THE MECHANISMS OF BROMINATION OF MONO- AND DIOXO-PYRIMIDINES

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ABSTRACT

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The kinetics of bromination of mono- and dioxo-pyrimidines have been studied. 2-Oxo- and 4-oxo-pyrimidines are brominated through their covalent hydrates or pseudo-bases to form adducts which undergo acid-dependent elimination to give the corresponding 5-bromo-products. Similar adducts have been identified during the bromination of a number of dioxo-, amino- and oxo-amino-pyrimidines. The reversal of these derivatives in the presence of iodide ion has been noted.

The uracils react with bromine to give addition products which dehydrate under acidic conditions via rate-determining deprotonation of 5H. In the presence of bromine, the adducts obtained from N-1 unsubstituted uracils may rapidly aromatise through a novel "bromine catalysed" process. The diastereomerisation of these adducts have also been noted.

4,6-Dihydroxy-pyrimidine and 6-methyl-uracil may be directly brominated to 5,5-dibromo-derivatives. These products are debrominated to 5-bromo-compounds upon reaction with the parent pyrimidines in the presence of bromide ion and acid.

To my mother and father

ACKNOWLEDGEMENTS

The author is indebted to Dr. Oswald S. Tee for his patient and liberal direction of this work. He thanks Mr. Masaki Endo for making some of the "pK" measurements, and Dr. Robin T. B. Rye for providing him with mass spectra, as well as for several discussions. Finally, he is sincerely grateful to Ms. Xenia Kirkpatrick for preserving his sense of humor during the preparation of this thesis.

Contents

Index to Tables

Index to Figures

INTRODUCTION

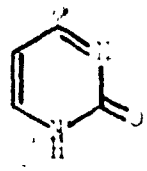
GENERAL INTRODUCTION

The occurrence of the pyrimidines in nucleic acids has stimulated considerable interest into the structure and reactivity of these derivatives[1]. The influence of the ring hetero-atoms causes significant deviation from classical aromatic behaviour, an estimate of which may be obtained from studies on reaction pathways[2]. This work is an extension of the author's previous investigation into the bromination of 2-pyrimidone[3] to other mono- and dioxo-pyrimidines.

Pyrimidones are rapidly brominated in aqueous acid to stable intermediates which convert to the corresponding 5-bromo-products, the rates of aromatisation being markedly dependent upon acid strength. Spectroscopic identification of these intermediates, as well as those derived from model substrates, and analysis of their decay kinetics as a function of acidity, leads to the formulation of individual reaction schemes. Assessment of the role of the functional groups in dictating the stability of the intermediates then allows mechanistic correlations to be made within these systems.

STRUCTURES OF THE PYRIMIDONES

The presence of potentially tautomeric groups in the pyrimidones has led to extensive studies on their fine structure[4]. 2-Pyrimidone, (1), has been shown to exist in its keto form by comparison of its u.v. and p.m.r.[5]



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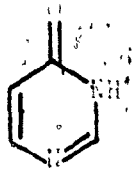

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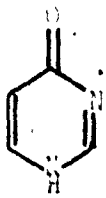

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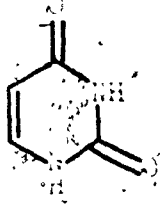

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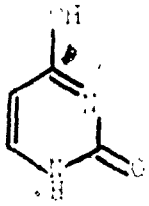

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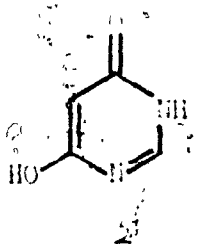
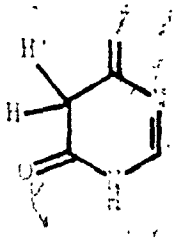
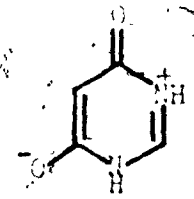
spectra[7], and ionisation data with those of fixed model compounds (eg. 2-methoxy-pyrimidine). For 4-pyrimidone, p.m.r. results suggest the predominance of 2A, with the tautomer 2B being present as a minor component[8]. Uracil occurs in the keto form 3 both in the solid state (as derived from X-ray diffraction studies[10-13]) and in solution, a conclusion in agreement with that arrived at from molecular orbital calculations[14]. However, recent evidence based on the correlation of time-averaged fluorescence spectra with photochemical triplet yields has pointed to the tautomer 4 as being the fluorescing species[15].

The structure of 4,6-dihydroxy-pyrimidine has not been conclusively established at present. An early spectral (I.R.) assignment of 5 as the major form[16,17] was contradicted by u.v. measurements which favored the dioxo-structure 6[18]. However, a more recent analysis of its p.m.r. spectrum has suggested that the enol-oxo form 5 predominates over the dioxo-tautomer 6, the two species being in equilibrium[8]. Other workers have proposed a number of alternative structures including the zwitter-







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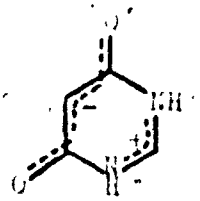

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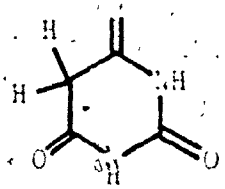

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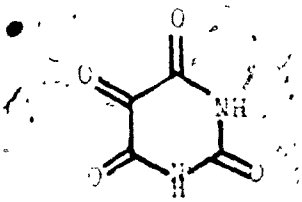

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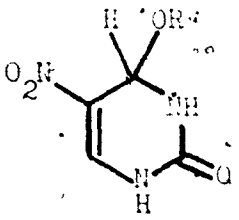
ion 7 [19] or the equivalent structure 8 [20,21].

The higher order pyrimidones, 2,4,6-trioxo-pyrimidine (barbituric acid) and 2,4,5,6-tetraoxo-pyrimidine (alloxan) exist preferentially in their oxo forms 9 and 10 respectively [22].

Tautomerism of this type has contributed greatly to the present confusion in the nomenclature of these compounds. Thus, 2 has been referred to as 4-hydroxy-pyrimidine, 4-pyrimidinol, 4-pyrimidone, 4-pyrimidinone, 4(1)-pyrimidone, 4(3)-pyrimidone, 1,4-dihydro-4-oxo-pyrimidine and 3,4-dihydro-4-oxo-pyrimidine [1a]. In this thesis, the 'dihydro' prefix has been dropped, and the above compound is referred to as 4-pyrimidone or 4-oxo-pyrimidine. Similar simplifications in nomenclature have been employed for other oxo-pyrimidines.



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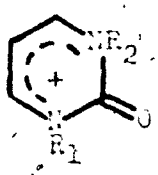

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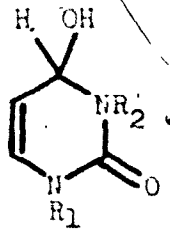


13

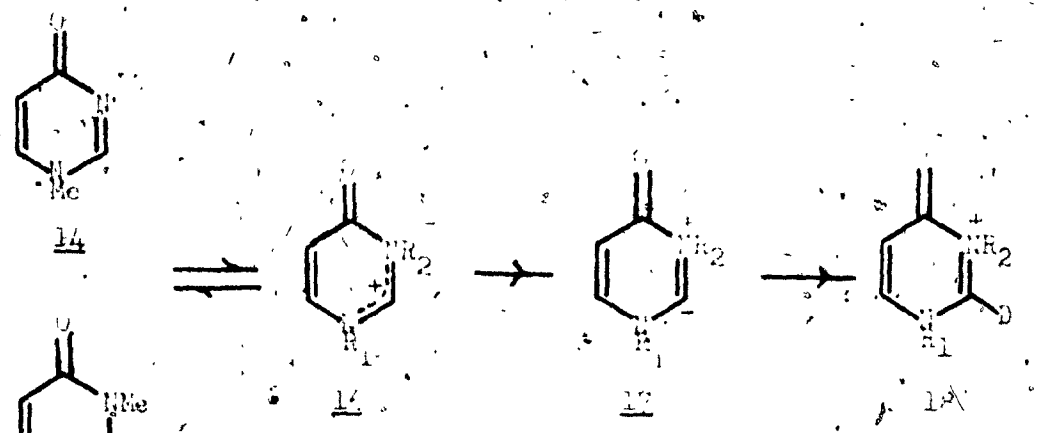
REACTIONS OF THE PYRIMIDONES

Covalent Hydration

Solvent addition to π-deficient aromatic and hetero-aromatic systems is well established [23-26], and has been shown to apply to the pyrimidines [27]. Fox et al. [28] have identified adducts 11 (R=D or H) generated from 5-nitro-2-pyrimidone, and Tee has observed similar behaviour for the quaternary salts of 2-pyrimidone (12 ⇌ 13) [29]. The presence of hydrates, even in small proportions, may greatly influence the reactivity of these systems towards electrophilic substitution, and their formation has been postulated in isotope exchange [30] and in bromination [3]. Recent work has shown that covalent amination of N-heterocyclic compounds may also occur in liquid ammonia solutions [31,32].

Hydrogen-Deuterium Exchange

The acid-catalysed deuteriation at the 5-position of the 2-oxo-pyrimidinium ion (12; R_1=R_2=H) proceeds by way of its covalent hydrate 13 (R_1=R_2=H); as suggested by its increased reactivity with respect to 2-pyridone, and its similarity in kinetic behaviour to that of the



14 ⇌ 17 → 12 → 18

A: R_1=D, R_2=Me; B: R_1=Me, R_2=D; C: R_1=R_2=Me

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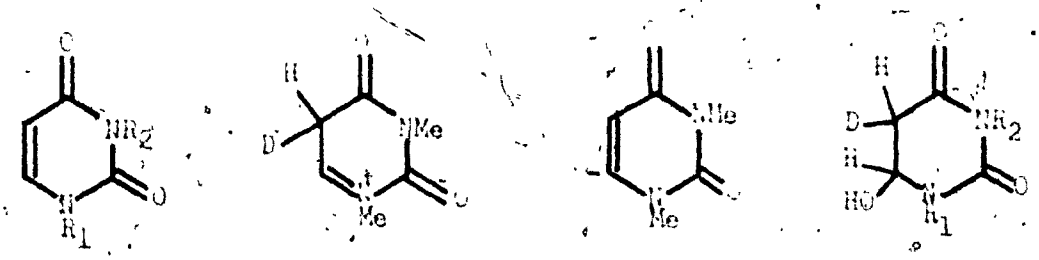
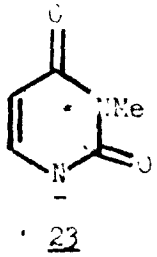


19 20 21 22

quaternary ion 12 (R_1=R_2=Me)[30].

The rates of exchange at the 2-position of 1-methyl-4-pyrimidone (14) and 3-methyl-4-pyrimidone (15) are invariant with changes in pD, whereas the 1,3-dimethyl-derivative 16C shows a first-order dependence on base concentration[33]. It has been suggested that this arises from rapid pre-equilibrium protonation of substrate 14 or 15, followed by rate-determining ylid formation and subsequent deuteriation[34,35]. Ylids have also been shown to be of importance in the hydrogen-deuterium exchange of pyrimidine N-oxides[36].



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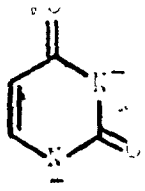

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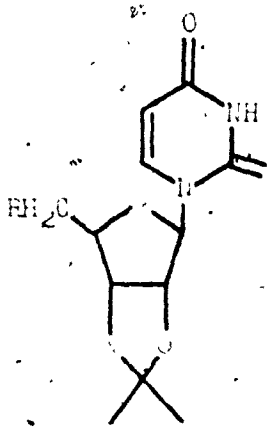

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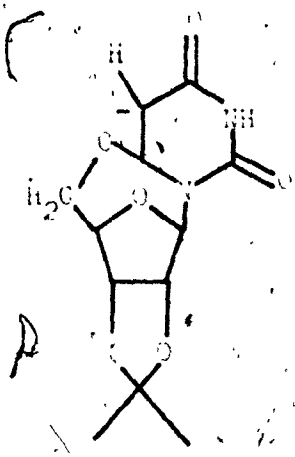

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Kinetic studies have revealed that uracil (19; R_1=R_2=H) exchanges its 5H in acidic D_2O solutions, whereas in basic media deuteriation occurs at both the 5 and the 6 positions[30a]. The acid-catalysed process is ascribed to reaction via the cation 20, whereas the carbanion 21 is invoked for the base-induced exchange of 6H. Loss of 5H in alkaline media is presumed to take place via the hydrate 22 (R_1=R_2=Me), and has been independently confirmed and extended to 1-methyl-uracil (19; R_1=Me, R_2=H)[37*].

Rate profiles for the base-catalysed dedeuteriation of 3-methyl-uracil-5d (5d-18; R_1=H, R_2=Me) and uracil-5d (5d-19; R_1=R_2=H) suggest participation of the anion 23 for the former, and the dianion 24 for the latter[37]. Neighboring group effects have been noted during the exchange

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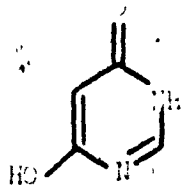
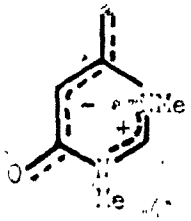
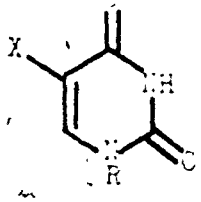
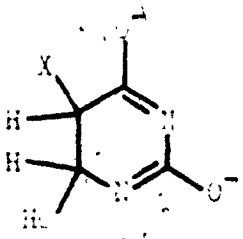
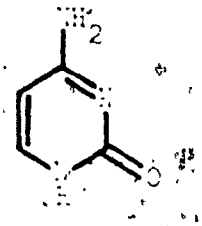
* Exchange of the pyrimidine ring protons in nucleosides has recently been observed[38].











of 5H in 2',3'-O-isopropylidene-uridine (22; R=OH). This compound undergoes reaction by anchimeric assistance of the 5'-oxy-anion 26; as demonstrated by the stability of its deoxy derivative 25 (R=H) under similar conditions[30].

Acid-base catalysis has been qualitatively shown to be operative for isotope exchange at the 5-position of 4,6-dihydroxy-pyrimidine[2,21] (5), and the 1,3-dimethyl-derivative 27[21].

Nitration

2-Pyrimidone and uracil are nitrated in strong acid to their corresponding 5-nitro-derivatives, the reaction occurring through free base species[40].

Hydrolysis

Garrett's investigations into the hydrolysis of the 5-halo-uracils 29 (R=H, X=F, Cl, Br, I)[41] and of the corresponding uridines 29 (R=ribosyl, X=Cl, Br, I)[42] have shown that whereas 5-chloro- and 5-fluoro-uracil are degraded directly to non-chromophoric products, the bromo- and iodo-derivatives are initially hydrolysed to barbituric acid and uracil respectively by elimination of HX or HOX from intermediates such as 22 (X=Br, I). Deiodination in the conversion of 29 (X=I) to uracil involves loss of a positive iodonium ion[43]. Similar work on 5-trifluoromethyl-uracil (29; R=H, X=CF_3) has suggested that reaction proceeds through the attack of hydroxyl ion on both the neutral species and the mono-anion to yield 5-carboxy-uracil which is subsequently decarboxylated at elevated temperatures by the action of alkali[44].

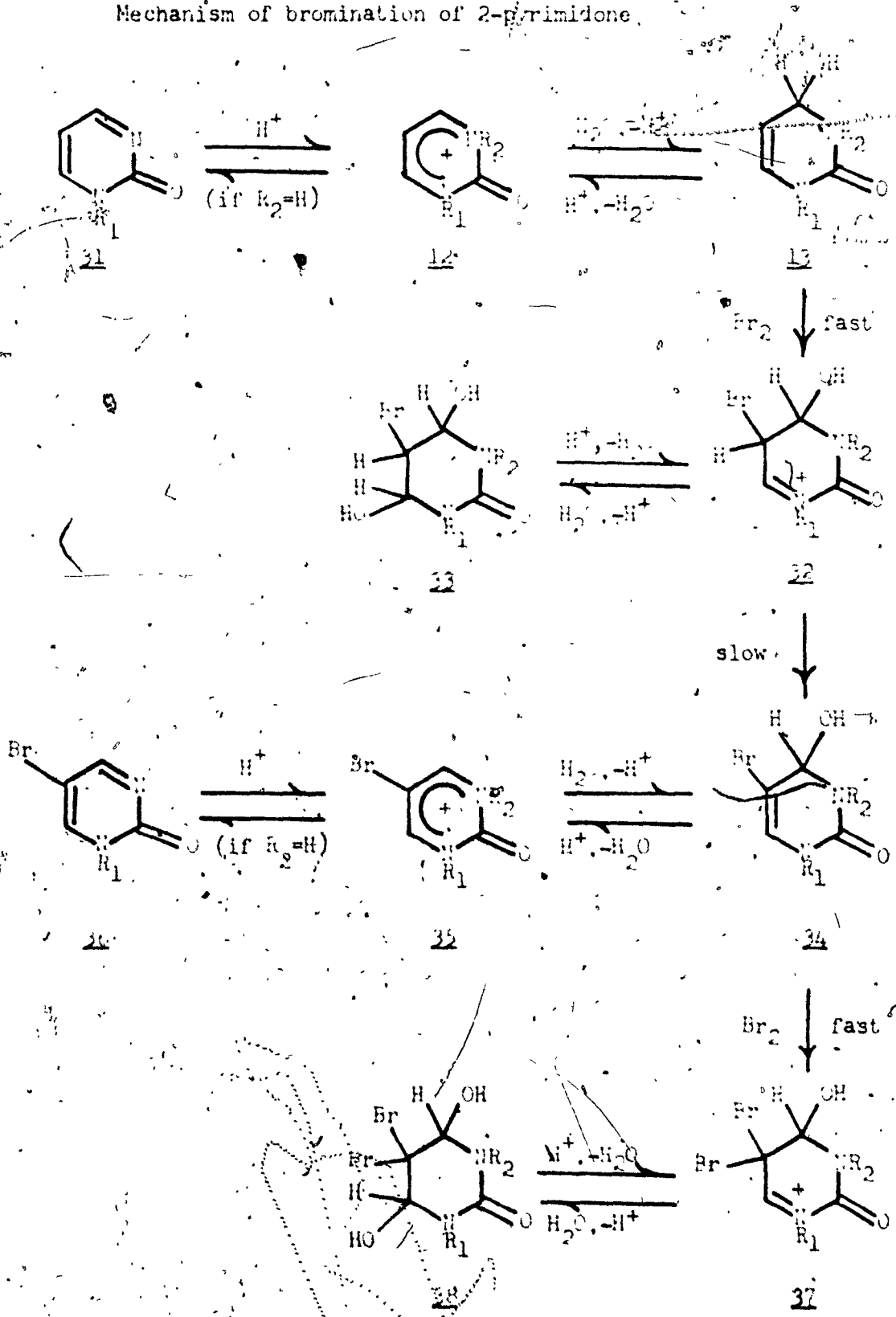
The kinetics of base-catalysed cleavage of barbituric acid and its derivatives[45], cytosine (30; R=H) and cytidine (30; R=ribosyl)[46], have also been reported.

