00	"	0.1(9)@	
Me H Cl	1.20	0.500	30	0.04	0.511
	0.95	0.400	"	0.07	0.411
	0.79(5)	0.350	"	0.02(3)	0.361
	0.610	0.250	"	0.007	0.261
H H Cl	1.65	2.00	30	**	
	0.412	0.500	"	0.009	0.511
	0.319	0.400	"		0.411
	0.219	0.350	"		0.311
	0.188	0.250	"	0.002	0.261

** 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

Run No.	Py($\times 10^{-3}$M)	Br$_2$($\times 10^{-3}$M)	$k \times 10^3$(mins^{-1})	λ(nm.)	H$_2$SO$_4$(M)
4A'	2.89	2.30	1.08	375	0.500
5A'	3.66	2.33	1.10	"	"
6A'	2.53	1.59	1.05	"	"

$$k_D = 1.08 \times 10^{-3} \text{ mins}^{-1}$$

$$k_H = 6.38 \times 10^{-3} \text{ mins}^{-1}$$

$$k_H/k_D = 5.91$$

PART 4 - DISCUSSION

1,2-DIHYDRO-1,3-DIMETHYL-2-OXO-PYRIMIDINIUM 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 $\pi - \pi^*$ 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[24]. The bromination of a 2-sulfonamido-pyrimidine in methanol has been proved to proceed via a tetrahydro-pyrimidine intermediate[24] (18).
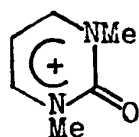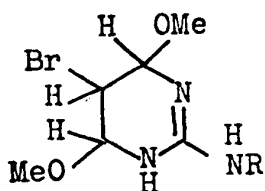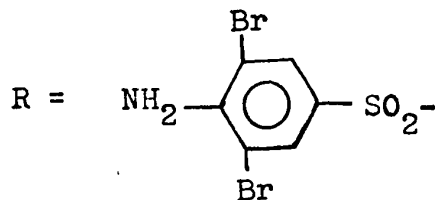

25   18

Fig. 6

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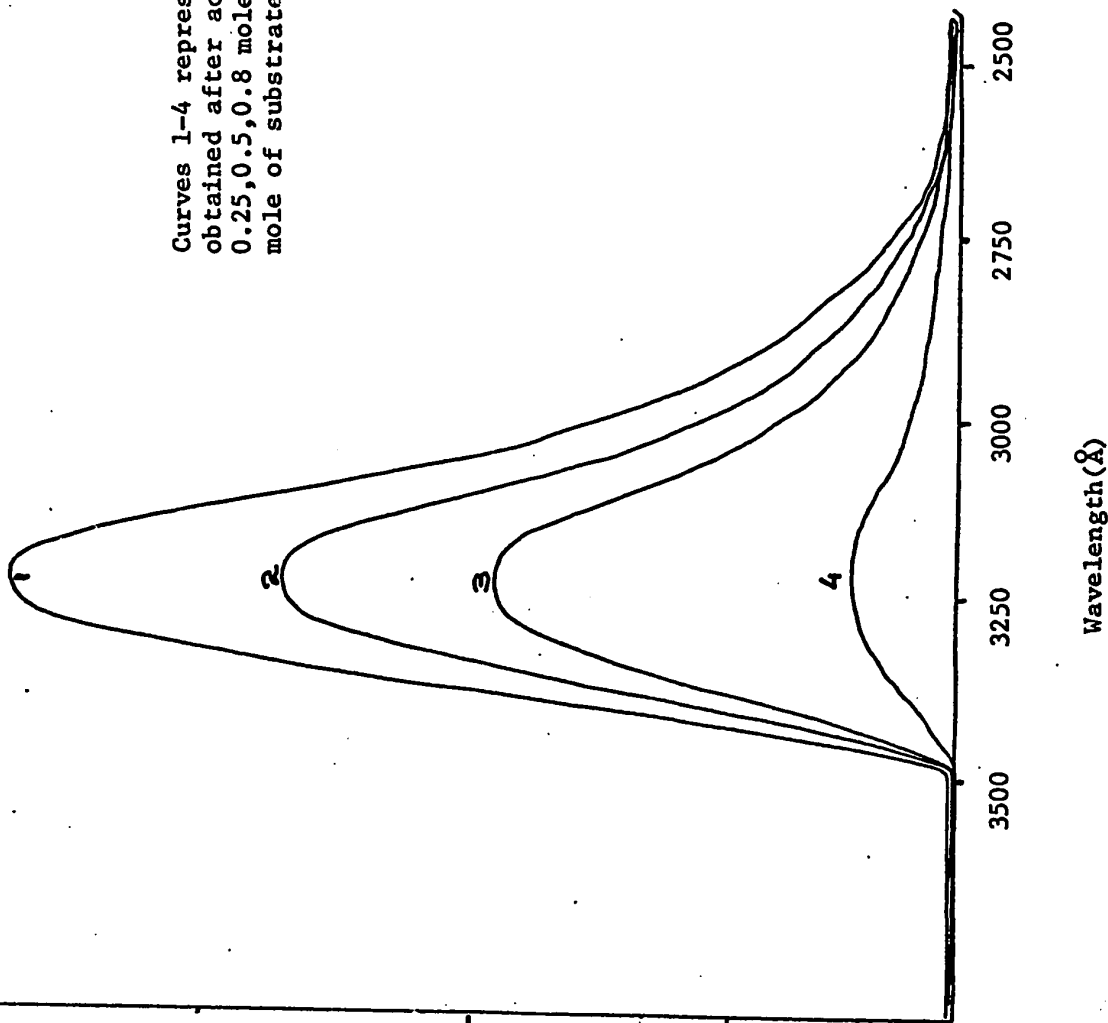of 1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium hydrogen sulfate

Curves 1-4 represent spectra
obtained after addition of 0,
0.25,0.5,0.8 moles of Br_2 per
mole of substrate

The work of Baev et al.[23] 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
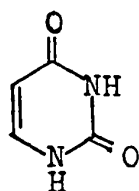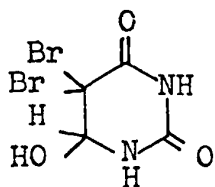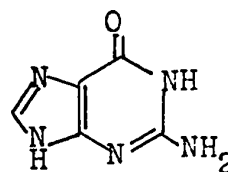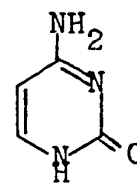

11   13   27   14

range 0.05-0.69M H_2SO_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> Br*

In all cases where Py>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
$[H_3O^+]$ typical of first-order acid catalysis. The
bimolecular rate constant can be calculated to be $1.24 \times 10^{-2} M^{-1}$
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[3], 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

25 **26** **28** **29**
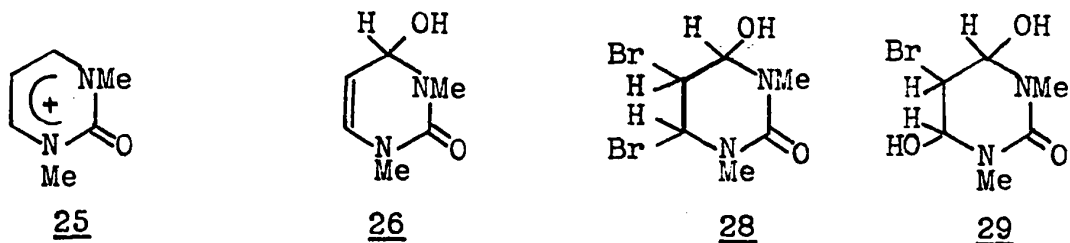
have the structure (28) or (29). The former is unlikely,
since the reaction of bromine with (32) gives a product
that has been identified as (33). Recent work on the
bromination of 2-sulfonamido-pyrimidines[50-52] has shown
that (30), (R_1=Me;R_2=R_3=H) and (30), (R_1=R_2=R_3=H) may be
isolated from methanolic and acetic acid-water solutions
respectively[50]. The bromination of 2-sulfonamido-5-methyl-
pyrimidine[51] yields (30),(R_1=R_2=H;R_3=Me) in aqueous
solution, and (30),(R_1=R_3=Me;R_2=H) in methanol, while
2-sulfonamido-4-methyl-pyrimidine[52] is brominated to (30)
(R_1=R_2=Me;R_3=H) by bromine in methanol.


32 **30** R_4 =

31 **33**
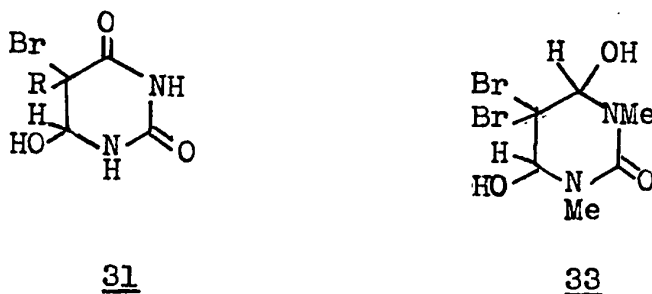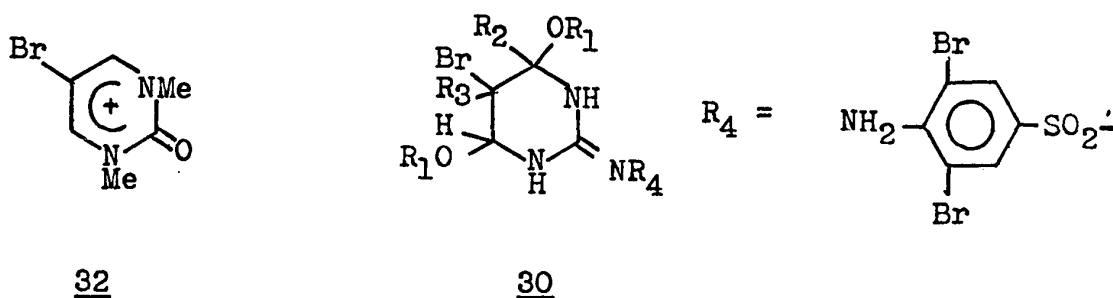
Thymine is known to be brominated to (31),(R=Me)[53], and
the bromination of uracil has been postulated to occur via
(31),(R=H)[37]. In the case of uracil, the intermediate (31),
(R=H) converts to 5-bromo-uracil in the presence of acid.

Bromination involving an addition-elimination mechanism
has also been demonstrated in quinolines. The N-cyano-
quinolinium ion (34) is brominated via its pseudo-base (35)
to form an adduct (36)[54].
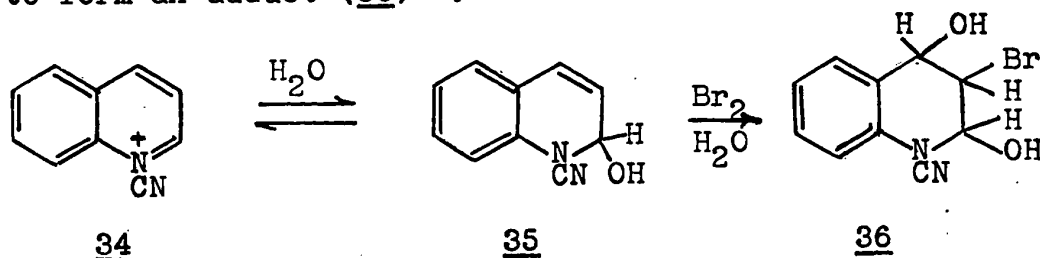
On the basis of the above evidence it is reasonable to
assume that (29) is the structure of the intermediate
formed in the present study. Attempts to isolate the
intermediate (29) were unsuccesful, and yielded white
labile materials which readily transformed to the 5-bromo-
compound (32). The kinetic results (Table3;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).
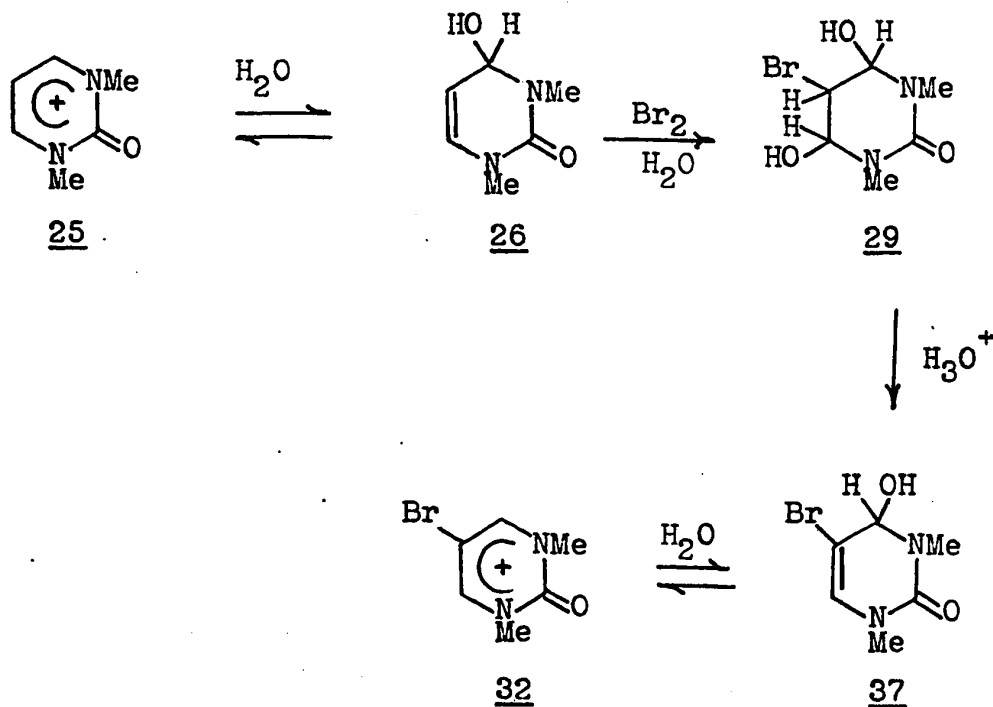
The pseudo-base formation of (32) has been observed by Tee[22], and it is probable that (32) is formed through the intermediacy of (37).