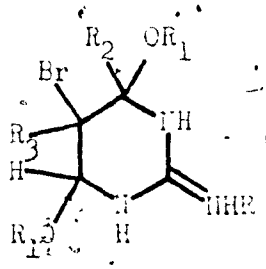
Bromination

The salts of 2-pyrimidone (12; R_1=R_2=H), its N-methyl (12; R_1=Me, R_2=H) and N,N-dimethyl (12; R_1=R_2=Me) derivatives, react rapidly with bromine in aqueous acidic solutions to yield intermediates which are converted to their 5-bromo-products 32 (Fig.1, p.9)[3]. Initial attack of bromine occurs on the covalent hydrates 13 (R_1=R_2=H or R_1=Me, R_2=H) or pseudo-base 13 (R_1=R_2=Me), as confirmed by the inhibitory effect of acid on the

Fig. 1

Mechanism of bromination of 2-pyrimidone





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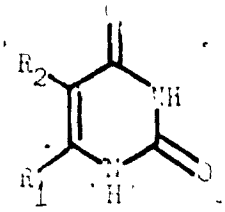

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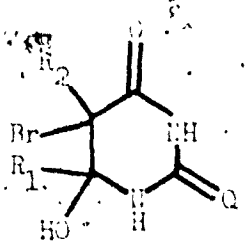

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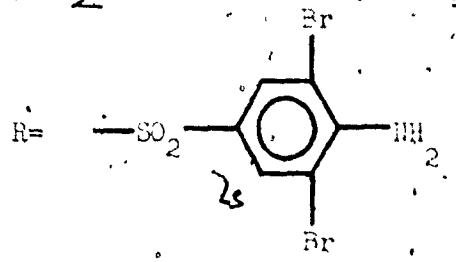
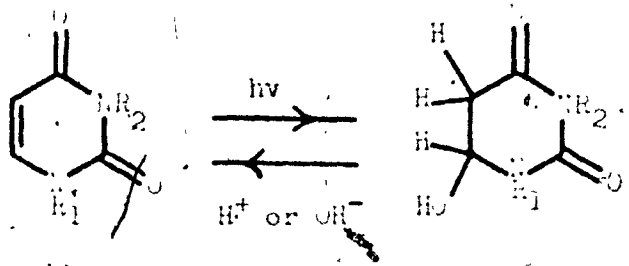


reactivity of the cation 12 (R_1=R_2=Me).

Evidence for the assignment of the hexahydro-pyrimidines 34 as the reaction intermediates is available from p.m.r. studies (p.30), as well as by comparison to structurally analogous systems. Barbieri et al. have isolated intermediates 39 (R_1=Me, R_2=R_3=H) and 39 (R_1=R_2=R_3=H) from the bromination of 2-sulfonamido-pyrimidines in methanol and acetic acid-water solutions respectively[47,48]. Similarly, 2-sulfonamido-5-methyl-pyrimidine yields 39 (R_1=R_2=Me; R_3=H) in aqueous media, and 39 (R_1=R_2=Me; R_3=H) in methanol[49], while methanolic solutions of 2-sulfonamido-4-methyl-pyrimidine are brominated 39 (R_1=R_2=Me; R_3=H)[50]. Orotic acid (40; R_1=COOH, R_2=H) is known to form the isolable adduct 41 (R_1=COOH, R_2=H)[51] and uracil (40; R_1=R_2=H) and thymine (R_1=H, R_2=Me)[52] give rise to the products 41 (R_1=H, R_2=Br)[1] and 41 (R_1=H, R_2=Me) respectively on treatment with excess bromine. It has also been proposed that uracil reacts with one equivalent of bromine to give 41 (R_1=R_2=H)[53,54].

The rates of formation of the 5-bromo-2-pyrimidones 35 are of the first



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order with respect to acid, and involve rate-determining deprotonation of 5H in the cation 32, as indicated by a large primary isotope effect for the quaternary salt 5-deuterio-12 (R_1=R_2=Me). Second-order rate constants are comparable within these systems, and suggest similar mechanisms[3]. The 5-bromo-products (35) undergo further bromination to give the stable 5,5-dibromo-substituted pyrimidines 37[3].

Photohydration and Photodimerisation

Pyrimidones may undergo hydration or dimerisation under the influence of ultra-violet radiation[52-57]. This phenomenon has been linked to genetic mutation and has consequently been examined in some detail.

Irradiation of aqueous solutions of uracil (12; R_1=R_2=H) and 1,3-dimethyl-uracil (12; R_1=R_2=Me) leads to the hydrates 42 (R_1=R_2=H) and 42 (R_1=R_2=Me) respectively[58-61], whereas similar treatment in frozen matrices results in dimerisation[62-66]. The kinetics of hydration[67-70], as well as the insensitivity of the process towards triplet quenchers[56], suggest the singlet state to be the reactive species. The rates of dehydration are

catalysed by acids and bases[60,67] and show isotope effects in keeping with rate-determining loss of 5H in 42[71].

EXPERIMENTAL

METHODS

The substrates studied give rise to strong absorption bands in the middle u.v. region (Table 1, p.14)[72]. Addition of bromine results in the rapid decrease of these peaks and the slow appearance of absorptions appropriate to the corresponding 5-bromo-pyrimidones (Table 2, p.19). Rates of product formation are of the first-order under the conditions employed, and may be analysed by the equation

$$\ln (A_\infty - A_t) = \ln (A_\infty - A_0) - kt \qquad \text{---(1)}$$

where A_0 and A_∞ represent absorbances at time t = 0 and infinity respectively, k being the first-order rate constant. It can be shown that a first-order reaction is complete to the extent of 99.9% after 9.97 half-lives, and therefore for kinetic purposes it may be considered to be over after ten half-lives.

Kinetic procedures were essentially similar to those described earlier[3a]. All measurements were made on a Cary model 14 recording spectrophotometer with a slit height of 20 mm.. Temperature was controlled by circulating water from a Heslab model TE9 constant temperature bath maintained at 30.00 ± 0.02°C, through the cell holders, which were found to be at a temperature of 29.3 ± 0.05°C. For the slower runs, aliquots of substrate and bromine solution, (estimated by addition of potassium iodide and titration of the liberated iodine with sodium thiosulfate) were rapidly

Table 1

U.v. spectral parameters of the pyrimidones

	pH or H_0	λ max (log ϵ)	ref.
4-Pyrimidone	-1.0	251(3.47), 224(3.69)	73
1-Methyl-4-pyrimidone	0.0	250(3.42), 220(4.01)	74
3-Methyl-4-pyrimidone	-0.4	258(3.47), 228(3.96)	74
1,4 (3,4)-Dihydro-1,3-dimethyl-4-oxo-pyrimidinium perchlorate	0.20	262(3.47), 231(4.06), <200(>4.0)	*
Uracil	4.4	259.5(3.91)	75
1-Methyl-uracil	5.4	267.5(3.99), 207.5(3.94)	75
3-Methyl-uracil	3.0	258.5(3.86)	75
6-Methyl-uracil	4.62	261(4.00)	76
1,3-Dimethyl-uracil	1.0	266.0(3.95)	75
4,6-Dihydroxy-pyrimidine	2.0	253(3.98)	18

* This work

Table 2

U.v. spectral parameters of the 5-bromo-pyrimidones

5-bromo-	pH or H	λ_{max} (log ϵ)	ref.
4-Pyrimidone	4.0	303(3.[illegible]), 283(3.67)	77
5,4 (3,4)-Dihydro-1-methyl-4-oxo-pyrimidinium bromide	0.20	269(3.7[illegible]), 246(3.91), <200(>4.0)	*
3-Methyl-4-pyrimidone	4.0	283(3.77), 236(3.60)	77
1,4 (3,4)-Dihydro-1,3-dimethyl-4-oxo-pyrimidinium bromide	0.20	277(3.72), 245(3.84), <200(>4.0)	*
Uracil	7.0	274(3.[illegible])	
1-Methyl-uracil	4.0	284(3.[illegible]), 215(3.97)	5
3-Methyl-uracil	4.0	275(3.[illegible]), 215(3.[illegible])	5
6-Methyl-uracil	0.20	27[illegible](3.93), 213(3.96)	*
1,3-Dimethyl-uracil	7.0	282(3.90)	
4,6-Dihydroxy-pyrimidine	0.20	20[illegible](4.0[illegible]), 204(4.36)	*

* This work

mixed, and the mixture introduced into the sample cell, one cm. cells being used in all cases. The faster runs (half-life of three minutes or less), required pre-equilibration of a measured volume (usually 2 mls.) of substrate solution in the sample cell, and the addition of reactant solution in microlitre quantities. The absorbance was continously recorded against a solvent reference for at least one half-life for the slower, and several half-lives for the faster runs, A_∞ being measured after ten half-lives. Data were fitted to eqn. (1) using least squares techniques. Correlation coefficients generally exceeded 0.9998 for the slower runs, and 0.9996 for the faster reactions.

All kinetic runs were carried out in sulfuric acid solutions in the concentration range of 0.10M to 5.00M. Weaker acids were not used since at acidities less than 0.10M H_2SO_4, the hydrobromic acid formed by the reaction of bromine with substrate would have to be taken into account. At acidities outside the pH scale (ie. > 1M H_2SO_4), the Hammett acidity function H_0[79] was used as a measure of acid strength. However, since the ionisation characteristics of the substrates studied were not determined, slopes derived from log (k) vs. H_0 plots are compared only for structurally related compounds. It is emphasized that correlations with other systems using techniques such as the Bunnett treatment[80] have not been attempted. It might be mentioned in this context that the interpretation of reaction kinetics in terms of mechanism in strongly acidic or basic media has recently been reviewed by Rochester[1,82].

Hydronium ion concentrations in sulfuric acid solutions were calculated from normality using 1.2×10^{-2} for the second dissociation constant of

sulfuric acid[84]. In the high acid region (above 11 H_2SO_4), Wt. % acid at 25°C was converted to normality using appropriate density values[85], and corresponding values of H_0 for the latter were fitted to a power series which then allowed direct conversion of normality to H_0.

All calculations were carried out on a Hewlett-Packard 2114A computer using routines coded in either BASIC or FORTRAN. A brief description of the programmes frequently used follow.

ILS calculates least-squares corrected first-order rate constants from absorbance-time values. The equilibrium or infinity value may be iteratively adjusted to give the best correlation coefficient. The output includes a plot of $\ln(A_\infty - A_t)$ with time.

NONLIN attempts to fit experimental data to a given equation. For an equation of the form $y = f_1(c_1x) + f_2(c_2x) + \cdots + f_n(c_nx)$, the derivatives $\partial y/\partial c_i$, i = 1 to n are required.

CFIT attempts to fit experimental data to a power series.

XYPLT is used with a digital plotter, and provides high resolution two-dimensional plots of input data pairs. A variety of plotting symbols are available.

Reactive intermediates were generated by the addition of molecular bromine to a solution (or suspension) of substrate in D_2O or D_2O - DCl. P.m.r. spectra of the resulting solutions were scanned repeatedly on a Varian A-60A instrument equipped with a V-6058A spin decoupling unit, until crystallisation of the 5-bromo-products occurred. Line positions were found to be reproducible only to within 4-5 Hz owing to the variation in acidity caused by the formation of HBr.

The mass spectrum was measured on a Perkin-Elmer-Hitachi RMU 7E instrument at 70 eV, and at a source temperature of 170°C.

MATERIALS

The melting points given below are uncorrected. Elemental analyses were performed by Galbraith Labs. Inc., Knoxville, Tennessee.

The following compounds were obtained commercially: 2-pyrimidone hydrochloride (recrystallised from ethanol-water before use), 2-amino-pyrimidine, uracil, 6-methyl-uracil, thymine, cytosine, 5-bromo-cytosine, 2,4-dimethoxy-pyrimidine, 4,6-dihydroxy-pyrimidine, orotic acid (Aldrich), 4-pyrimidone, 1-methyl-uracil, 3-methyl-uracil (Het. Chem. Co.), 1,3-dimethyl-uracil (Nutritional Biochemical Corp.).

The following compounds were obtained from Dr. C.S.Tee: 1-methyl-2-pyrimidone hydrochloride, 4,6-bis-trifluoromethyl-2-pyrimidone.

The following compounds were prepared according to literature methods: 4-pyrimidone [86], 1-methyl-4-pyrimidone [87], 3-methyl-4-pyrimidone [87], 1,4(3,4)-dihydro-1,3-dimethyl-4-oxo-pyrimidinium iodide [30a], 4,6-dimethoxy-pyrimidine [88], 1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium hydrogen sulfate [3], 5-deuterio-uracil [37], 5-deuterio-1,3-dimethyl-uracil [37], 5-bromo-uracil [53], 5-bromo-1,3-dimethyl-uracil [53], 5,5-dibromo-6-hydroxy-dihydro-uracil [53], 5-bromo-6-hydroxy-dihydro-thymine [52], 5-bromo-6-methyl-uracil [89], 5,5-dibromo-6-hydroxy-dihydro-orotic acid [51].

5-bromo-4-pyrimidone

Bromine (1.6g., 0.01moles) in 10 mls. of absolute methanol was added to a stirred solution of 4-pyrimidone (0.96g., 0.01moles) in 30 mls. of absolute methanol, and stirring was continued until the bromine colour disappeared. Solvent removal under reduced pressure and recrystallisation from ethanol gave 1.43g. (58%) of the hydrobromide.

M.p. 239-241° dec., lit. [60] 243-244° dec., lit. [91] 252-255° dec..

P.m.r. (D_2O/DSS) δ 8.52 (d, area 1), δ 8.90 (broad s, area 1), $J_{2,6}$=1.0 Hz.

5-bromo-3-methyl-4-pyrimidone

Bromine (1.6g., 0.01 moles) in 20 mls. of absolute methanol was added to a stirred solution of 3-methyl-4-pyrimidone (1.10g., 0.01moles) in 50 mls. of absolute methanol; and stirring was continued until the bromine was decolorised. Solvent removal under reduced pressure, and recrystallisation from water and then from ethanol-ligroin (35-60°) gave 0.9g. of the bromo-pyrimidine. Concentration of the filtrate afforded a further 0.6g. of the product. Yield = 62%.

M.p. 152-155°, lit. [77,92] 158-159°.

P.m.r. ($CDCl_3$/TMS) compared favorably with literature values .

5-bromo-1-methyl-4-pyrimidone hydrobromide

Bromine (0.4g., 0.0025moles) in 5 mls. of absolute methanol was added to 1-methyl-4-pyrimidone (0.275g., 0.0025moles) in 10 mls. of absolute methanol. Solvent removal under reduced pressure, and recrystallisation from water gave 0.27g. (40%) of the hydrobromide.

M.p. 243-244° dec..

P.m.r. (D_2O/DSS) δ 3.83 (s, area 3), δ 8.38 (d, area 1), δ 8.70 (d, area 1).

Anal. Calcd. for $C_5H_6N_2O\,Br_2$: C, 22.25; H, 2.24; N, 10.38; Br, 59.21.
Found: C, 22.15; H, 2.19; N, 10.31; Br, 59.47.

5-bromo-4,6-dihydroxy-pyrimidine

Bromine (1.60g., 0.01moles) in 10 mls. of absolute methanol was added to a suspension of 4,6-dihydroxy-pyrimidine (1.12g., 0.01moles) in 10 mls. of absolute methanol. Solvent removal under reduced pressure followed by recrystallisation from water afforded 1.61g. (84%) of the brominated material.

M.p. 261-263° dec., lit.[90] 263-264° dec..

P.m.r. (DMSO-d6/TMS) δ 7.82 (broad s, area 2), δ 8.50 (s, area 1).

5,5-dibromo-6-hydroxy-6-methyl-dihydro-uracil

Bromine (3.2g., 0.02 moles) was added to a suspension of 6-methyl-uracil (1.26g., 0.01moles) in 15 mls. of water. The reaction mixture was stirred in a stoppered flask for 30 mins., refrigerated and filtered. Recrystallisation from acetone-ligroin (35-60°) gave 2.28g. (88%) of the dibromo-compound[93].

M.p. 232-234° after darkening above 200°.

P.m.r. (DMSO-d6/TMS) δ 1.73 (s). A singlet at δ 2.22 with approximately 20% of the integrated intensity of the peak at δ 1.73 was also observed. This probably represents the isomer where the hydroxy group adopts an equatorial position with respect to the ring.

Anal. Calcd. for $C_5H_6N_2O_3Br_2$: C, 19.89; H, 2.00; N, 9.28; Br, 52.93.
Found: C, 19.74; H, 1.88; N, 9.22; Br, 52.85.

5,5-dibromo-2-methoxy-4,6-dioxo-hexahydro-pyrimidine

4,6-Dihydroxy-pyrimidine (0.56g., 0.00 moles) was suspended in 5 mls. of absolute methanol, and bromine was added with stirring until a permanent colour was obtained. The temperature of the mixture rose during addition, and carbon dioxide was evolved. Refrigeration of the mixture and filtration afforded a pale yellow material which was found to contain some of the starting material. The bromination process was repeated to give 1.23g. (82%) of the product as white crystals which were recrystallised from acetone-ligroin (35-60°).