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
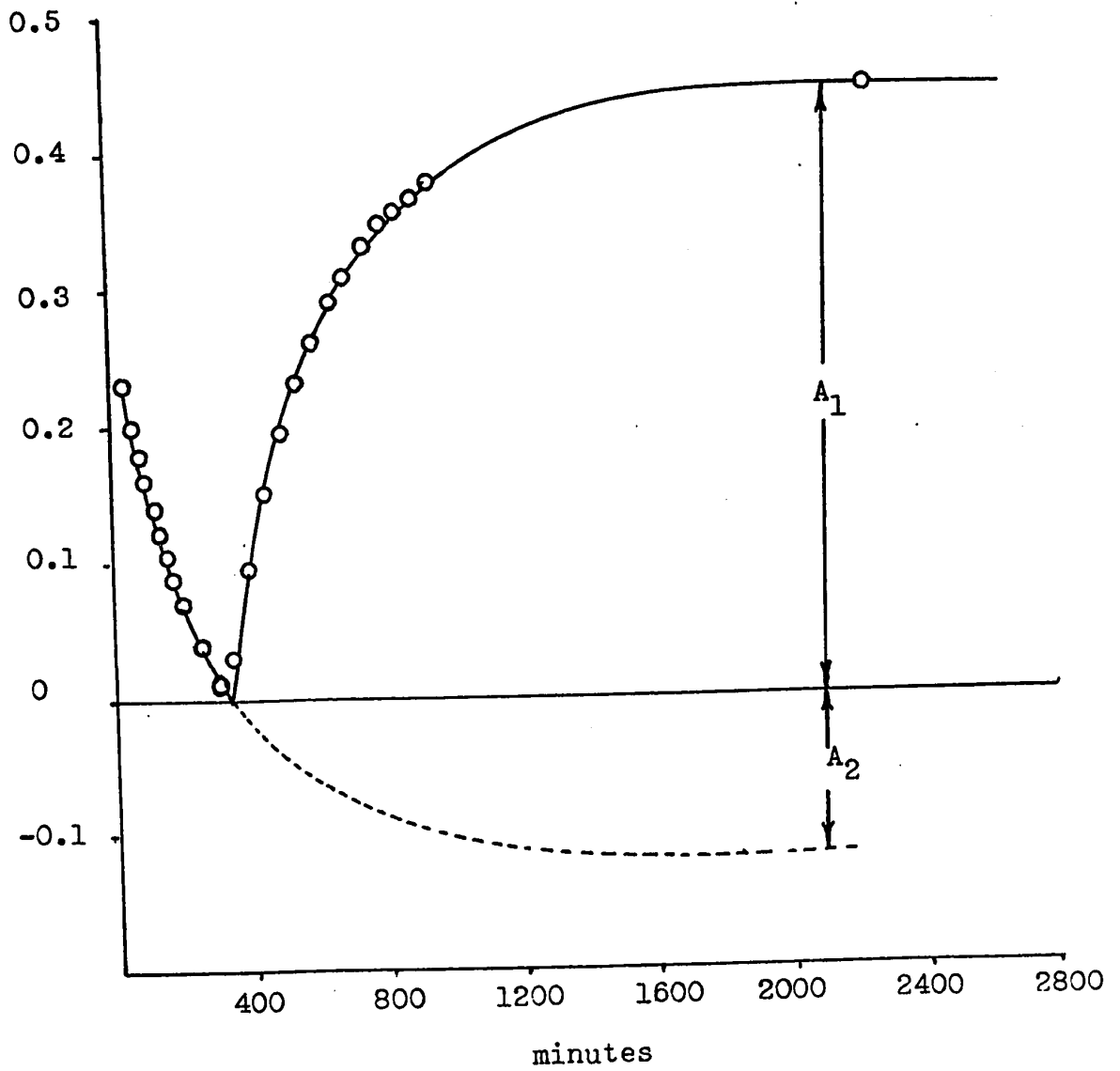the decreasing region is complicated, since although the

Fig. 7

Absorbance-time plot for the case where Py<Br<2Py

Run No.: H14

Absorbance

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 'e_1' and 'e_2' be the extinction coefficients of the 5-bromo-product (32) and bromine respectively, then $A_1/e_1 = A_2/e_2$. 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*).