M.p. the compound melted at 177-178° with strong effervescence, resolidified to a yellow material which darkened above 220° and melted with decomposition at 232-240°.

P.m.r. ($DMSO-d_6$) δ 3.33 (s, area 3); δ 5.47 (t, area 1), δ 9.78 (d, area 2), J = 3.1 Hz. Addition of D_2O led to the collapse of the low field signals to a singlet.

Mass spectrum (run at a source temperature of 170°) did not show a molecular ion peak corresponding to m/e 302, but showed triplets of intensity ratio 1:2:1 at m/e 203, 201, 200 and at 202, 200, 198.

Anal. Calcd. for $C_5H_4N_2O_3Br_2$: C, 19.9; H, 2.00; N, 9.24; Br, 52.93. Found: C, 19.97; H, 1.90; N, 9.2; Br, 52.92.

5-deuterio-1,4(3,4)-dihydro-1,3-dimethyl-4-oxo-pyrimidinium iodide

1,4(3,4)-Dihydro-1,3-dimethyl-4-oxo-pyrimidinium iodide (0.5g., 0.002 moles) was refluxed in 4 mls. of 2N DCl for 27 hours. Solvent removal under reduced pressure and recrystallisation from ethanol yielded 0.4g. (80%) of the deuteriated derivative.

P.m.r. (D_2O) showed no trace of the 5-proton.

1,4(3,4)-dihydro-1,3-dimethyl-4-oxo-pyrimidinium perchlorate

0.5g. (0.003moles) of the corresponding iodide in 10 mls. of water was stirred with silver perchlorate (0.42g., 0.002moles) for 30 minutes. Solvent removal under reduced pressure at room temperature gave a yellow product which was recrystallised from methanol to give 0.2g. (65%) of the perchlorate.

M.p. 133-134°.

P.m.r. (D_2O) was identical to that of the starting derivative.

Similar conversion of the iodide salt of the 5-deuterio material yielded the perchlorate in 75% yield.

5-bromo-1,4(3,4)-dihydro-1,3-dimethyl-4-oxo-pyrimidinium perchlorate

To 1,4(3,4)-dihydro-1,3-dimethyl-4-oxo-pyrimidinium perchlorate (0.45g., 0.002moles) in 10 mls. of absolute methanol was added bromine (0.32g., 0.002moles) in 5 mls. of absolute methanol, and the mixture was allowed to stand at room temperature for 1 hour. The product (0.25g., 71%) was collected and recrystallised from ethanol.

M.p. darkens above 220°, changes into a semi-solid material which melts at 260-270° with decomposition.

P.m.r. (D_2O) δ 3.77 (s, area 3), δ 4.02 (s, area 3), δ 8.72 (s, area 1), δ 9.75 (broad s, area 1).

Anal. Calcd. for $C_6H_5N_2O_2BrCl$: C, 23.74; H, 2.66; N, 9.23; Br, 26.33.
Found: C, 23.75; H, 2.60; N, 9.17; Br, 26.49.

5-bromo-1,4(3,4)-dihydro-1,3-dimethyl-4-oxo-pyrimidinium Bromide

To 1,4(3,4)-dihydro-1,3-dimethyl-4-oxo-pyrimidinium iodide (0.5g., 0.002 moles) in 10 mls. of absolute methanol was added bromine (0.4g., 0.003 moles) in 5 mls. of absolute methanol, and the mixture was shaken vigorously for 5 minutes. Ether was stirred into the solution until solid material appeared. The product was collected after refrigeration and recrystallised from methanol. Yield 0.11g. (10%).

M.p. 231-233° dec..

P.m.r. (D_2O) was identical to that of the corresponding perchlorate.

5-deuterio-3-methyl-4-pyrimidone

3-Methyl-4-pyrimidone (0.55g., 0.005moles) was heated in 2% DCl at 80° for 40 hours.[33] Solvent removal under reduced pressure yielded a red oil which was dissolved in hot benzene and filtered through 'Norite'. Evaporation of the solvent yielded a pale yellow material which was sublimed at 90° at 1mm. to yield 0.23g. (92%) of the deuteriated product.

M.p. 133-135°.

P.m.r. (D_2O) showed that isotope incorporation had occured to an extent of 92% at the 5-position, and 63% at the 2-position.

Similar attempts to prepare 5-deuterio-4-pyrimidone were unsuccesful, and resulted in extensive decomposition of the substrate.

2-deuterio-3-methyl-4-pyrimidone

3-Methyl-4-pyrimidone (0.55g., 0.005moles) was heated in 5 mls. of D_2O for 15 hours at 80°.[33] Solvent removal under reduced pressure followed

by azeotropic distillation with benzene gave a white material which was recrystallised from benzene to yield 0.44g. (70%) of the labelled derivative. M.p. 128-130°.

P.m.r. (D_2O) showed that > 95% exchange had occured at the 2-position.

5-deuterio-6-methyl-uracil

This compound was prepared from 6-methyl-uracil with a yield of 88% and with an isotopic purity of > 95% by the method reported by Santi et al.[37] for the deuteriation of uracil.

Complex formation during the bromination of mono-oxo-pyrimidines

The addition of bromine to solutions of 2-pyrimidone, its N-methyl- and N-dimethyl derivatives, its 5-bromo-compounds and 4-pyrimidone in concentrated HCl leads to highly colored compounds. A typical experiment is as follows:

Bromine (1.6g., .01 moles) was added to 2-pyrimidone (1.33g. .01 moles) as the hydrochloride in 10 mls. of concentrated HCl. A yellow solid (0.57g.) gradually crystallised out of solution. The p.m.r. spectrum in concentrated DCl showed peaks corresponding to 2-pyrimidone. On addition of D_2O to the solution additional signals corresponding to 33 (R_1=R_2=H) (p. 9) appeared. The ratio of the area of these peaks to those of the residual 2-pyrimidone signals was 1:1. Thus, the complex consists of at least two molecules of 2-pyrimidone and one molecule of bromine. In the presence of water, one of the pyrimidine molecules reacts with the bromine to give 33 (R_1=R_2=H).

Volumetric Solutions

Solutions of sulfuric acid and sodium thiosulfate were prepared from commercial (Anachemia) volumetric concentrates.

DISCUSSION

SPECTROSCOPIC STUDIES

Previous studies on the bromination of oxo- and amino-pyrimidines have suggested that these reactions may occur through addition-elimination mechanisms[1]. Barbieri et al. have isolated hexahydro-pyrimidine adducts from the reaction of bromine with sulfonamido-pyrimidines in methanol (p. 10), and orotic acid is known to add HOBr to form 5-bromo-6-hydroxy-dihydro-orotic acid 47 (p. 10). In general however, the reactivity of intermediates of this type precludes their isolation and characterisation, and their formation has not been directly demonstrated in most instances.

In aqueous solutions, the u.v. spectra of the parent oxo- and amino-pyrimidines (structures on pp. 30,33,34,38) are removed upon addition of bromine, and are slowly replaced by absorptions appropriate to the corresponding 5-bromo-products. The rates of bromo-pyrimidine appearance are of the first-order at fixed acidities, and are discussed elsewhere in this thesis. P.m.r. spectra of the reaction mixtures (in D_2O or D_2O-DCl) confirm the formation of non-aromatic adducts, and line positions and coupling constants for these are reported in Table 3 (p. 27). Similar data for the substrates and their 5-bromo-products are presented in Tables 4 (p. 28) and 5 (p. 29) respectively.

Table 3

P.m.r. spectral parameters of intermediate adducts obtained during the bromination of oxo- and amino-pyrimidines

Compound[a]		Solvent	Chemical shift (δ) 2,4H	5H	6H	N-Me	J (Hz) 5,6
44	A	D_2O	-,-	4.22-4.4[illegible] (m)	5.0[illegible]-5.2[illegible] (m)	2.9[illegible]-3.03	-
	B	"	-,-	4.33-4.45 (m)	5.00-5.15 (m)	2.92-2.98	-
	C	"	-,-	4.32-4.3[illegible] (m)	4.90-5.05 (m)	-	-
46		"	-,-	4.62-4.70 (m)	-	-	-
48		1N DCl	-,-	4.5[illegible] (s)	5.42 (d)	-	2.2
51	A	4N DCl	8.93,-	4.90 (d)	5.42 (d)	-	3.4
	B	6N DCl	8.98,-	5.05 (d)	5.47 (d)	3.75	3.2
	C	"	9.17,-	5.14 (d)	5.33 (d)	3.57	4.0
61	A	D_2O	-,-	4.37 (d)	5.10 (d)	-	2.2
	B	"	-,-	4.62 (d)	5.38 (d)	3.20	2.4
	C	"	-,-	4.58 (d)	5.32 (d)	3.17	2.4
	D	"	-,-	4.50 (d)	5.10 (d)	3.13,3.15	2.4
58		1N DCl	-,-	5.28 (d)	5.55 (d)		2.3

[a] Structures on p. 32; [b] equivalent to 6H; [c] indistinguishable from 6H.

Table 4

P.m.r. spectral parameters of the oxo- and amino-pyrimidines

Compound (X=H)	Solvent	Chemical Shift (δ) 2,4H	5H	6H	N-Me	J (Hz)	Ref.
43A	0.1 N D_2SO_4	-,-	6.73	8.40	-	4,6=5,6=6	30
B	D_2O	-,-	6.43	7.94	3.45	4,6=4;5,6=7;4,6=2	"
C	"	-,-	7.00	8.00	3.92	4,5=5,6=7	"
47	0.1 N D_2SO_4	-,-	6.79	8.20	-	4,5=5,6=5	
45	$DMSO-d_6$	-,-	7.75	-	-	-	
49A	"	8.20,-	6.37	7.95	-	5,6=6.3;2,6=0.5;2,5=1.0	27
50	"	8.30,-	6.02	7.72	3.50	5,6=7.0;2,6=2.5;2,5=0.5	"
49B	"	8.50,-	6.42	7.95	3.45	5,6=6.0;2,5=0.5	"
52A	"	-,-	5.47	7.40	-	5,6=7.6	
B	D_2O	-,-	5.79	7.61	3.34	5,6=7.8	
C	"	-,-	5.85	7.50	3.26	5,6=7.4	
D	0.1 N D_2SO_4	-,-	5.83	7.59	3.40,3.25	5,6=7.5	30
57	D_2O	-,-	6.15	7.74	-	5,6=8.0	95

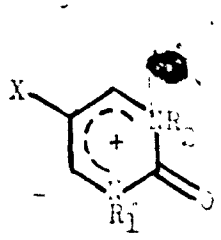
*Structures on pp. 30, 33, 34, 38

Table 5

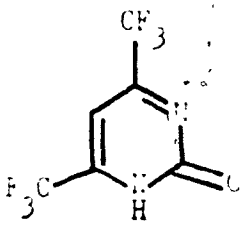
P.m.r. spectral parameters of the 5-bromo-oxo- and amino-pyrimidines

Compound (X=Br)	Solvent	Chemical shift (δ) 2,4H	6H	Me	J (Hz) 2,4	4,6
43A	DMSO-d6	-, 8.48	8.48	-	-	-
B	"	-, 8.49	8.33	3.33	-	3.0
C	"	-, 8.05	8.05	3.33	-	-
49A	"	8.03, -	8.50	-	1.0	-
5C	"	8.10, -	8.38	3.35	2.2	-
49B[b]	"	9.42, -	8.94	3.32	-	-
52A	DMSO-d6	-, -	8.16	-	-	-
D	"	-, -	8.25	3.20, 3.30	-	-
57	DCl (conc.)	-, -	8.13	-	-	-

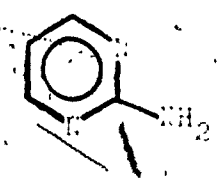
*Structures on p. 30, 33, 34, 38



43



42



47

A: $R_1=R_2=H$
B: $R_1=Me$, $R_2=H$
C: $R_1=R_2=Me$

Mono-oxo- and amino-pyrimidines

The kinetics of bromination of the 2-oxo-pyrimidinium ion (43A; X=H), its N-methyl (43B; X=H) and N,N-dimethyl (43C; X=H) derivatives to the 5-bromo-pyrimidines 43 (X=Br) suggest the intermediacy of the hexahydro-pyrimidines 33 (p. 9). These findings are substantiated by p.m.r. spectra, which, for each compound show two sets of multiplets in the δ 4-6 region, the N-methyl resonances occurring at higher field. For 5-deuterio-43C, the multiplet at lower field simplifies to a pair of singlets. Similar simplification is obtained by the spin decoupling of either multiplet which causes the other to collapse to two sharp singlets (Fig. 2 p. 31). These results are well correlated with structure 44*, and suggest that 44 exists in two major diastereomeric forms. Similarly, the bromination of 4,6-bis-trifluoromethyl-2-pyrimidone (45) leads to an adduct whose spectrum consists of a multiplet centred at δ 4.66, and to which is assigned structure 46.

Addition of bromine to a D_2O solution of 2-amino-pyrimidine (47) gives a

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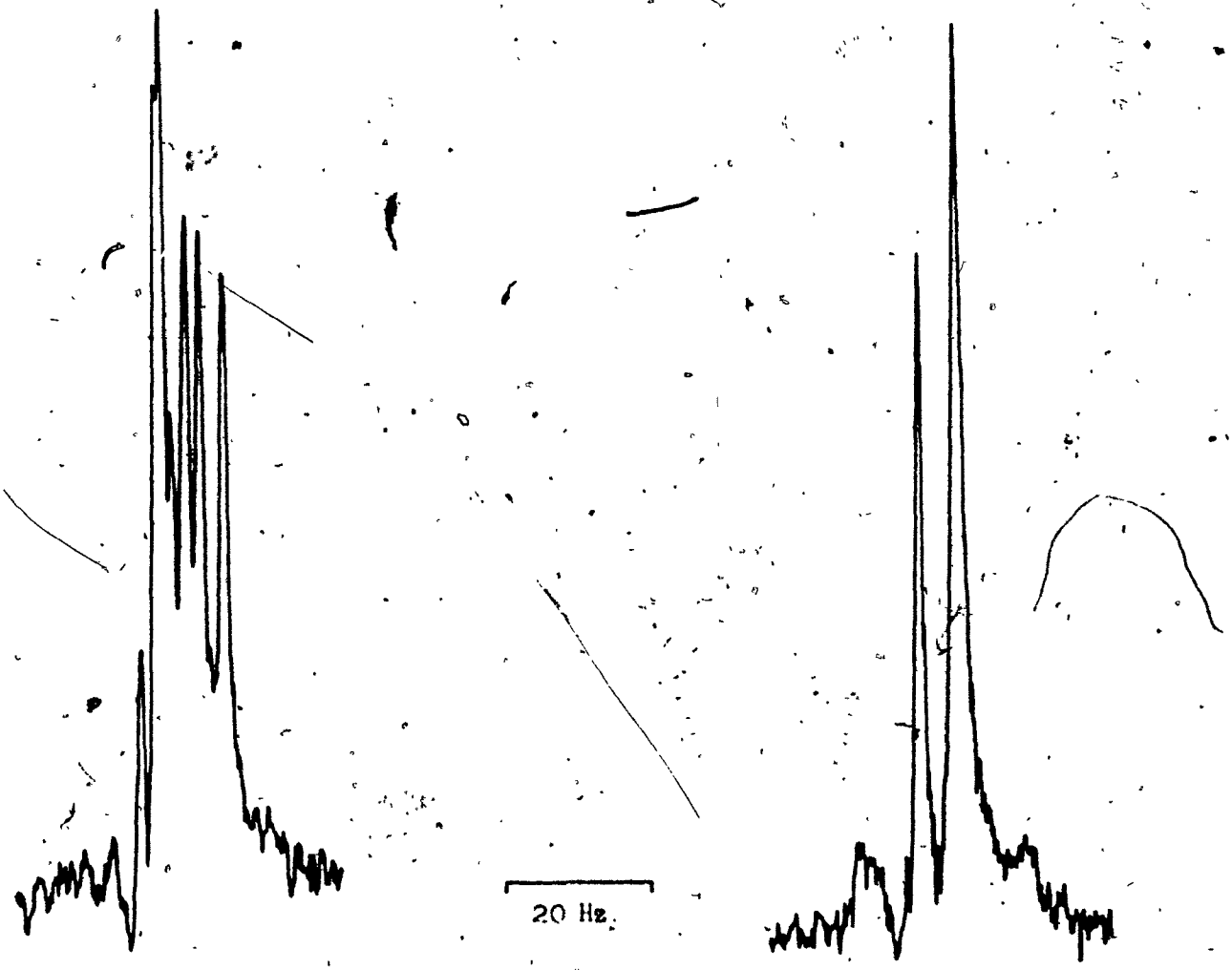
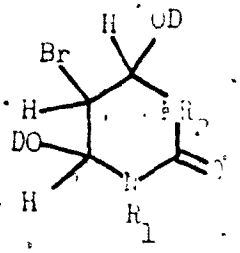
* Structures on p. 32

Fig. 2

P.m.r. spectrum of the 5-proton in the intermediate obtained from the bromination of 1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium hydrogen sulfate



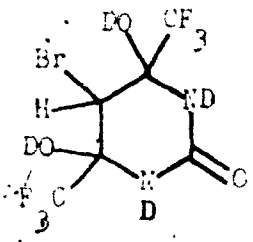


44

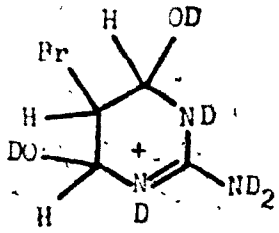
A: $R_1=R_2=H$

B: $R_1=H$, $R_2=Me$

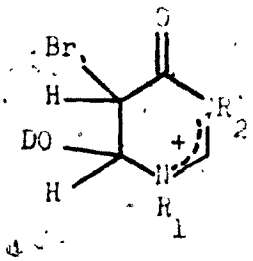
C: $R_1=R_2=Me$



46



48



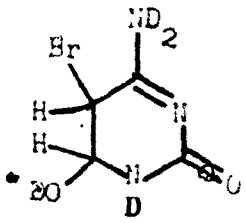
51

A: $R_1=R_2=H$

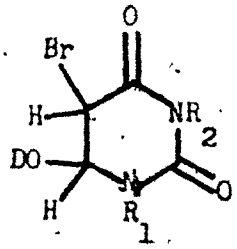
B: $R_1=Me$, $R_2=H$

C: $R_1=H$, $R_2=Me$

D: $R_1=R_2=Me$



58



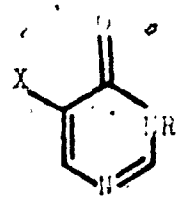
61

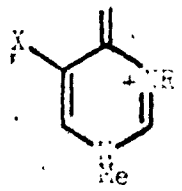
A: $R_1=R_2=H$

B: $R_1=Me$, $R_2=H$

C: $R_1=H$, $R_2=Me$

D: $R_1=R_2=Me$





42

A: R=H
B: R=Me

precipitate which dissolves on treatment with DCl. The p.m.r. spectrum of the resulting solution consists essentially of a doublet at δ 5.42 and a triplet at δ 4.40, which is consistent with the hexahydro-pyrimidine structure 48*. Line positions compare well with those reported by Barbieri for the intermediates derived from the bromination of 2-sulfonamido-pyrimidines in methanol[47-50].