Fig. 8

Rate plot for the case where Py<Br<2Py

$-\ln(A_{\infty}-A_t)$ Run No. H14*

minutes
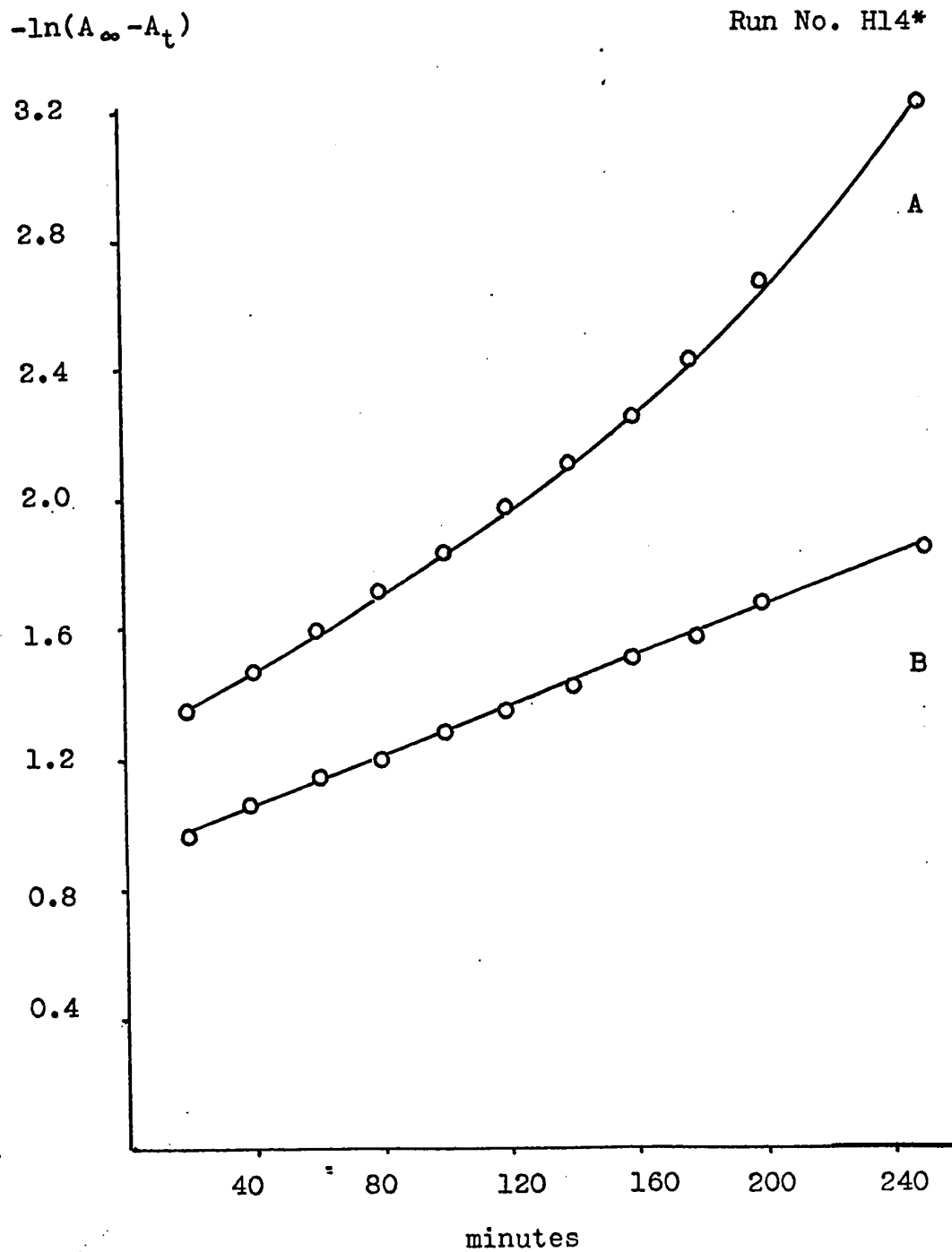
(ii) Results for the H_0 region

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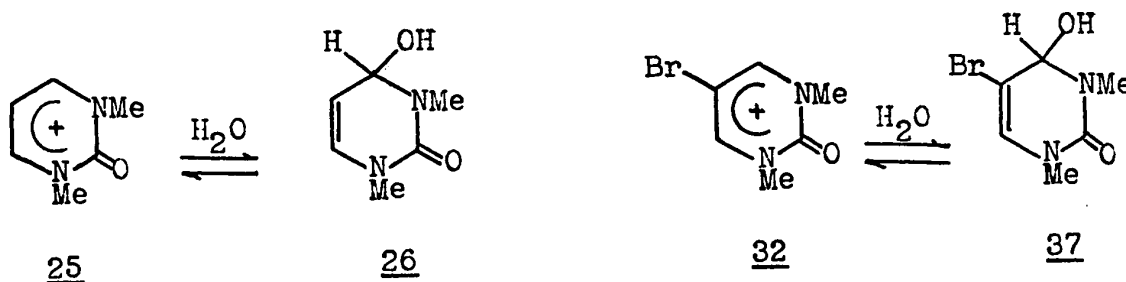
A first-order plot for the rate of product formation is
significantly curved. This apparent deviation from simple
first-order behaviour may be explained by considering the
sequence in Table 9 (p.56),(R_1=R_2=Me).

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

Table 9

Mechanism of bromination of 2-pyrimidones
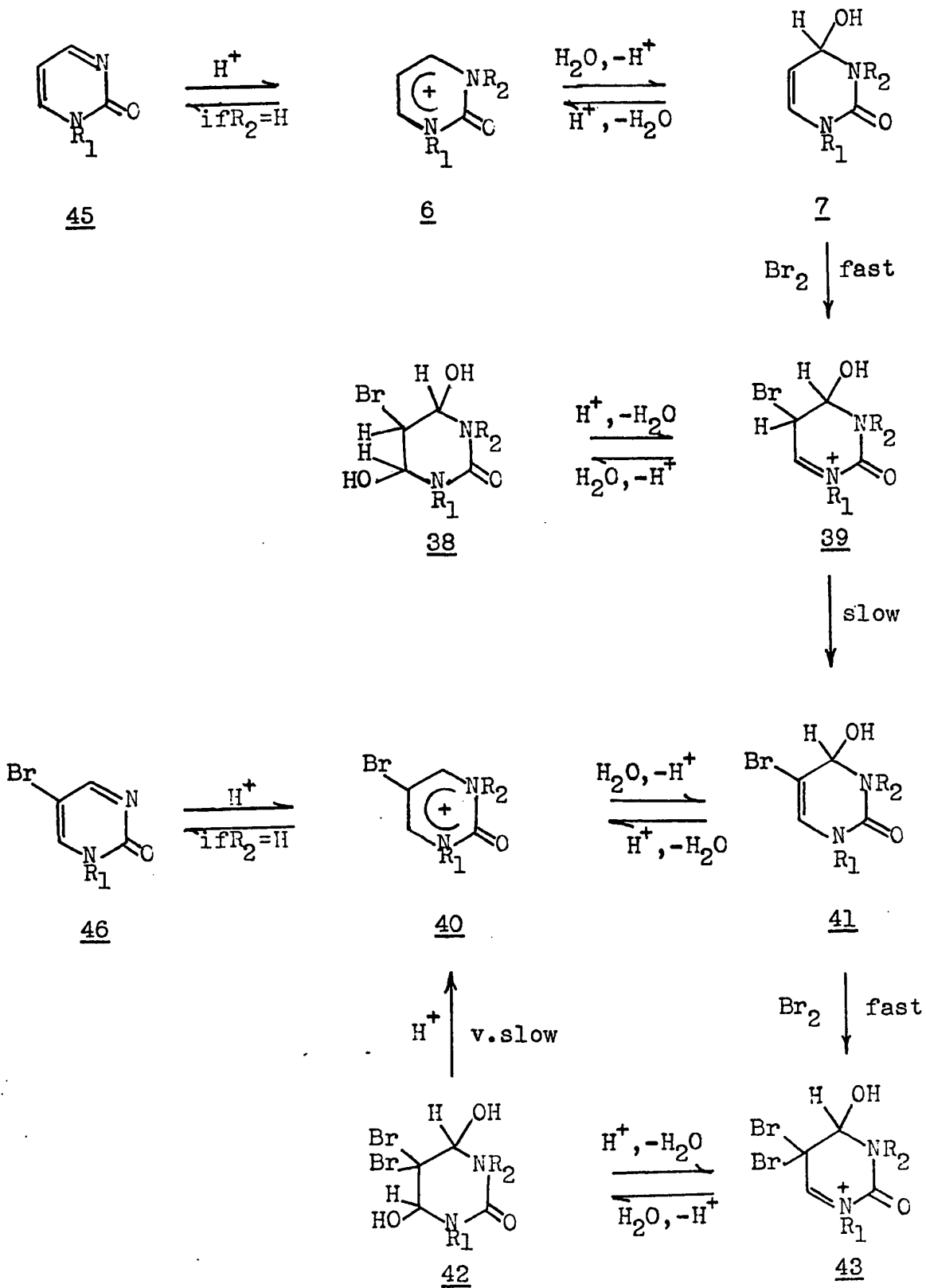
On the other hand, since the rate of dehydration of (38)
increases with acidity, the small amount of the brominated
product (40) formed would compete with the substrate (6)
for the remaining bromine, and a portion of (40) would be
converted to the dibrominated product (42).