P.m.r. spectra of adducts obtained from the bromination of 4-pyrimidones (49A, X=H) and its N-mono-methyl-derivatives 49B (X=H) and 50 (X=H) show AX quartets for the 5,6 protons, which for 5-deuterio-49B (X=H) collapses to a singlet. The 2H signals which are absent for 2-deuterio-49B (X=H) occur at lower field. These intermediates are likely to be the tetra-hydro-pyrimidine derivatives 51* and kinetic data for the appearance of the corresponding 5-bromo-compounds 42 (X=Br) or 50 (X=Br) may be rationalised in terms of these assignments.

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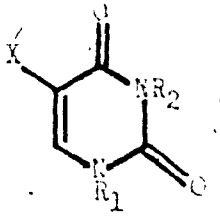
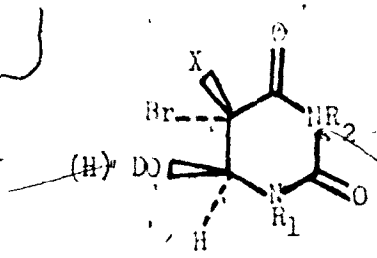
* Structures on previous page



52



53

A: $R_1=R_2=H$
B: $R_1=Me$, $R_2=H$
C: $R_1=H$, $R_2=Me$
D: $R_1=R_2=Me$

Di-oxo- and oxo-amino-pyrimidines

Wang has studied the bromination of uracil (52A, X=H) and its 1,3-dimethyl-derivative 52D (X=H), and has suggested the rapid formation of adducts 53, and the subsequent conversion of these to the aromatic 5-bromo-products 52A or D (X=Br)[53]. Although independent confirmation is available for 1,3-dimethyl-uracil, it has been suggested that uracil itself is directly brominated to a 5,5-dibromo-derivative[54]. The kinetics of appearance of the 5-bromo-derivatives 52 (X=Br) obtained from uracil, its N-mono-methyl-derivatives 52B (X=H) and 52C (X=H) and its 1,3-dimethyl-derivative 52D (X=H) are similar (p.50), and suggest that these are formed from structurally related intermediates. P.m.r. spectra obtained immediately after the addition of bromine show two well resolved doublets which simplify to singlets for 5-deuterio-52A (X=D) and 5-deuterio-52D (X=D), implying that under these conditions, reaction proceeds by way of the intermediates 61*. Previous studies have shown that dihydro-uracils exist in half-chair configurations, the 5 and

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* Structures on p. 32

6 carbon atoms being out of plane [illegible]. The magnitude of the coupling constants obtained from 21 suggests that 6H and 6H adopt equatorial positions, and the spectral values obtained for 21D in the present study compare closely with those reported for 13D (X=H) [illegible]. Adducts obtained from the fluorination of uracils [illegible] or from the photohydration of 5-fluoro-uracil [illegible] show similar spectra.

The conversion of the N-methylated adducts 11C or D to 12 (X=Br) is accompanied in each case by the appearance of a new signal 3-4Hz downfield of the 6H doublet, the intensity of which passes through a maximum and then decreases (Figs. 3, 4) [illegible] Analogous changes occur at higher field, where a similar growth and decay of an additional singlet upfield of the N-methyl lines is observed. Similarly, the intermediates obtained from 5-deuterio-11A or B show a singlet for 6H as well as an additional peak downfield of 6H which increases to a maximum and decreases in the manner described above. Repeated integration with time shows that the area of the 6H signal decreases far more rapidly than that of the 6H peak. However, the combined area of the 6H signal and that of the additional peak downfield of the 6H resonance, maintains a constant ratio to the high field N-methyl signals.

The 6H region then consists of three peaks, a doublet corresponding to 6H in 13, as well as a singlet at lower field. It is unlikely that the latter peak originates from ring-opened products, since the reaction of 21D (X=H) with bromine which leads to the 5-bromo-derivative 12D (X=Br)

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* Structures on p. 32, pp. 36, 37

Fig. 3

P.m.r. spectrum of 5H and 6H in the adduct obtained immediately after the addition of bromine to 1-methyl-uracil

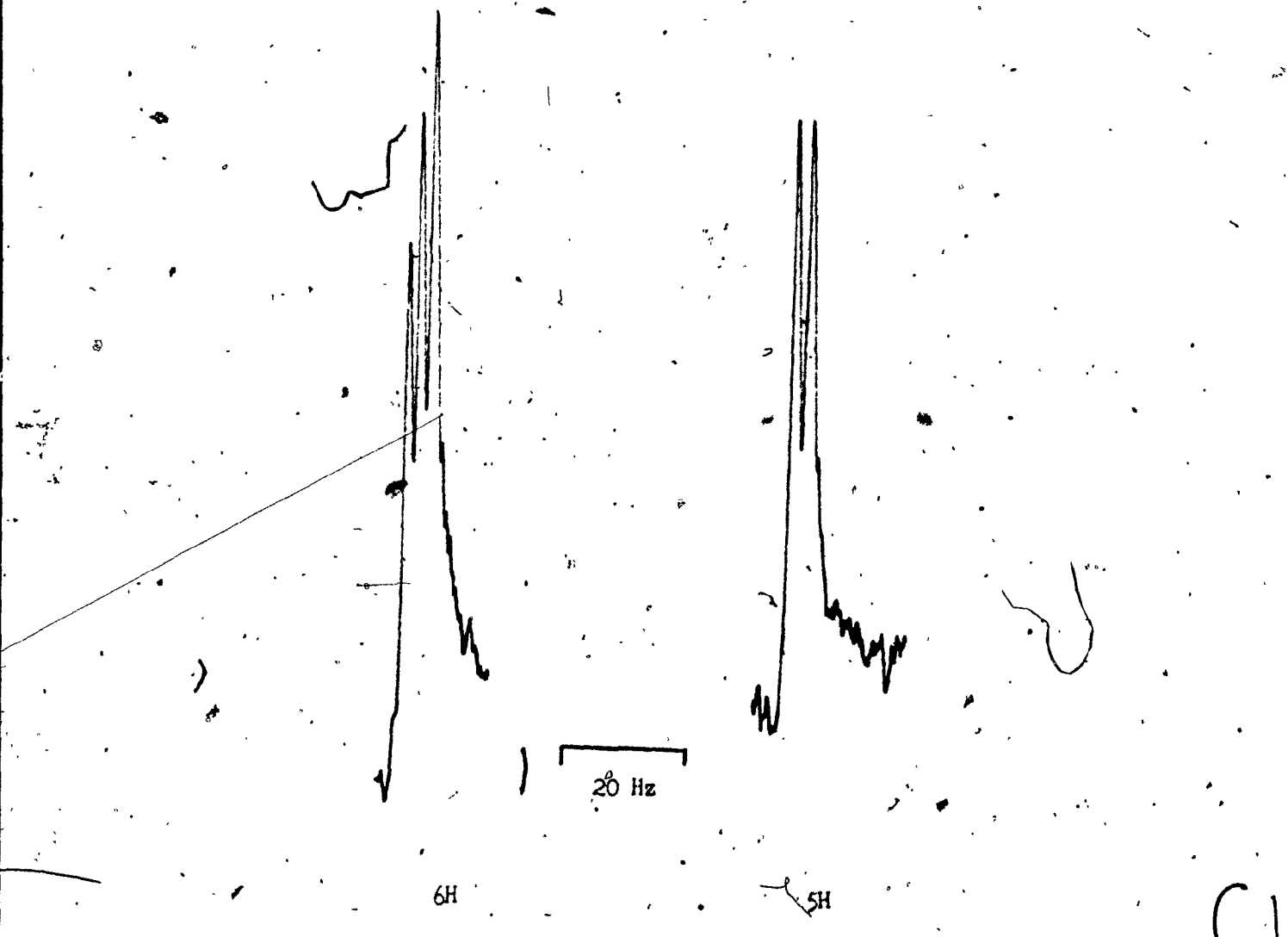
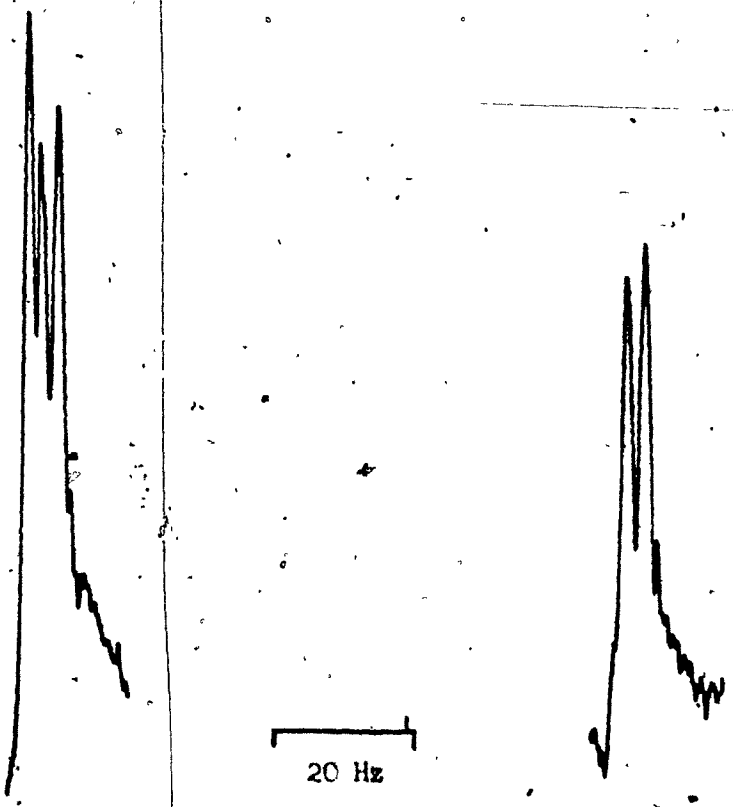
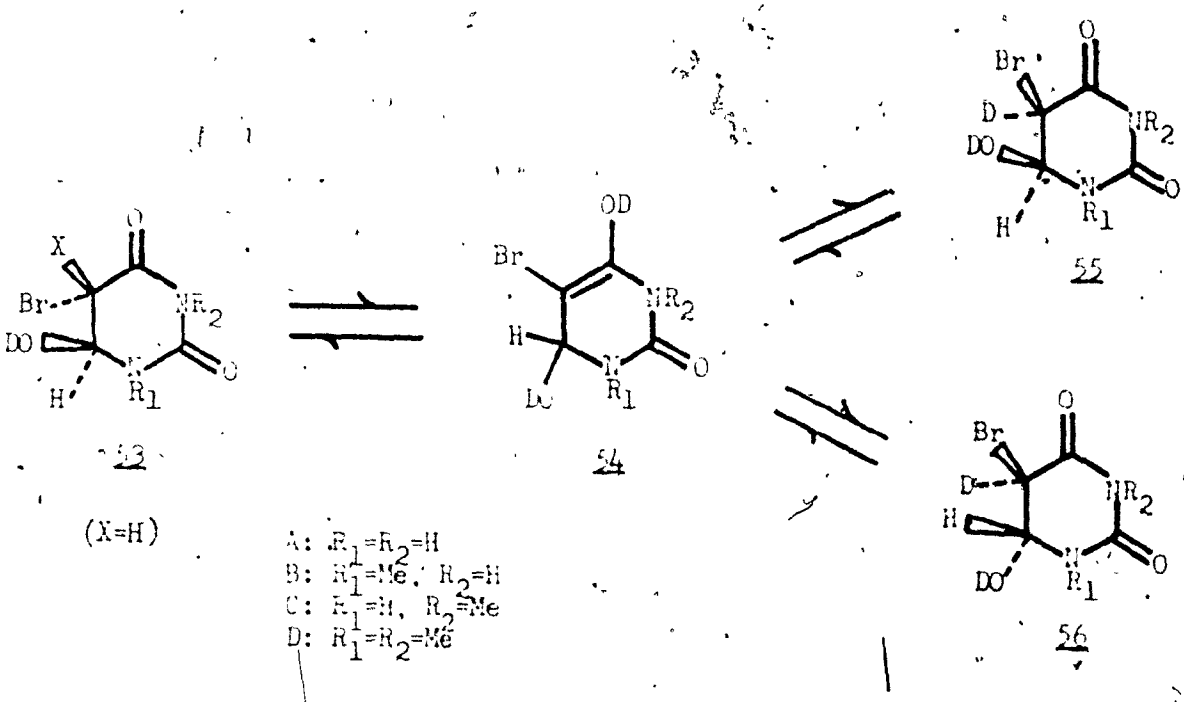


Fig.4

P.m.r. spectrum of 5H and 6H in the adduct obtained four hours after the addition of bromine to 1-methyl-uracil





has been shown to proceed essentially to completion [93]. Also, the acid-catalysed hydrolysis of dihydro-uracil occurs via rupture of the N_3-C_4 bond to give a β-ureido-propionic acid [104]. Hence, if the additional singlet arises from a cyclic species related to 53, the likely structures for the latter would be 54 or 55.

Structure 54 is excluded since the first-order rate of appearance of the 5-bromo-derivatives 52 (X=Br) is subject to an appreciable isotope effect for the 5-deuterio-substrates (p.53). This observation is inconsistent with any appreciable build-up of intermediates such as 54. The additional peak is therefore assigned to structure 55. This implies that conversion of the trans-adduct 53 to the aromatic products is accompanied by slow diastereomerisation to the exchanged cis-adduct 55* through the intermediacy of 54.

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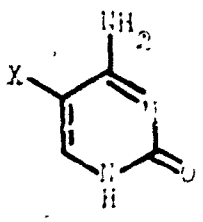
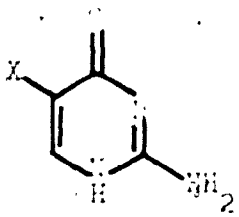
* The diastereomerisation of deoxy-uridine photohydrates has been reported [105]

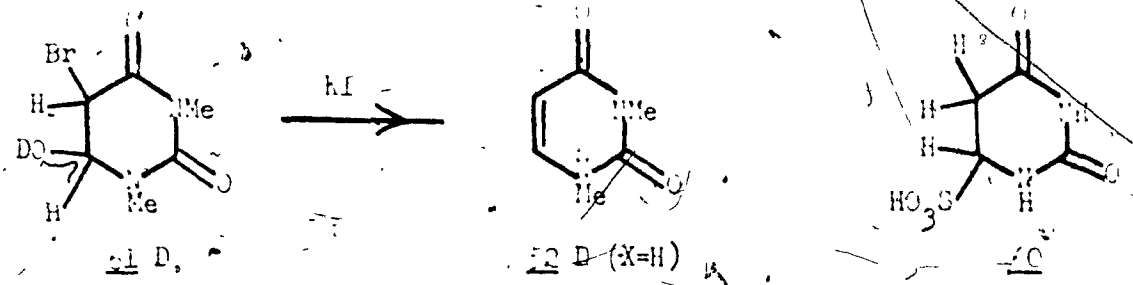




For the parent compound 44A (X=H) exchange of ¹H occurs to a lesser extent, and the intensity of the low-field singlet is consequently minimised. However, a fourth peak appears midway between the ¹H doublet, reaches a maximum intensity, and decays. This in all probability arises from the trans-deuterio-product 44. It is not entirely clear why both cis and trans-exchanged products are obtained from 43A, while the N-methylated derivatives form the trans-product exclusively. Although an attempt was made to follow the kinetics of exchange, the relatively small differences in line position, and the ease with which the 5-bromo-products crystallise out of solution prevented accurate measurement.

The reaction of cytosine (57; X=H) with bromine leads to an intermediate whose p.m.r. spectrum consists of a simple AB quartet, which is easily understood in terms of structure 58 (p. 32). Intermediate formation however, could not be detected in the bromination of isocytosine (59; X=H), which converted rapidly to the 5-bromo-derivative 59 (X=Br).

Treatment of the adducts identified in the present study with potassium iodide led to the regeneration of the starting pyrimidines. Thus, the reaction of 61D with potassium iodide gave 1,3-dimethyl-uracil (structures overleaf). Precedent for reactions of this type has previously been established. For example, the 5,5-dibromo-derivatives of barbituric acid



51 D, 52 D (X=H) 60

and uracil convert easily to their mono-bromo-derivatives[1]. It was hoped that the reversal of the uracil adducts would confirm the occurrence of isotope exchange at the 5-position. However, the trans-adduct reversed at a much faster rate than did the cis isomer, as evidenced by the faster disappearance of the 6H doublet in 53 with respect to the singlet attributed to 55.

A correlation may be made between the the structure and stereochemistry of these intermediates with those derived from the thermal addition of bisulfite ion to uracil and cytosine derivatives[104-113]. Thus trans-addition of sodium bisulfite to uracil leads to the adduct 60 which may be reversed to uracil also with trans stereochemistry by the action of base[106]. Isotope exchange from these and other related adducts have previously been recorded[114,115,116]. The photohydrates of uridine and cytidine undergo deuteriation in heavy water, and Hayatsu has recently shown that deuterium incorporation into the bisulfite adduct of cytidine-5'-phosphate occurs in neutral D_2O solutions[110].

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*Structures on p. 38.

KINETIC STUDIES

4-Pyrimidone

In aqueous solutions, the long-wavelength u.v. absorption band of 4-pyrimidone decreases rapidly on addition of bromine, two mole equivalents of the latter being required for complete elimination of all spectral absorptions above 210 nm.. In acidic media (0.1 - 1. M H_2SO_4), the reaction is perceptibly slower, and the decrease in absorbance is accompanied by shifts to longer wavelengths. Measurement of the differential spectrum of the reaction mixture by use of a reference containing substrate solution shows that the former contains appreciable quantities of the 5-bromo-derivative 61 (R_1=R_2=H). At higher solvent acidity (4.0 M H_2SO_4), the absorbance decrease corresponding to the bromination of 4-pyrimidone is followed by a relatively slow increase arising from the formation of the product 63 (R_1=R_2=H). Evidence obtained from p.m.r. studies (p.30) suggests the intermediate formation of the tetrahydro-pyrimidine 62 (R_1=R_2=H), and the reaction sequence may be outlined as shown on the following page.

Spectrophotometric titration of the 5-bromo-4-pyrimidone 63 (R_1=R_2=H) with bromine shows a 1:1 relationship, and although product identification was not pursued, the dibrominated derivative is likely to be the adduct 64 (R_1=R_2=H).

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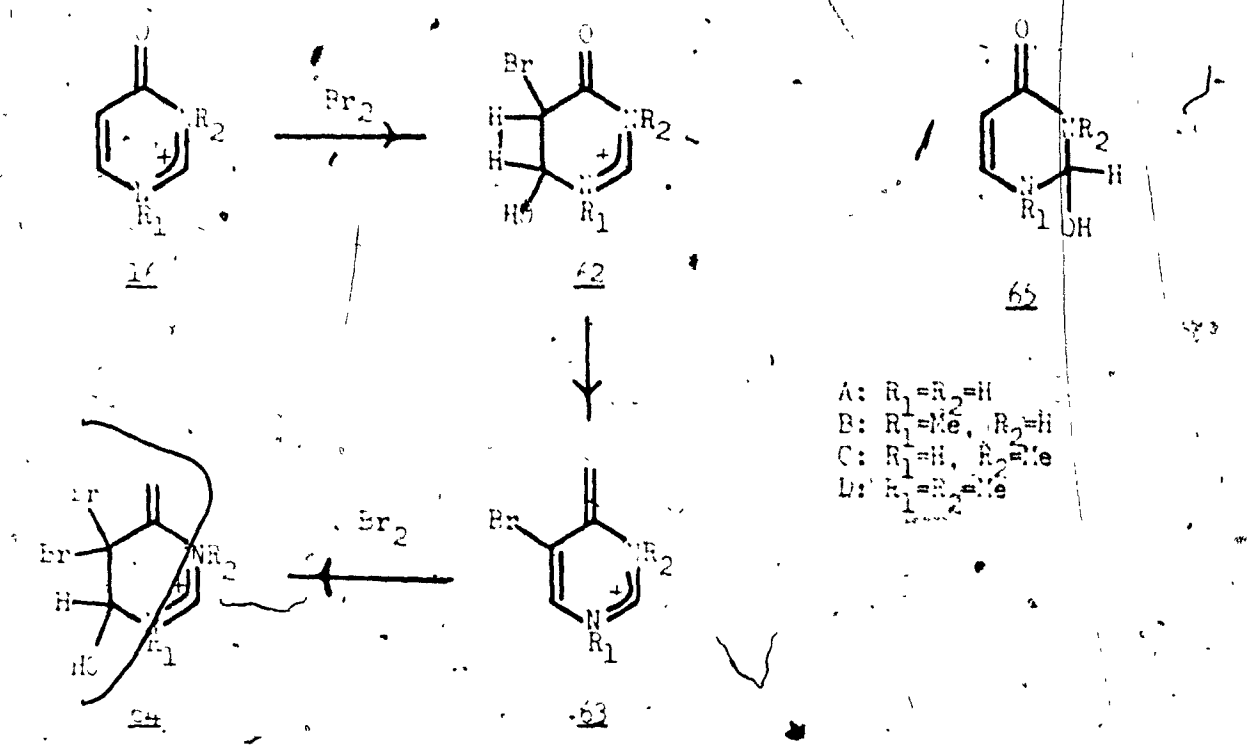
* Structures overleaf



16 62 65

64 63

The inverse dependence of the rate of bromination of 16 on acidity implies that the substrate undergoes reaction via a free base form. For the quaternary ion 16 (R_1=R_2=Me) this is almost certainly the pseudo-base 65 (R_1=R_2=Me), (pseudo-base formation from 63 is discussed in the Appendix) and thus by analogy, for the parent substrate 16 (R_1=R_2=H) and the 1-mono-methyl-derivatives 16 (R_1=H,R_2=Me), the covalent hydrates 65 (R_1=R_2=H), 65 (R_1=H,R_2=Me) and 65 (R_1=Me,R_2=H) respectively. The formation of 62 from 16 is then represented by the pathway 16 → 65 → 69 → 63 → 62 (p.44).

Under conditions where the concentration of 16 and bromine are of comparable magnitude, the initial bromination step 16 to 62 does not reach completion before appreciable conversion of 62 to 63 occurs, and thus complex kinetic behaviour for the formation of 63 is encountered. However, in the presence of an excess of 16, the rate of disappearance

of bromine is increased relative to the rate of aromatisation of 62 to 63, and the latter process may be analysed by first-order procedures if the initial half-life of the reaction is neglected. Data obtained by this technique for the parent compound 14 (R_1=R_2=H), its 1-mono-methyl derivatives 16 (R_1=H, R_2=Me) and 17 (R_1=Me, R_2=H), and the dimethyl salt 16 (R_1=R_2=Me) are collected in Table 6 (p. 45), and plotted against the acidity function H_0 in Fig. 6 (p. 46).

The reaction of bromine with 62 is rapid, and the product 69 may either be deprotonated to 70 or be attacked by water to form the adduct 68*. This partitioning of 69 is expected to be governed by the ratio k_4:k_5. The intermediates obtained from 4-pyrimidone, its 3-methyl and N,N-dimethyl-derivatives are preferentially converted to the dihydro-pyrimidine derivatives 62 via 68, the direct formation of 70 being immeasurably small. However, for the 1-methyl-compound, two distinctly different processes are observable. A sharp increase of absorption appropriate to 71 (R_1=Me) is noted immediately after mixing, and this is followed by a relatively slow appearance of 71 (R_1=Me). The rate constants k_4 and k_5 must therefore be more comparable for the 1-methyl-derivative, and although accurate measurement of product distribution is prevented by the errors associated with mixing, it is estimated that their ratio approximates unity.

The aromatisation of 62 to 63 is inverse acid catalysed, and slopes obtained from log k_{obs} vs. H_0 plots range from 0.36 for the 1-methyl

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* Structures overleaf

Fig. 5

Mechanism of bromination of 4-pyrimidone

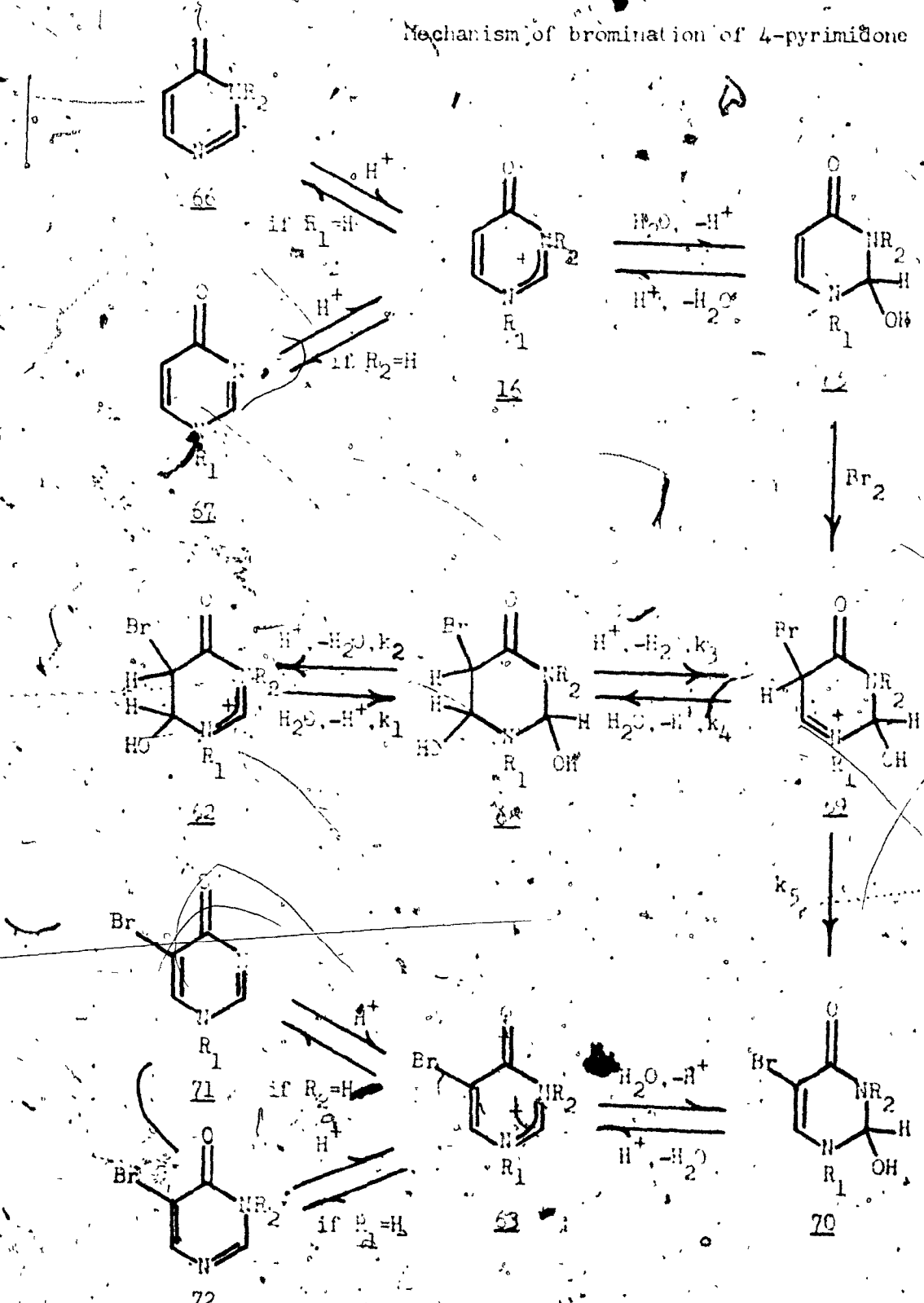


Table 4

Variation of the rates of appearance of the 5-bromo-4-pyrimidones with H_0

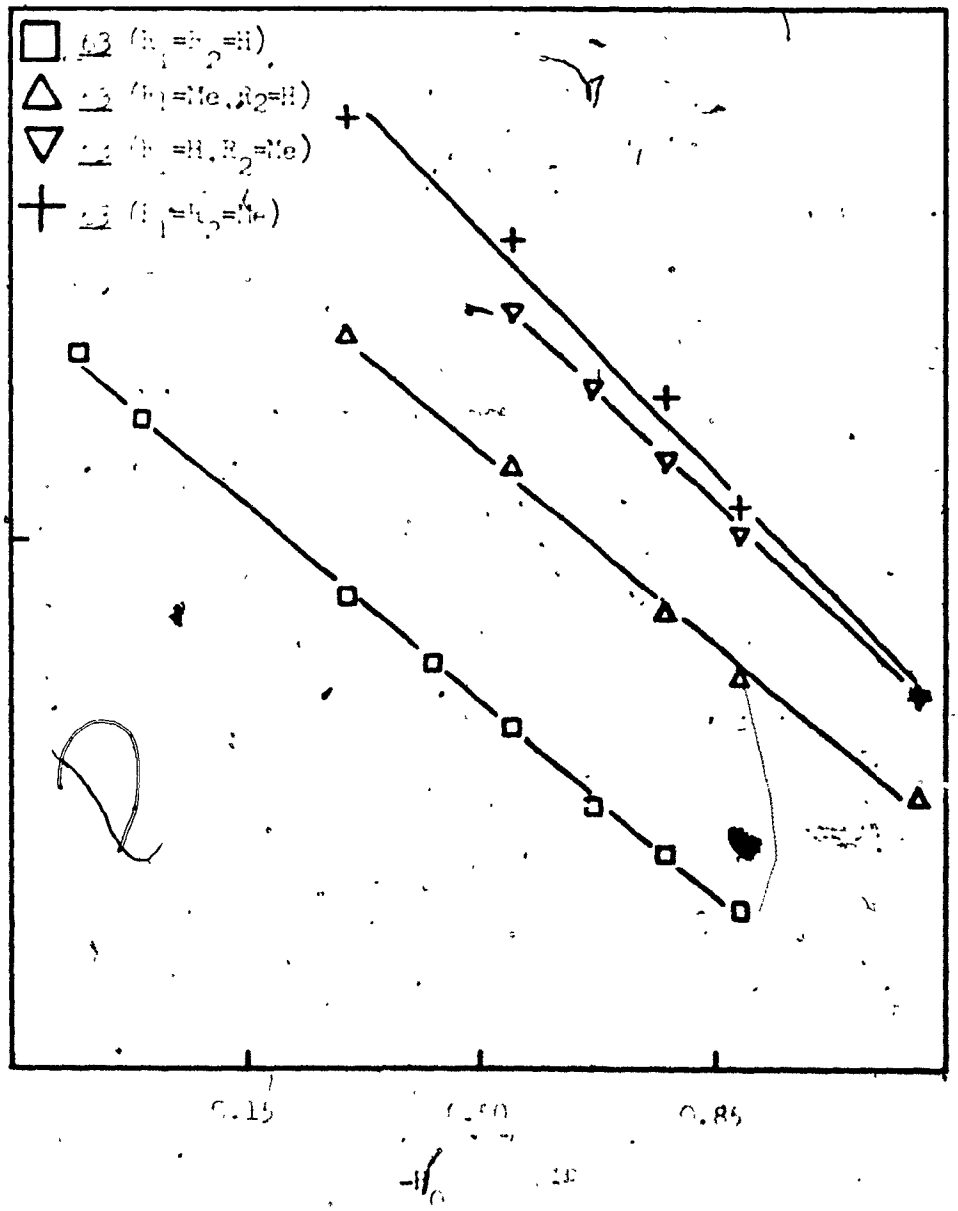
H_2SO_4 (N)	H_0	$k \times 10^3$ sec^{-1} 63 (R_1=R_2=H)[a]	63 (R_1=Me, R_2=H)[a]	63 (R_1=H, R_2=Me)[b]	63 (R_1=R_2=Me)[a]
1.00	0.10	18.7			
1.20	0.01	17.0			
2.00	-0.30	13.0[c]	19.2	26.8	
				14.0[c,d]	
2.40	-0.43	11.7			
2.80	-0.55	10.6	15.7	22.2	20.0
3.20	-0.67	9.42			17.8
3.60	-0.78	8.77	12.6	17.5	16.0
4.00	-0.89	8.03	11.4	14.8	14.2
5.00	-1.16		9.52	11.1	11.1
					5.95[c,d]

[a] Average of four determinations, [b] eight determinations, [c] six determinations

[d] refers to the 5-deuteric-substrate

Fig. 6

Variation of the rates of appearance of the 5-bromo-4-pyrimidones with H_0 ~ 1 :



derivative to 0.45 for the 3-methylated compound (Fig.6, p.46). These values cannot be interpreted quantitatively since the acidity functions appropriate to these derivatives are not available. However, the similarity in the acidity dependence of the reaction rates strongly suggests that the parent pyrimidine and its N-methyl derivatives undergo reaction by essentially the same mechanism.

The absence of a significant isotope effect for the conversion of 5-deuterio-12 (R_1=H, R_2=Me) (k_H/k_D = 1.58) and 5-deuterio-12 (R_1=R_2=Me) (k_H/k_D = 1.57) to 13 (R_1=H or Me, R_2=Me) suggests that the loss of 5H is either only partially rate-determining, or that the deprotonation has an early transition state. Furthermore, the rate of formation of 13 is significantly retarded in D_2SO_4 (the rate of appearance of 13 (R_1=H, R_2=Me) has a rate constant of 1.37×10^{-2} sec^{-1} in 2.10N D_2SO_4 (average of four determinations), from which k_{H_2O}/k_{D_2O}=1.67), implying that the rate controlling step either involves a solvent molecule, or is preceded by a kinetically important proton transfer, or possibly both [117-119].

The most attractive rationale for these observations appears to involve attack of water on 62 to form the intermediate 68, which, after protonation and dehydration to 69, converts to 70. For the mechanism shown in Fig. 5 (p.44),

$$\frac{d[68]}{dt} = -k_1[62] + k_4[69] - k_2[68]h_X - k_3[68]h_Y$$

and

$$\frac{d[69]}{dt} = k_3h_Y[68] - (k_4 + k_5)[69]$$

where h_X and h_Y are defined by the equations

$$H_X = -\log h_X, \quad \text{and} \quad H_Y = -\log h_Y,$$

and where H_X and H_Y are acidity functions appropriate to the conversions 68 → 62, and 68 → 69 respectively.