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.58).
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 H_2SO_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 H_2SO_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_∞)
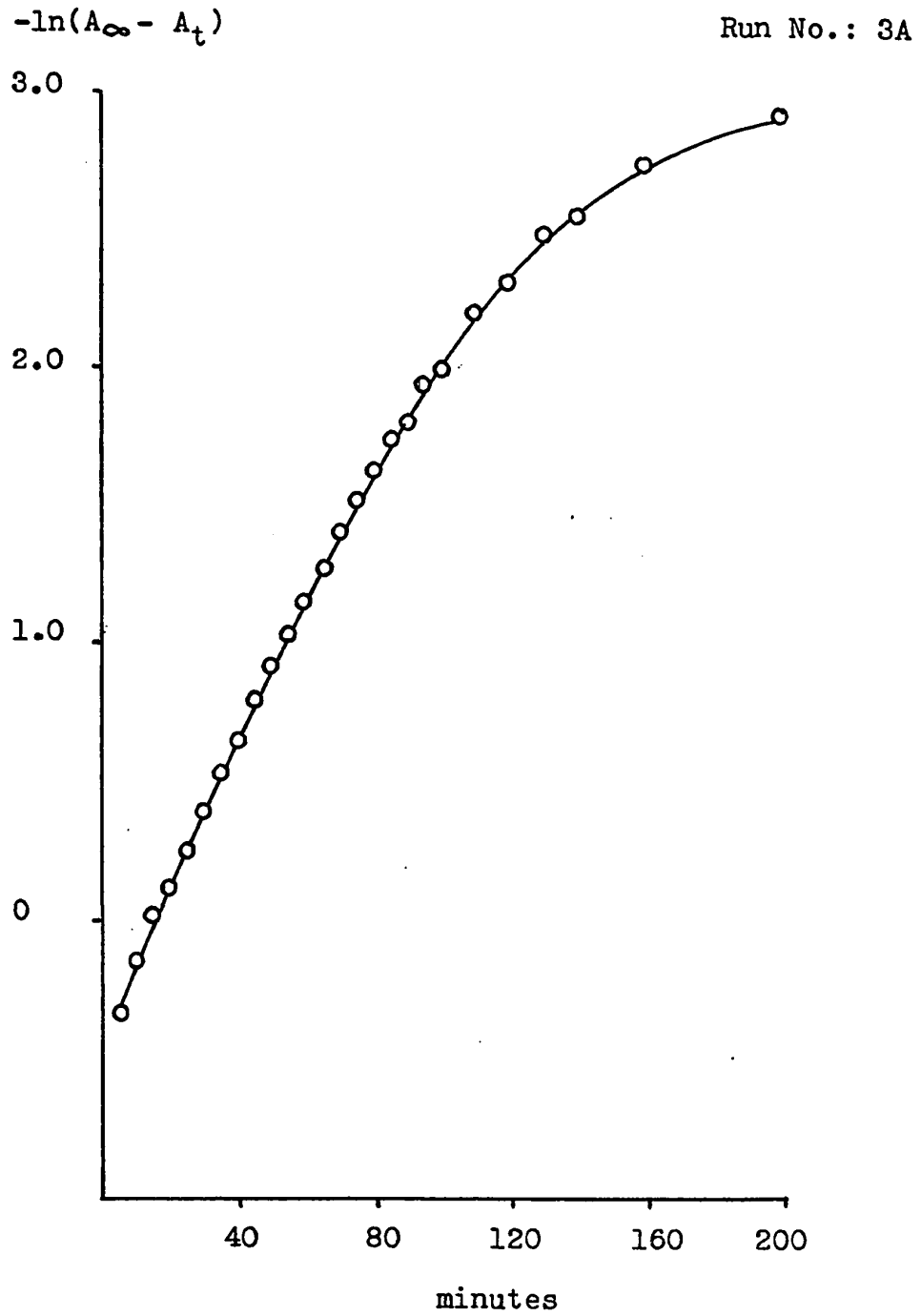
any significant extent during the time of measurement, it
influences the 'A_∞' to some small extent. Hence on lowering
'A_∞' slightly to correct for this reaction, a simple first-
order plot should be obtained for the rate of appearance
of the 5-bromo-product (40). A first-order plot using a
corrected 'A_∞' is shown in Fig.10,(p.60). Rate constants
obtained in this manner showed a linear dependence on
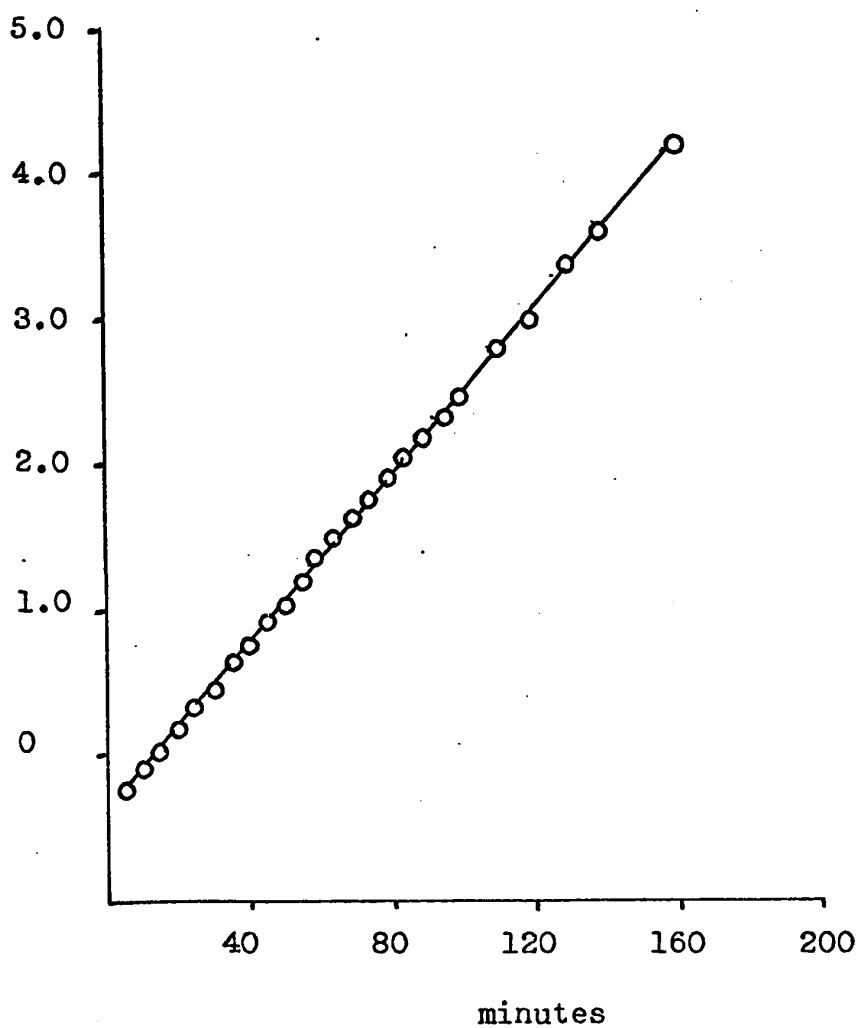acidity ie. log k vs. H_0 gave a straight line (Fig. 3,
p.35,Table 4,p.34).