If 62 and 69 are present in steady-state concentrations,

$$\underline{62} = \frac{k_1[\underline{62}] + k_4[\underline{69}]}{k_2 h_X + k_3 h_Y} \qquad \text{---(2)}$$

and

$$\underline{69} = \frac{k_3 h_Y[\underline{68}]}{k_4 + k_5} \qquad \text{---(3)}$$

ie. the rate equation is given by

$$\text{rate} = k_{obs}([\underline{62}] + [\underline{68}] + [\underline{69}]) = k_5[\underline{69}] \qquad \text{---(4)}$$

or

$$k_{obs} = \frac{k_1 k_3 k_5 h_Y}{k_1(k_4 + k_5) + k_2 h_X(k_4 + k_5) + k_3 h_Y(k_1 + k_5)} \qquad \text{---(5)}$$

Now, $k_2 h_X \gg k_1$, ie. under equilibrium conditions $[\underline{62}] \gg [\underline{68}]$,

$$\text{and } k_{obs} = \frac{k_1 k_3 k_5 h_Y}{k_2 h_X(k_4 + k_5) + k_3 h_Y(k_1 + k_5)} \qquad \text{---(6)}$$

If the acidity functions appropriate to the formation of 62 and 69 from 68 are identical, ie. $H_X = H_Y$, the eqn. (6) reduces to

$$k_{obs} = \frac{k_1 k_3 k_5}{k_2(k_4 + k_5) + k_3(k_1 + k_5)} \qquad \text{---(7)}$$

On the other hand, if H_X is more sensitive to changes in acidity than is H_Y, an inverse dependence of rate on acidity is to be expected. A quantitative evaluation of the data in Table 4 (p.45) cannot be made on the basis of eqn. (6) since values for H_X and H_Y are unavailable. However, the above analysis qualitatively accounts for the observed results, and it is concluded that the reaction follows the mechanism outlined in Fig. 5 (p.44).

Thus, the bromination of 2-oxo- and 4-oxo-pyrimidines proceeds via essentially similar mechanisms. Initial attack of bromine occurs rapidly on neutral covalent adducts to lead to stable tetrahydro- or hexahydro-pyrimidine intermediates, which undergo slow elimination to yield the substituted products. These in turn react further with bromine to give dibromo-pyrimidine derivatives. The kinetics of this latter reaction have been measured, and are discussed in the Appendix (p.90).

Uracil[120]

Owing to their biochemical importance, the reactions of the uracils (19)* have come under extensive investigation[121]. Early studies on the bromination of these pyrimidines have suggested that the reaction proceeds to the dibromo-derivatives 81[122-125]. It was subsequently proposed that under synthetic conditions uracil[53,105] and 1,3-dimethyl-uracil[53] react rapidly with bromine to yield intermediates proposed to be 74A,D*, which convert to their corresponding 5-bromo-uracils. These in turn react rapidly with bromine to give the 5,5-dibromo-derivatives 81*, which revert to the 5-bromo-derivatives under the influence of strong acid. This view was criticised by Moore and Anderson[54] who found that whereas 1,3-dimethyl-uracil and uridine (19; R_1=ribose, R_2=H) require equivalent quantities of bromine for complete reaction, as determined by spectrophotometric and potentiometric titration in an acetate buffer of pH 4.76, uracil itself reacts rapidly with two mole equivalents of bromine. The difference in reactivity for the latter was attributed to the direct formation of the 5-bromo-uracil 79A, and its subsequent bromination to the dibromo-derivative 81A, the ultimate conversion to 5-bromo-uracil being attributed to the bromination of uracil by the dibromo-derivative 81A. Under more strongly acidic conditions, however, the intermediates 74 may be directly observed by p.m.r. spectroscopy (p. 34), and it seems likely that the extent of bromination of uracil is dependent upon the acidity of the medium.

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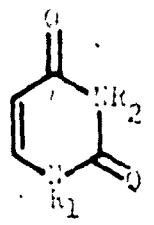
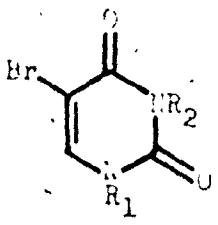
* Structures overleaf



78



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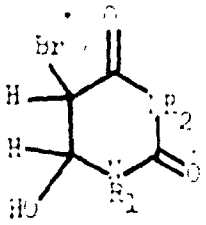
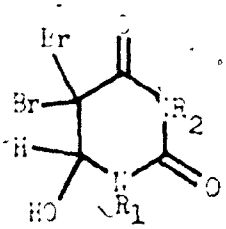


74



81

A: $R_1=R_2=H$; B: $R_1=Me, R_2=H$; C: $R_1=H, R_2=Me$; D: $R_1=R_2=Me$.

Confirmation of this is available from the titration behaviour of the uracils with respect to bromine in both strongly and weakly acidic solutions. These measurements were made by adding aliquots of a solution of bromine to measured volumes of substrate solution, the spectrum of the resulting solution being scanned immediately after mixing. The usual titration procedure which requires incremental addition of bromine to the reaction mixture could not be used, since any 5-bromo-product 79 formed during titration would react further with bromine. This is of particular importance at higher acidity, where the rates of formation of 79 are large enough to cause significant error.

Data obtained from these measurements are summarised in Table ? (p.52). For the N-1 substituted uracils, the long wavelength u.v. absorption bands collapse smoothly on addition of equivalent quantities of bromine. For 3-methyl-uracil (as for uracil itself)[54], stepwise addition of bromine in solvents of low acidity is accompanied by shifts to longer wavelengths as well as by decrease in absorption, suggesting the rapid formation of 5-bromo-3-methyl-uracil, and the simultaneous bromination of 3-methyl-uracil and 5-bromo-3-methyl-uracil. At higher acidities, both

Table 7

Results for the titration of the uracils with bromine

	[Substrate]:[Br_2] ref.	
	Low acid (≤ 0.1 N H_2SO_4)	High acid (4.00 N H_2SO_4)
Uracil	1:2 [54]	1:1
1-Methyl-uracil	1:1	-
3-Methyl-uracil	1:2	1:1
1,3-Dimethyl-uracil	1:1 [54]	-
Uridine	1:1 [54]	-
6-Methyl-uracil	1:2	-

uracil and 3-methyl-uracil react with only one equivalent of bromine, no change in wavelength being apparent. This implies that where N-1 is substituted, or in strong acids, where in some intermediate it may be predominantly protonated, rapid conversion to the 5-bromo-derivatives is suppressed.

The rates of appearance of the 5-bromo-products 72 from the adducts 74 were measured spectrophotometrically. At constant acid concentrations, first-order kinetics were observed, and the rate constants listed in Tables 8 (p.54) and 9 (p.55) were obtained. These data are plotted against $[H_3O^+]$ in Fig. 7 (p.56) and the acidity function H_C in Fig. 8 (p.57) respectively. The linear dependence of the observed rate on acidity suggests an acid-catalysed elimination from 74. Furthermore, the observed isotope effects (4.32 for deprotonation from 74A and 3.42 for loss of 5H in 74D) identify the cleavage of the C_5 - H bond in the intermediate 74 to be rate-determining.

These results are in good general agreement with those obtained for the dehydration of uracil photohydrates. The reconstitution of 1,3-dimethyl-uracil from its photohydrate is acid-base catalysed [66,67], and in the acidity range of pH 1-5 occurs with $k = 3.24 \times 10^{-2}$ M^{-1} sec^{-1} at 20° and with an activation energy of 22.4 Kcal mole^{-1}. Similarly, 5-methyl-6-hydroxy-dihydro-uracil 82 (X=H), which was prepared by the reduction of 82 (X=Br), decomposed to thymine (5-methyl-uracil) with

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* Structures on p. 58

Table 8

Variation of the rates of appearance of the 5-bromo-uracils with $[H_3O^+]$

H_2SO_4 (N)	$[H_3O^+]$ (M)	$k \times 10^3$ (min^{-1})*			
		uracil	1-methyl uracil	3-methyl uracil	1,3-dimethyl uracil
0.100	0.059	0.483		0.826	
0.250	0.135	0.656			0.405
0.300	0.160	0.681		1.37	
0.500	0.261	0.861	0.498	1.68	0.907
0.700	0.361			2.06	
0.750	0.386	0.987	0.809		1.54
0.850	0.436		0.908		1.84
1.00	0.511	1.15	1.11	2.64	2.18

* Average of two determinations

Table 9

Variation of the rate of appearance of the 5-bromo-uracils with H_0.

H_2SO_4 (N)	H_0	$k \times 10^3$ (min^{-1})[a]			
		uracil	1-methyl uracil	3-methyl uracil	1,3-dimethyl uracil
1.20	0.01	1.30	1.43	2.95	3.11
1.60	-0.15	1.74			5.08
2.00	-0.30	2.11	3.29	5.61	7.16
					2.12[b,c]
2.40	-0.43	2.58			10.6
3.00	-0.61	3.76			16.9
3.60	-0.78	4.83	11.4	13.1	
4.00	-0.90	5.88	15.4	17.7	37.1[d]
		1.36[b,d]			10.6[b]

[a] Average of two determinations unless otherwise specified; refers to the 5-deuterio-substrate; [b] single determination; [c] three determinations; [d]

Fig. 7

Variation of the rate of appearance of the 5-bromo-uracils with $[H_3O^+]$

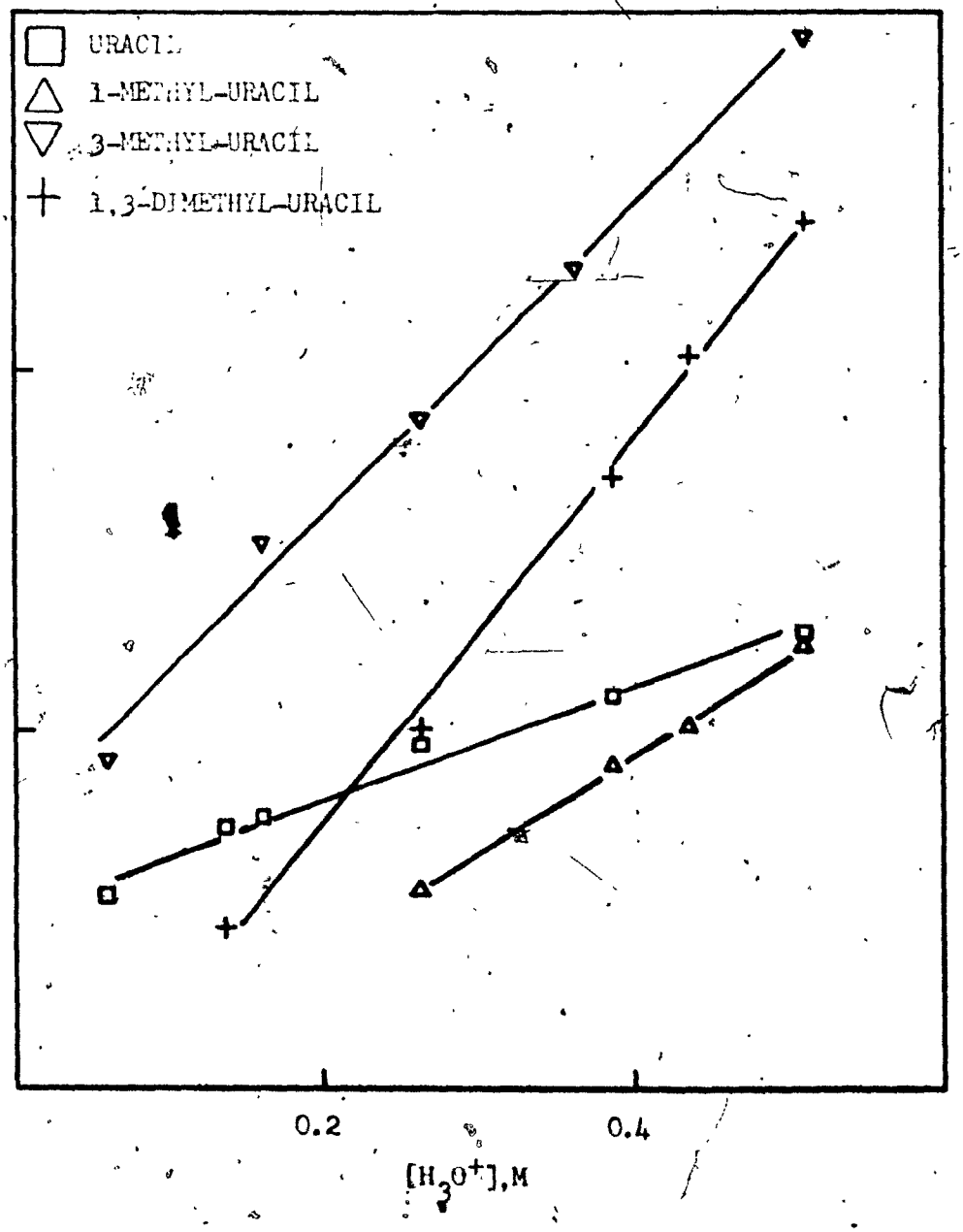
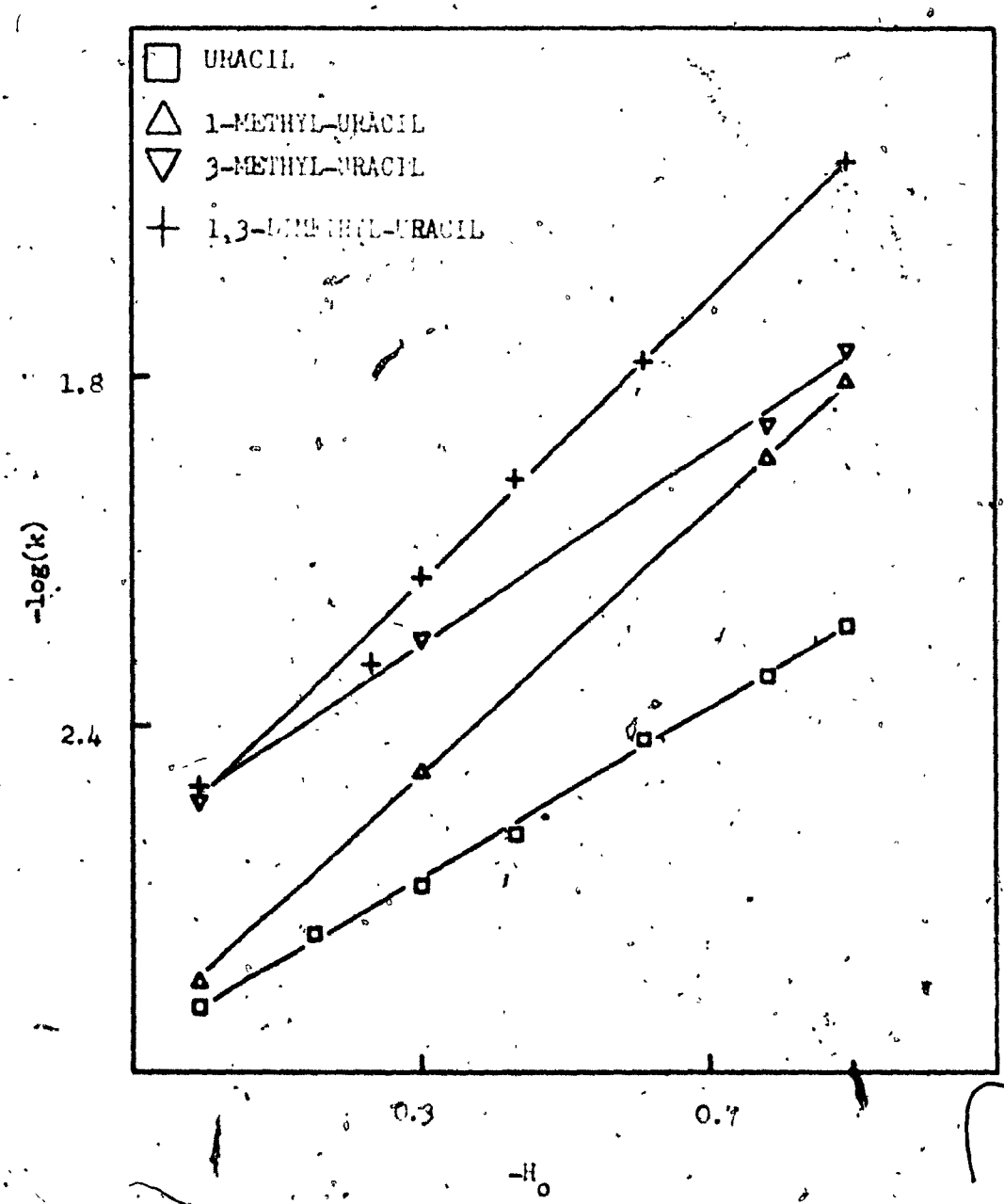
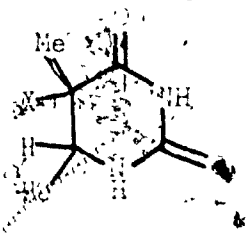


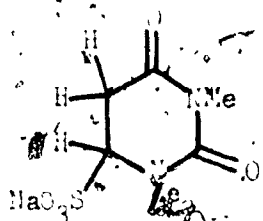
Fig. 8

Variation of the rate of appearance of the 5-bromo-uracils with H_o





82



83

a half-life of approximately 8 hours at pH 7.2[127]. This finding appears to invalidate the proposal that the inability to detect photohydrates of thymine is a consequence of the rapid reversal of the adduct 82 (X=H)[128].

The similarities in isotope effect between the dehydration of the adducts obtained from bromination and those derived from photosensitization further illustrate the related mechanisms involved in these processes. The photohydrate of uridine reverses 1.6 times as fast as its photodeuterate at a pH of 1.6[129] and k_{H_2O}/k_{D_2O} for the photohydrate reaction is measured to be 6.5[122]. Wacker[130] and others[131] have observed significant isotope effects for the aromatisation of 5-deuterio- or tritio-uracil photohydrates and recent studies on the base-catalysed desulfonation of 83 have shown that 83 is converted to 1,3-dimethyl-uracil 4.10 times faster that its 5-deuterio-derivative[132].

Examination of Figs. 7 (p.56) and 8 (p.57) shows that these rate profiles may be categorised into two different classes which are differentiated by the presence or absence of a methyl substituent on N-1. Class 1 profiles which are comprised of uracil and 3-methyl-uracil are characterised by large positive intercepts on the Y-axis as shown in

Fig. 7, and have similar slopes (0.73 for 74A and 0.84 for 74C) against H_0 in Fig. 8. The presence of these intercepts suggests an acid independent process ie.

74 ⇌ 75 ⇌ 77 → 78 (Fig. 9, p.66)

on species such as 77A,C which exist in equilibrium with the adducts 74A,C.

Class 2 profiles appear to intersect with the positive 'hydronium ion' axis in Fig. 7 and the slopes obtained from Fig. 8 are of comparable magnitude ie. 1.14 for 74b and 1.22 for 74b. The apparent negative intercepts in Fig. 7 suggest a small contribution from a process having a non-linear rate dependence on acidity. This may easily be explained if additional intermediates such as 74a,b are taken into account. Thus, if elimination from both the cation 74 and the dication 77 be considered, then

$$\text{rate} = k_{obs}([74] + [75] + [76] + [77]) = k_1[74] + k_2[77]$$

where $K_1 = \dfrac{[74][H^+]}{[76]}$; $K_2 = \dfrac{[74][H^+]}{[75]}$; $K_3 = \dfrac{[75][H^+]}{[77]}$

and k_1 and k_2 represent the rate constants defined in Fig. 9 (p.66).

On substitution,

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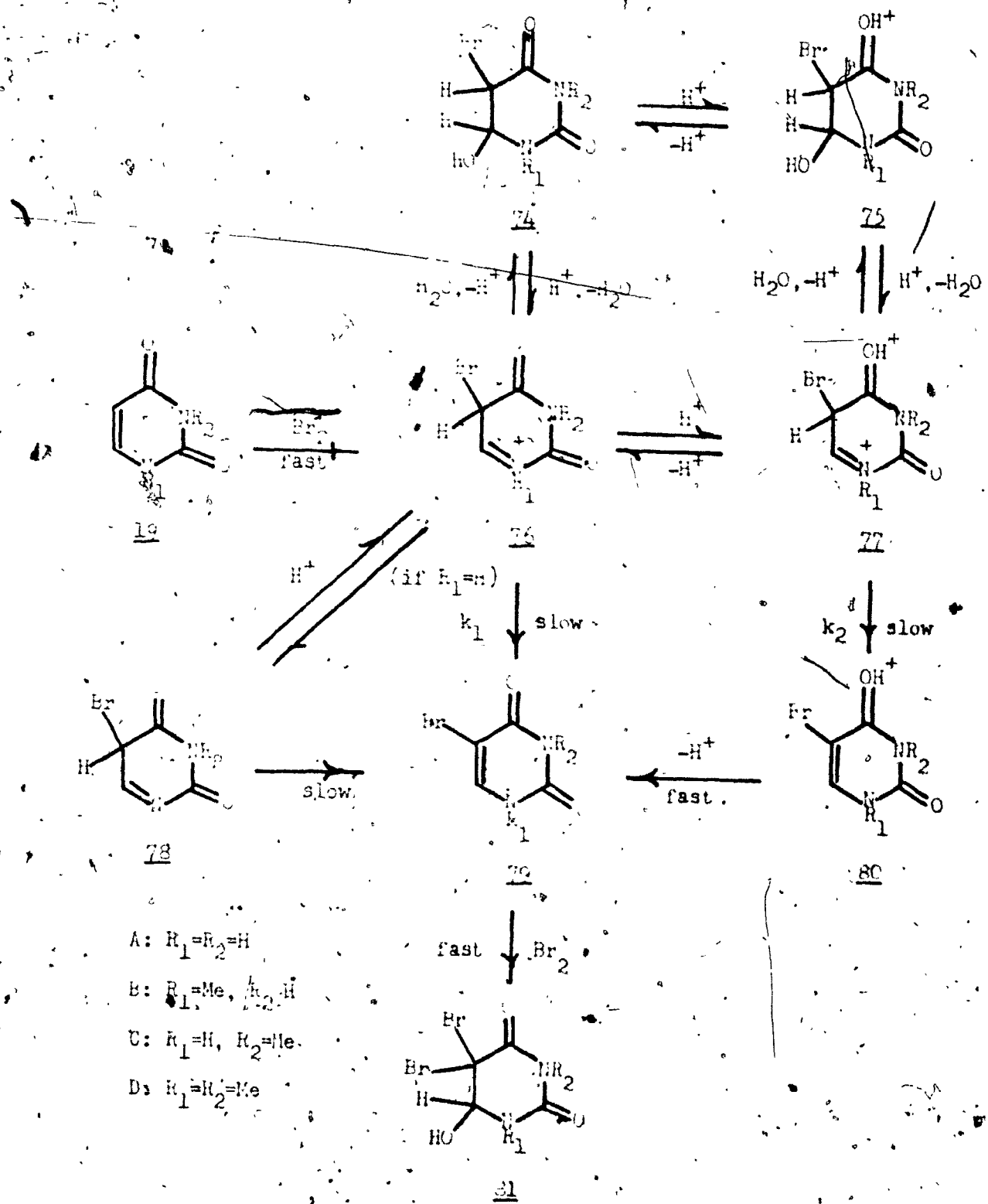
* Structures overleaf

Fig.

Mechanism of bromination of the uracils



$$k_{obs}\left(\frac{[76]K_1}{[H^+]} + \frac{[76]K_2}{K_2} + [76] + \frac{[76]K_1[H^+]}{K_2K_3}\right) = k_1[76] + \frac{k_2[76]K_1[H^+]}{K_2K_3}$$

ie. $$k_{obs} = \frac{k_1K_2K_3[H^+] + k_2K_1[H^+]^2}{K_1K_2K_3 + K_1K_3[H^+] + K_2K_3[H^+] + K_1[H^+]^2} \quad --- (8)$$

Now, K_1, K_2 or $K_3 \gg [H^+]$, since under the present conditions of acidity; it is probable that $[\underline{74}] \gg [\underline{76}]$, $[\underline{74}] \gg [\underline{76}]$ and $[\underline{74}] \gg [\underline{77}]$.

Thus, $$K_1K_2K_3 \gg (K_2K_3[H^+] + K_2K_3[H^+] + K_1[H^+]^2)$$

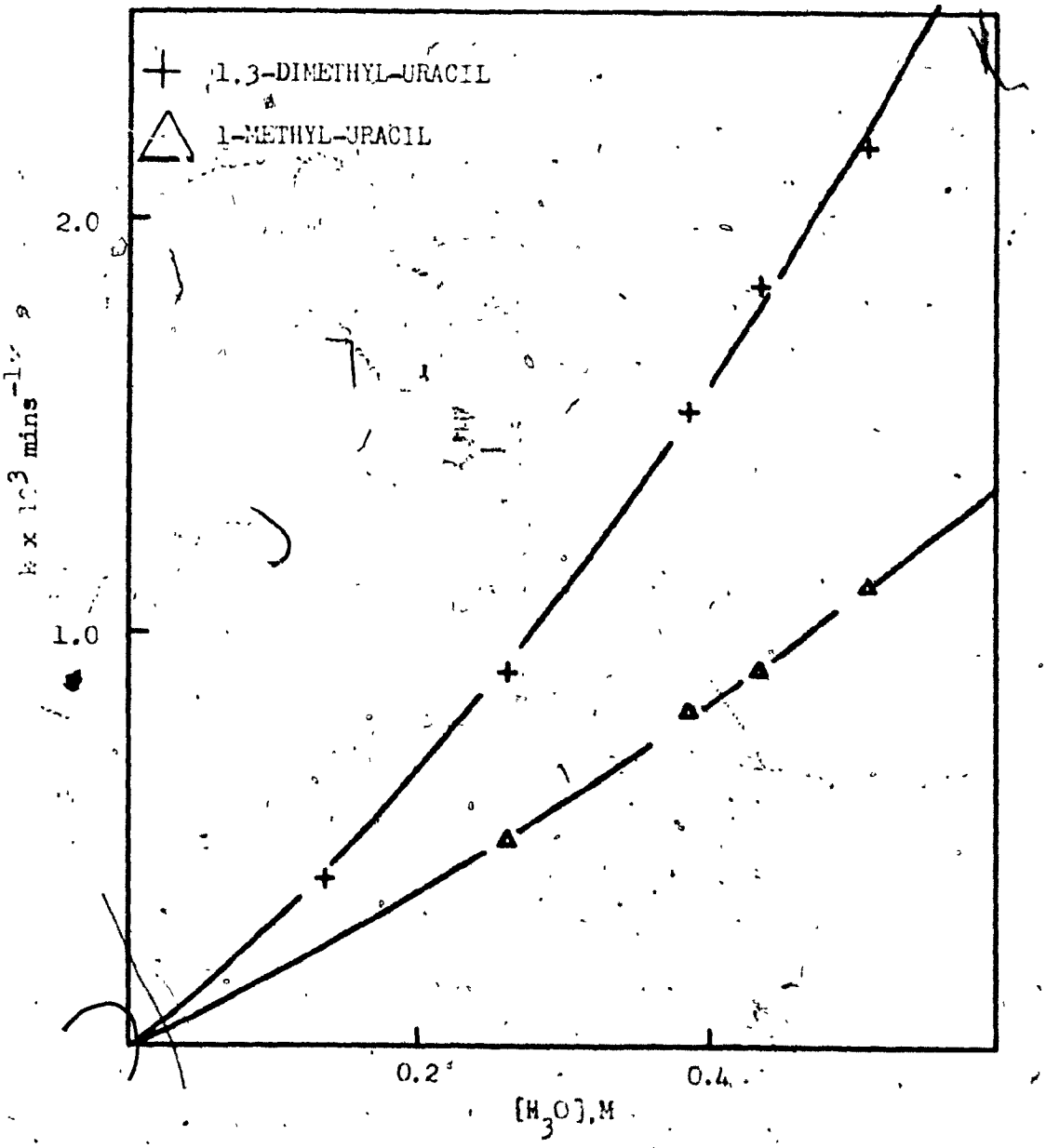
and $$k_{obs} = \frac{k_1[H^+]}{K_1} + \frac{k_2[H^+]^2}{K_2K_3} \quad --- (9)$$

Rate constants governed by the above equation would show a linear as well as a parabolic dependence on acidity. However, if the contribution from the parabolic process were small, the overall rate profile would approximate linearity but would exhibit an apparent negative intercept. Non-linear least-squares fitting of the data to eqn. (9) leads to $k_1K_1 = 1.69 \times 10^{-3}$ M^{-1} min^{-1} for 1-methyl-uracil and 2.73×10^{-3} M^{-1} min^{-1} for 1,3-dimethyl-uracil, and $k_2K_1K_2 = 0.40 \times 10^{-4}$ M^{-2} min^{-1} and 3.1×10^{-3} M^{-2} min^{-1} for 1-methyl-uracil and 1,3-dimethyl-uracil respectively. Curves generated using these values fit the data well, and are illustrated in Fig. 10 (p.62).

It must be mentioned, however, that for the derivatives exhibiting Class 1 behaviour, these dicationic processes, if present, would tend

Fig. 10

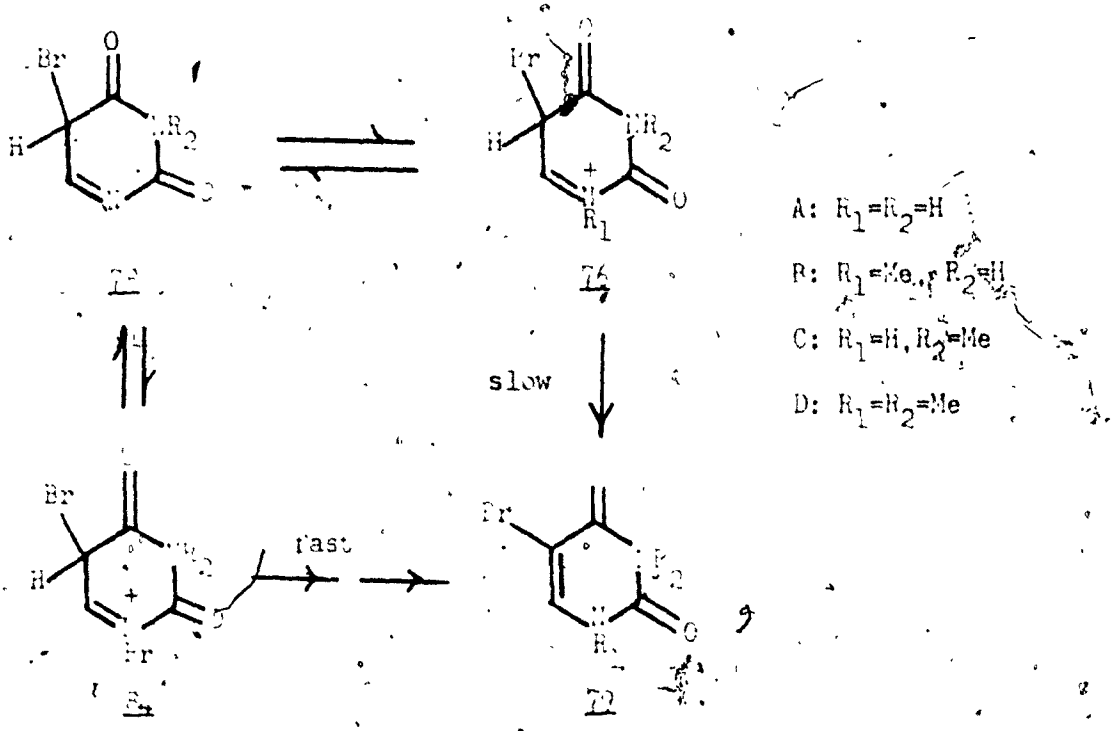
Variation of the rates of appearance of the 5-bromo-derivatives of 1-methyl-uracil and 1,3-dimethyl-uracil allowing for reaction via dicationic species



to be masked by the water reaction on 78.

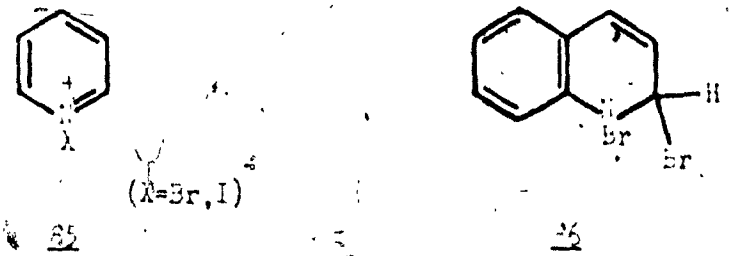
The rapid formation of the 5-bromo-derivatives 79A,C during titration with bromine in weakly acidic media cannot be rationalised by the dehydration kinetics of 74A,C or 75A,C, and therefore, an alternate pathway must be available. The absence of such behaviour for the N-1 substituted derivatives suggests that rapid conversion to 79A,C during titration, occurs through intermediates such as 78. However, since the decay kinetics of 78A,C are too slow to account for such behaviour, the rapid conversion to 79A,C must be caused by the bromine present during titration. Consequently, bromine must initially catalyse deprotonation from 78A,C to lead to the 5-bromo-compounds 79A,C, and then react further with 79A,C to form the 4,5-dibromo-derivatives 81A,C. Although the nature of this catalysis is not evident from these studies, it seems likely that the attack of bromine occurs on the nitrogen lone pair of the enamine 78 to give the transient N-bromo-intermediate 84 A,C, which rapidly aromatises to 79A,C, owing to the increased acidity of the 5-hydrogen atom, as shown in the scheme on the following page.

The absence of such effects at higher acidity (p. 52) implies that the intermediates 78A,C are predominantly protonated, ie. $[78_H] \gg [78]$ and $K_1 \gg K_4$, and the expected 1:1 titration result is obtained. Kinetic measurements made at 4.00N H_2SO_4, under conditions where the concentration of bromine exceeds that of 10A, show a slow decrease of the long wavelength bromine absorption band as the excess bromine is consumed by 79A as the latter is formed. The rate of bromine disappearance, however, is governed by the process 74A, 75A or 80A → 79A, and kinetic



values for the former compare well with those obtained for the increase of 79A .