Fig. 10

Rate plot for the high-acid region (corrected for A_∞)
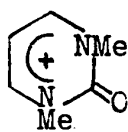
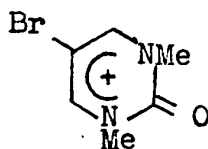$-\ln(A_\infty - A_t)$ Run No.: 3A

## (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).

25
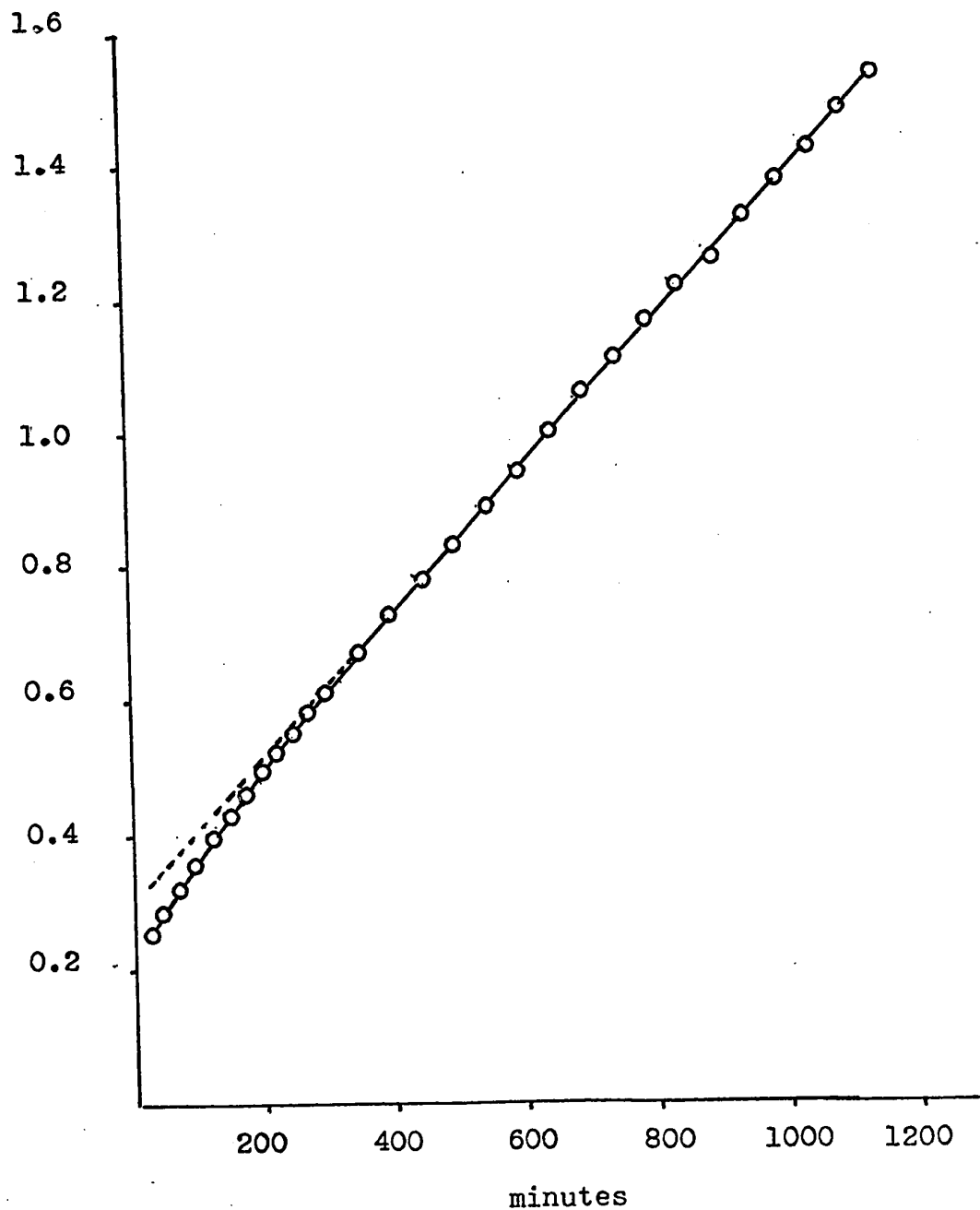
32
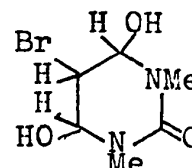
29

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).
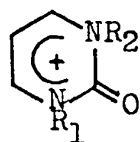
6
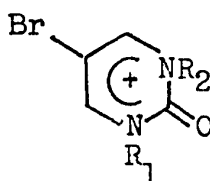
40
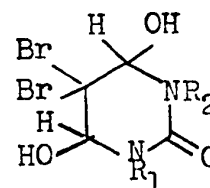
42

2-PYRIMIDONE HYDROCHLORIDE ($\underline{6}$)(R_1=R_2=H)

The mechanism of bromination of 2-pyrimidone hydrochloride ($\underline{6}$),(R_1=R_2=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 ($\underline{40}$),(R_1=R_2=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 ($\underline{42}$),(R_1=R_2=H).

The quaternary ion ($\underline{6}$),(R_1=R_2=Me) represents the fixed form of the parent cation ($\underline{6}$),(R_1=R_2=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),(R_1=R_2=H).
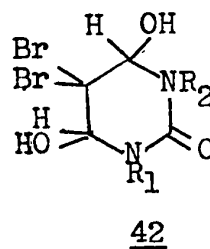

$\underline{6}$
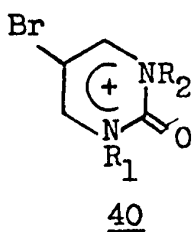
$\underline{40}$

$\underline{42}$

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 Br_2
per mole of substrate
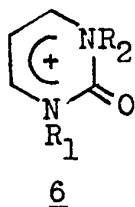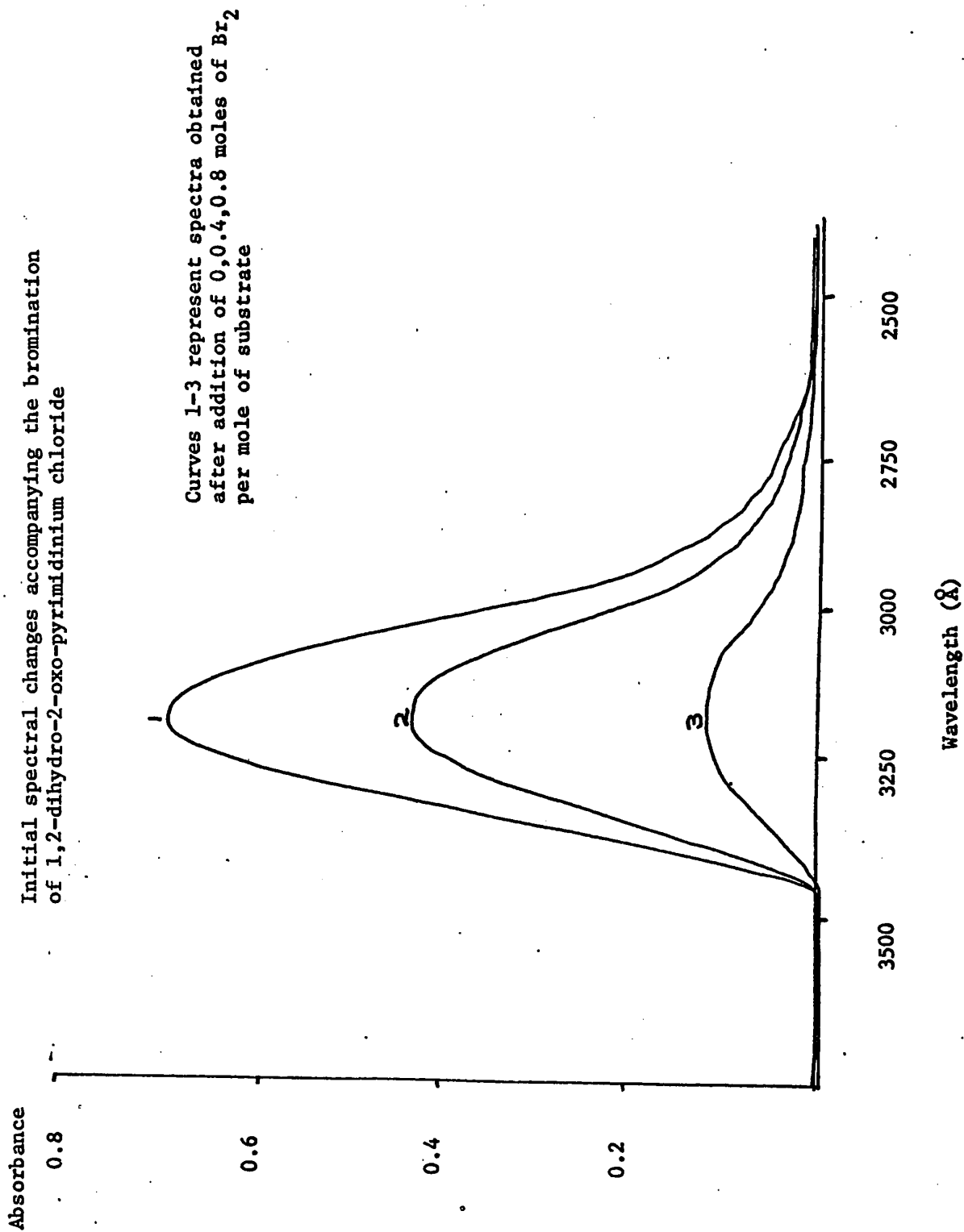
Fig. 13

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
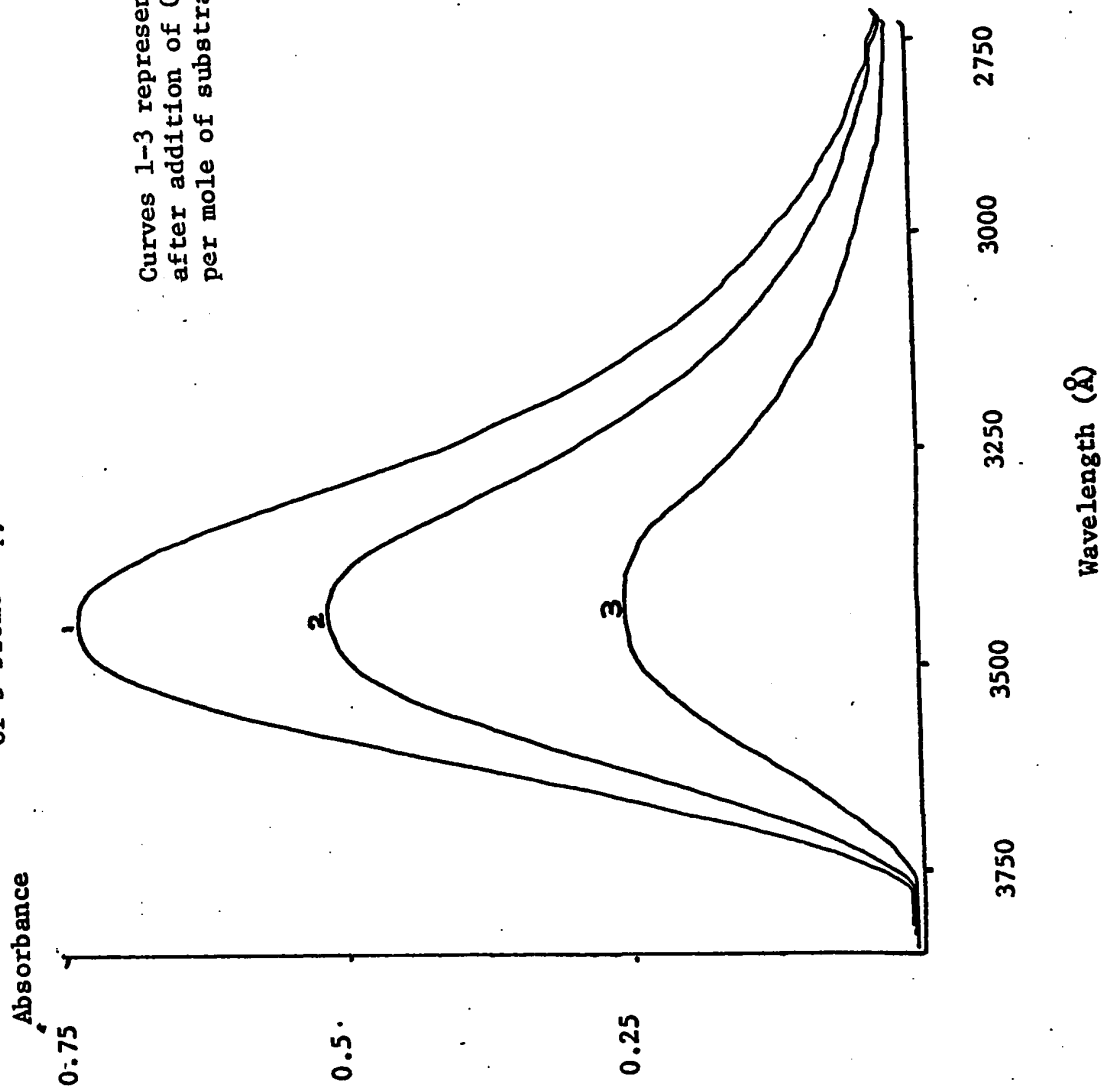
GENERAL SUMMARY

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[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[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.
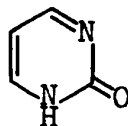
3
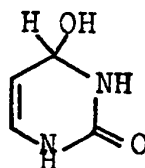
44

REFERENCES

1) T.L.V.Ulbricht, "Purines, Pyrimidines and Nucleotides", Vol.25 of "A Course in Organic Chemistry", (R.Robinson,Ed.), Pergamon Press, Oxford (1964).

2) A.R.Katritzky and C.D.Johnson, Ang.Chem.Int.Ed., 6 (7), 608, (1967).

3a) A.R.Katritzky, M.Kingsland and O.S.Tee, Chem.Comm., 289, (1968).

b) A.R.Katritzky, M.Kingsland and O.S.Tee, J.Chem.Soc., (B), 1226, (1968).

c) O.S.Tee, Ph.D. thesis, University of East Anglia, (1967).

4) J.J.Eisch, Adv.Het.Chem., 7 1, (1966).

5a) D.J.Brown, "The Pyrimidines", Vol.16 of "Chem. of Het. Cmpds.", (A.Weissberger,Ed.), Interscience, N.Y. (1962).

b) D.J.Brown, "The Pyrimidines Supplement 1", Vol.16 of "Chem. of Het. Cmds.", (A.Weissberger,Ed.), Interscience, N.Y. (1970).

6) K.Higashi, H.Baba and A.Rembaum, "Quantum Organic Chemistry", Interscience, N.Y. (1965).

7) A.R.Katritzky and J.M.Lagowski, Adv.Het.Chem., 1 368, (1963).

8) L.A.Paquette, "Principles of Modern Heterocyclic Chemistry", Benjamin, N.Y. (1968).

9) A.Albert, D.J.Brown and G.Cheeseman, J.Chem.Soc., 474, (1951).

10) D.J.Brown, Nature, 165 1010, (1950).

11) D.J.Brown, E.Hoerger and S.F.Mason, J.Chem.Soc., 211, (1955).

12) P.Bellingham, C.D.Johnson and A.R.Katritzky, J.Chem. Soc. (B), 1226, (1967).

13) R.M.Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds", Interscience, N.Y. (1967).

14) G.P.Bean, C.D.Johnson, A.R.Katritzky, B.J.Ridgewell and A.M.White, J.Chem.Soc. (B), 1219, (1967).

15) Ref. 5(a), p.321.

16) E.Kalatzis, J.Chem.Soc. (B), 96, (1969).

17) C.D.Johnson, A.R.Katritzky, M.Kingsland and E.F.V.Scriven, ibid 1 1, (1971).

18) M.E.C.Biffin, D.J.Brown and T.C.Lee, J.Chem.Soc. (C), 573, (1967).

19) H.Bredereck, R.Gompper and H.Herlinger, Ber. 91 2832, (1958).

20) D.J.Crosby and R.V.Berthold, J.Org.Chem., 25 1916, (1960).

21) D.J.Brown and R.V.Foster, Aust.J.Chem., 19 2321, (1966).

22) O.S.Tee, unpublished results.

23) A.A.Baev, A.D.Mirzabekov, V.I.Gorshkova and T.V.Venkstern, Dokl.Akad.Nauk.S.S.S.R., 152(2), 331, (1963).

24) W.Barbieri, L.Bernadi, G.Palamidessi and M.T.Venturi, Tet.Letters, 25 2931, (1968).

25) R.Foster and C.A.Fyfe, Rev.Pure and Appl.Chem., 16 61, (1966).

26) M.R.Crampton and V.Gold, J.Chem.Soc., 4293, (1964).

27) A.Albert and W.L.F.Armareggo, Adv.Het.Chem., $\underline{4}$ 1, (1965).

28) D.D.Perrin, ibid $\underline{4}$ 43, (1965).

29) L.P.Hammett and A.J.Deyrup, J.A.C.S., $\underline{54}$ 2721, (1932).

30) M.J.Jorgensen,and D.R.Hartter, ibid $\underline{85}$ 878, (1963).

31). K.Yates and J.B.Stevens, Can.J.Chem., $\underline{43}$ 529, (1965).

32) F.A.Long and J.Schulze, J.A.C.S., $\underline{86}$ 327, (1964).

33) A.J.Hinman and J.Lang, ibid $\underline{86}$ 3796, (1964).

34) J.F.Bunnett and F.P.Olsen, Can.J.Chem. $\underline{44}$ 1899, (1968).

35) K.Yates and R.A.McCelland, J.A.C.S. $\underline{89}$ 2686, (1967).

36) A.Albert, Angew.Chem.Int.Ed., $\underline{6}$ 919, (1967).

37) S.Y.Wang, J.Org.Chem., $\underline{24}$ 11, (1959).

38) A.M.Moore and S.M.Anderson, Can.J.Chem., $\underline{37}$ 590, (1959).

39) A.A.Frost and R.G.Pearson, "Kinetics and Mechanism", Wiley, N.Y. (1963).

40) M.Eigen, Ang.Chem.Int.Ed., $\underline{3}$ 1, (1964).

41) J.R.Dyer, "Applications of Absorption Spectroscopy of Organic Compounds", Prentice-Hall, N.J. (1965).

42) N.C.Barford, "Experimental Measurements: Precision, Error and Truth", Addison-Wesley, London (1967).

43) E.A.Guggenheim, Phil.Mag., (7), $\underline{2}$ 538, (1936).

44) C.J.Collins, Adv.Phys.Org.Chem., $\underline{2}$ 1, (1964).

45) J.G.Dick, "Quantitative Analytical Chemistry", McGraw-Hill (to be published).

46) International Critical Tables, $\underline{3}$ 56, (1928).

47) C.D.Johnson, A.R.Katritzky and S.A.Shapiro, J.A.C.S. $\underline{91}$ 6654, (1969).

48) W.Wagner, C.J.Hull and G.E.Markle, "Advanced Analytical

Chemistry", Reinhold, N.Y. (1958).

49) D.J.Brown and T.C.Lee, J.Chem.Soc., 211, (1955).

50) W.Barbieri, L.Bernadi, F.Luini and G.Palamidessi, Farm. Ed.Sci., 24 (6), 561, (1969).

51) W.Barbieri, L.Bernadi, F.Luini and G.Palamidessi, ibid, 25 (9), 702, (1970).

52) W.Barbieri, L.Bernadi, F.Luini and G.Palamidessi, ibid, 25 (9), 694, (1970).

53) C.Baudisch and D.Davidson, J.Biol.Chem., 64 234, (1925).

54) M.D.Johnson and J.H.Ridd, J.Chem.Soc., 283, (1962).

55) H.Zollinger, Adv.Phys.Org.Chem., 2 163, (1964).

56) H.C.Brown and R.S.Fletcher, J.A.C.S., 71, 1845, (1949).

57) K.J.Laidler, "Chemical Kinetics", McGraw-Hill, N.Y. (1965).

58) R.P.Bell and D.R.Marshall, J.Chem.Soc., 2195, (1964).