The formation of N-halogeno complexes is well established for other heterocyclic systems. Pyridine is known to form the stable complex 82[133], and more recently, intermediates such as 83 have been invoked in the bromination of quinoline, isoquinoline and 4-phenyl-pyrimidine in nitrobenzene slurries[134]. The occurrence of N-bromo-adducts has also



85 86

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* Similar behaviour may be observed for the 2-pyrimidones

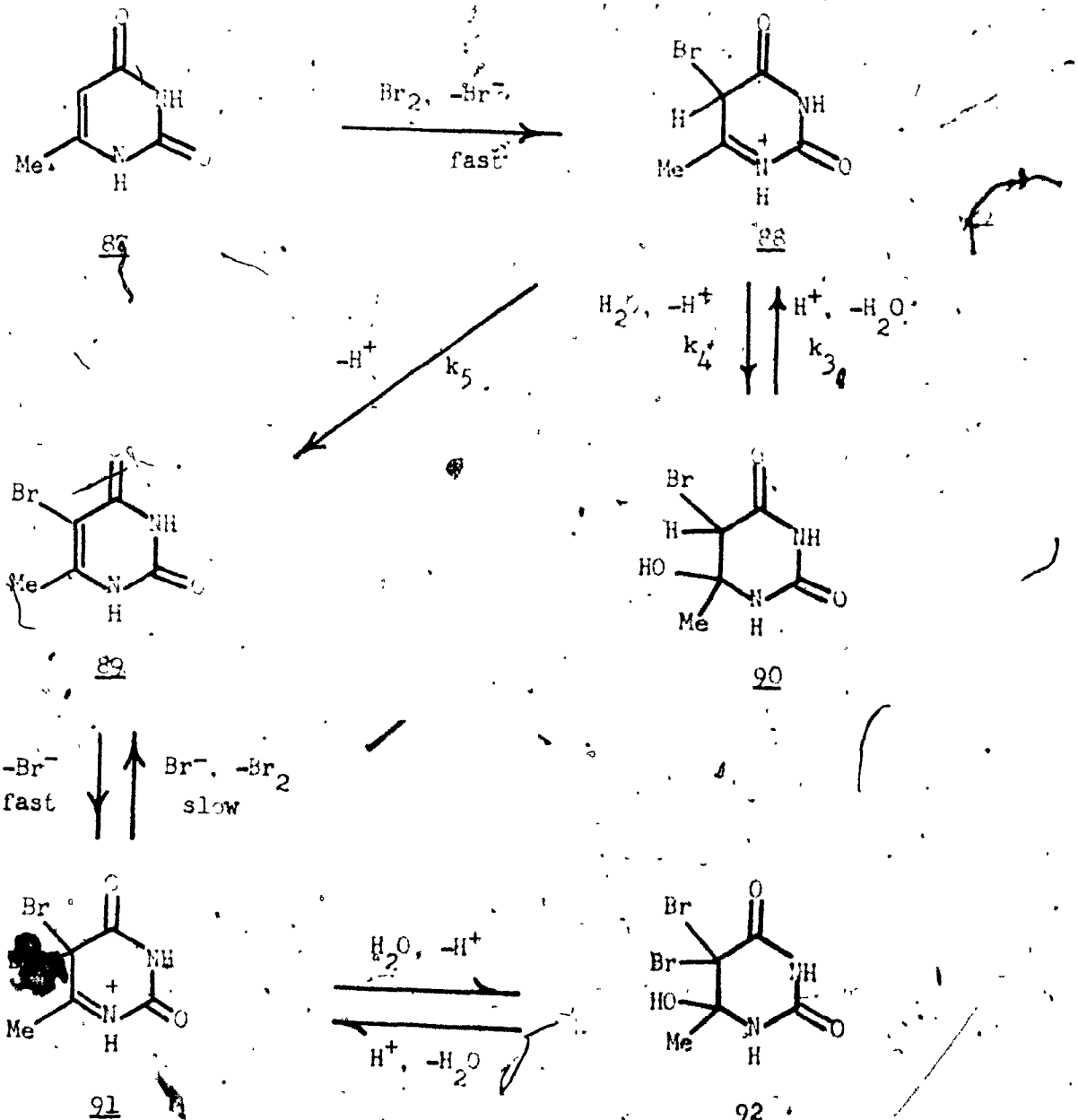
been postulated in the gas phase bromination of pyrimidines .

These conclusions appear to be applicable to other pyrimidine derivatives. Thus, both cytosine and orotic acid rapidly consume two mole equivalents of bromine during titration in buffered aqueous acids of pH 4.[51] . However, the adducts initially formed on bromination of the parent substrates are stable for several hours under identical conditions in the absence of bromine. Therefore, elimination from these adducts is catalysed by bromine, and presumably occurs by the mechanism operative for the similar process in the N-1 unsubstituted uracils.

The introduction of a 6-methyl group to the uracil ring considerably complicates its mechanism of bromination. Addition of bromine to solutions of 6-methyl-uracil 77 (p.74) in sulfuric acid leads to the formation of 5-bromo-6-methyl-uracil 81 by three distinctly different processes. A sharp increase of the u.v. absorptions appropriate to 81 is observed immediately after mixing, and this is followed by a relatively slow ($t_{1/2}$ = 1.40 mins. at 1.00 N H_2SO_4) build up of 81. Finally, a much slower reaction, the rate of which is dependent on acid strength as well as on bromide ion concentration ($t_{1/2}$ = 220 mins. at $[Br^-]$ = 3.60 x 10^{-3} M and at 1.00 N H_2SO_4) yields the 5-bromo-derivative 89. This final step is discussed in a later section (p.72) and is shown to be the conversion of the 5,5-dibromo-derivative 92 to 81 and bromine. The liberated bromine is taken up by unreacted 6-methyl-uracil to give a second equivalent of 81.

Fig. 11

Mechanism of bromination of 6-methyl-uracil



The formation of 92 under conditions where the concentration of 6-methyl-uracil exceeds that of bromine implies that the reaction of 6-methyl-uracil with bromine leads to the mono-bromo-derivative 92 which is subsequently brominated to 92. This in turn suggests that 6-methyl-uracil is brominated to 89 either directly or through unusually reactive intermediates.

The initial absorbance jump observed immediately after mixing occurs too rapidly to be followed by conventional spectrophotometric techniques. However, the second process leading to the formation of 92 is easily monitored, and pseudo-first-order rate constants obtained from these measurements are presented in Table 10 (p. 68) and plotted against $[H_3O^+]$ in Fig. 12 (p. 69). The linear dependence of rate on acid concentration and the slower rate of conversion obtained for 5-deuterio-6-methyl-uracil suggest the intermediacy of the adduct 96. Thus the processes 90 → 88 → 89 (p. 64) are equivalent to the conversion of 74 to 79 via 76 (p. 60), for the other uracils.

It appears that the attack of bromine on 6-methyl-uracil leads to the cation 88, which converts either directly to 89 (the 1-methyl-4-pyrimidone system behaves similarly (p. 43), or is attacked by water to form 90. This requires that the rate constants k_4 and k_5 be comparable. Hence, immediately following the disappearance of bromine under conditions where [6-methyl-uracil] >> $[Br_2]$, ie. before any conversion of 90 or 92 to 89 has occurred, the partitioning of 88 into 89 and 90 may be represented as follows:

Table 10

Variation of the rate of appearance of 5-bromo-6-methyl-uracil with $[H_3O^+]$

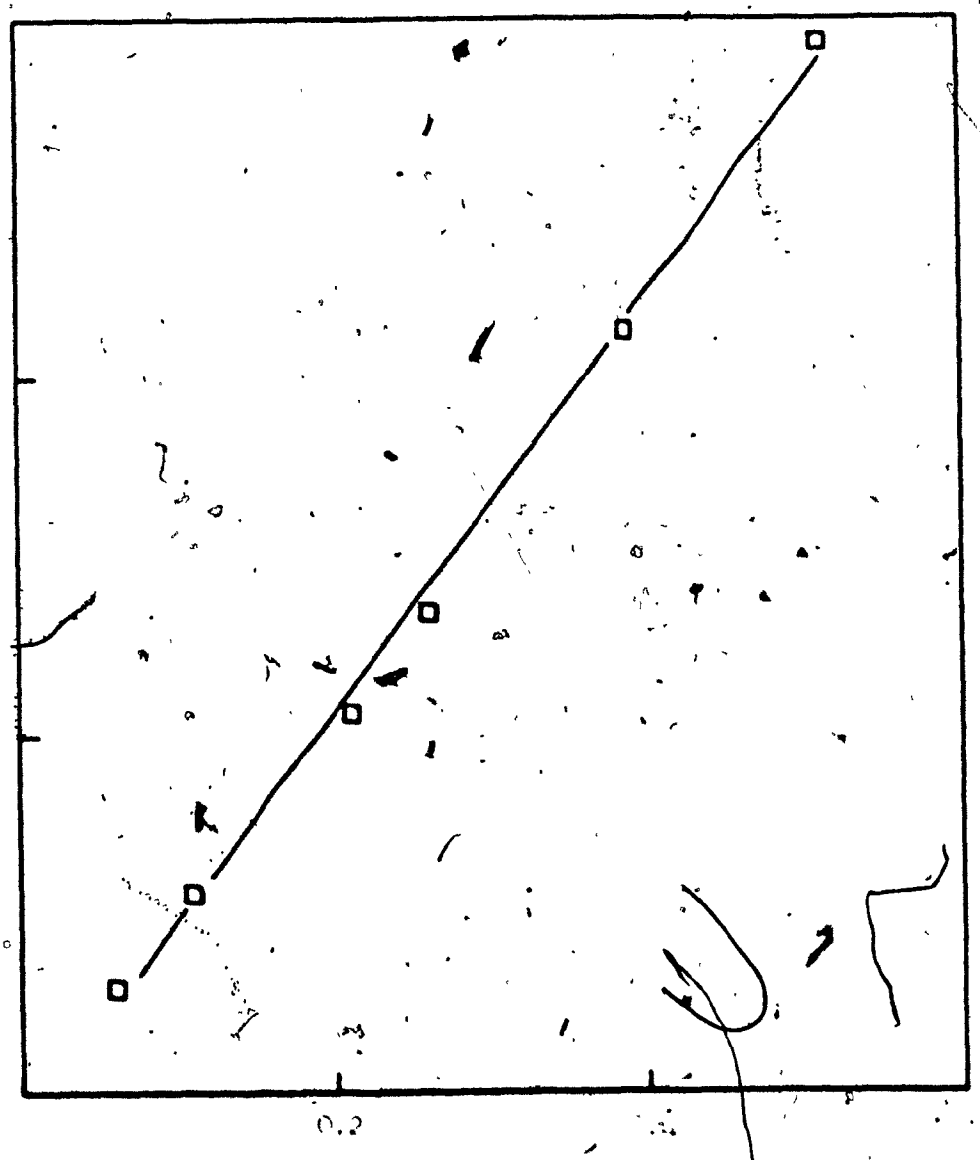
$[H_2SO_4]$ M	$[H_3O^+]$ M	k x 10^3 sec^{-1} [a]
0.100	0.059	2.92
0.200	0.110	5.56
0.400	0.211	10.6
0.500	0.261	13.4
0.750	0.386	21.2
1.00	0.511	28.8
		11.9 [b]

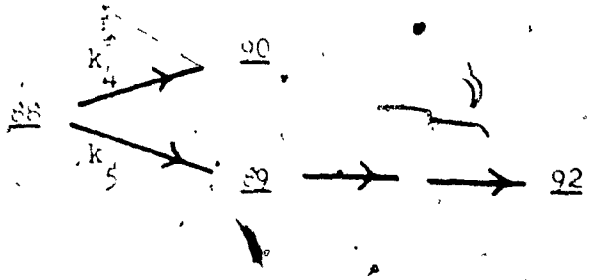
[a] [b]

Average of two determinations; refers to the 5-deuterio-substrate

Fig. 12

Variation of the rate of appearance of 5-bromo-6-methyl-uracil with $[H_3O^+]$





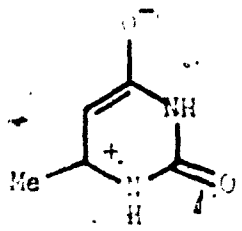
Now, since 92 is obtained from 88, the above scheme may be treated as two simple parallel reactions[136]. Also, since $[\underline{88}]_0 = [\underline{89}]_0 = [\underline{90}]_0 = 0$, ie. the initial concentrations of these species equal zero, the ratio $k_4:k_5$ may be calculated from the product distribution according to

$$\frac{[\underline{90}]}{[\underline{89}] + [\underline{92}]} \frac{k_4}{k_5} \qquad \text{---(10)}$$

Replacement of -H in 6-methyl-uracil with deuterium is expected to affect k_5, but leave k_4 virtually unaltered. Thus the isotope effect for the process 88 → 89 may be calculated from eqn. (10). In spite of the errors associated with calculations of this type, the isotope effect obtained ($k_H/k_D = 1.92$) compares reasonably well with that measured directly ($k_H/k_D = 2.33$) from the rate of appearance of 89 from 90.

Comparison of the reactivities of 90 and 74 (pp. 64,68) directly implicates the 6-methyl-group as the rate accelerating factor in the elimination step. The charge stabilising influence of the methyl group in the cation 88 may be compared to similar effects which are operative in the electrophilic substitution of aromatic and other unsaturated systems[137,138], and in all likelihood arise from similar origin.

The adduct 90 is also expected to be more reactive than 74 on the basis

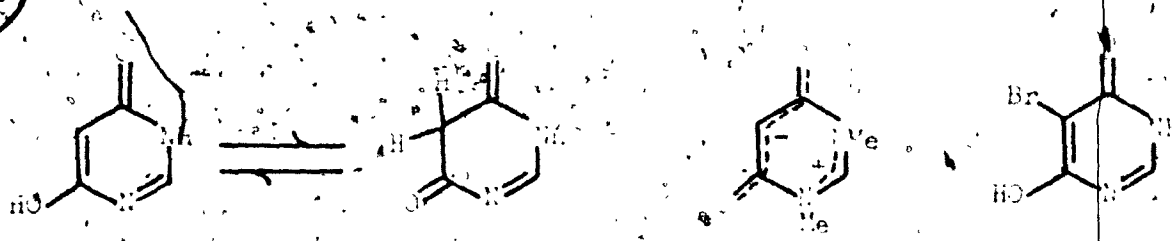


93

of steric hindrance. If the addition of 'HOBr' to 6-methyl-uracil occurs with trans stereochemistry, the bromine and methyl substituents in 90 would bear a cis relationship to each other and the equilibrium 90 ⇌ 88 would be shifted to the right.

These conclusions may find application in the photochemistry of uracil derivatives. Wang has found that the rate of hydration of 6-methyl-uracil is markedly slower than that of the parent molecule . Examination of the proposed intermediate 93 shows that the rate decrease may easily be accounted for by the stability afforded to 93 by the electron-releasing effect of the 6-methyl group.

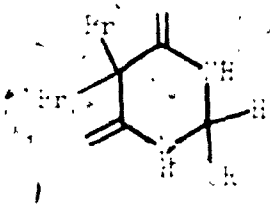
4,6-Dihydroxy-pyrimidine and 5-methyl-uracil [13]



2 3 24 26

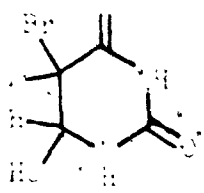
Although the major tautomeric component of 4,6-dihydroxy-pyrimidine in aqueous solutions is not known with certainty [14], p.m.r. studies in DMSO-d_6/D_2O solutions suggests that it exists predominantly in the enol-oxo form 2 with a small contribution from the dioxo component 3. In this medium, the 5-hydrogen shows slow exchange at ambient temperatures, but the rate is greatly increased by the addition of acids or bases [20]. Similar isotopic exchange occurs with the betaine 24 in acidic D_2O solutions.

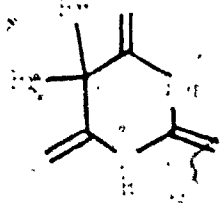
Since exchange at the 5-position of 2 occurs more easily than that of 2-pyrimidone [30], or uracil [30a], it might be anticipated that the analogous bromination of 2 would also be faster. Upon addition of two mole equivalents of bromine to a solution of 2 in aqueous sulfuric acid, the u.v. absorptions of 2 (λ max. 253 nm.) are removed, and the resulting solution has λ max. below 210 nm. with a significant tail end absorption extending beyond 240 nm.. With a stepwise addition of bromine the decrease in absorbance due to 2 is accompanied by spectral shifts to longer wavelengths, suggesting the intermediate formation of the 5-bromo-derivative 26 which has λ max. at 271 nm.. Spectrophotometric titration of 26 with bromine shows that one mole equivalent of bromine is required for



10C

complete reaction, isosbestic points being obtained at 215 nm. and 240 nm.. 1-Methyl-uracil behaves similarly on treatment with bromine. Two mole-equivalents of bromine are required for complete removal of the absorption maximum at 261 nm., the decrease in absorption being accompanied by bathochromic shifts. The 5-bromo-derivative 2 (p. 6), however, reacts sluggishly with one equivalent of bromine as evidenced by the elimination of its maximum at 277 nm., and the presence of an isosbestic point at 241 nm.. Under synthetic conditions 1 reacts with equivalent quantities of bromine in water, acetic acid or methanol to give 5-bromo-5,6-dihydroxy-pyrimidine (2). Addition of two mole equivalents of bromine to a methanolic suspension of 1 yields the 5,5-dibromo-derivative 10 (R=Me). Attempts to isolate a similar dibromo-derivative from water failed, the reaction being accompanied by extensive evolution of carbon dioxide. This probably arises from the decarboxylation of dibromo-malonic acid formed from the ring-opening of 10C (R=H). However, p.m.r. spectra of solutions obtained by the addition of an excess of bromine to a D_2O suspension of 1 shows a signal at δ 5.6, which gradually decays with the appearance of other signals which are attributed to decomposition products. Similar spectra are obtained on treatment of 1a with bromine. These observations, and the spectrophotometric titration data suggest the rapid formation and subsequent breakdown of the 5,5-dibromo-derivative 10C (R=H).





the compound 1" (R='e) liberates iodine from solutions of potassium iodide, and in the presence of bromide ion and acid, converts it to the bromo-pyrimidine ", during the course of which 1" itself is transformed to 1". The reactivity of 5,6-dibromo-pyrimidine derivatives are well established, as illustrated by the ready conversion of the uracil adduct 1" (R=Br), the thymine derivative 1" (R='e) and 5,5-dibromo-barbituric acid 1" to their mono-bromo-materials. Similar reversals also occur for mono-bromo adducts of the type 1" (R=H) as well as from those obtained from other 5,6- and 5,6-pyrimidines (p. 3").

Treatment of 5-methyl-uracil 1" (p. 1") with two mole equivalents of bromine leads to the adduct 1". The behaviour of 1" towards oxidising agents is similar to that exhibited by 1", to the extent that it liberates iodine from solutions of potassium iodide, and in the presence of bromide ion and acid, converts 5-methyl-uracil to its mono-bromo derivative 1", itself being converted to 1".

The reaction of 1" with bromine thus appears to involve the rapid formation of mono-bromo derivatives, which in turn are rapidly brominated to give the corresponding dibromo-pyrimidine derivatives. These subsequently react with substrate to yield the 5-bromo-products. The kinetics of the latter process were measured spectrophotometrically by

monitoring the appearance of the aromatic product at fixed wavelengths. The initial bromination steps were found to be too fast to be followed by conventional methods.

Under conditions where the concentration of [illegible] and bromine are comparable complex kinetic behaviour is encountered. However, linear first-order plots are obtained when the concentration of [illegible] exceeds that of bromine by a factor of four or more. First-order rate constants obtained in [illegible] M H_2SO_4 solutions are independent of substrate concentration but appear to be linearly dependent on bromine. Since the reaction of [illegible] with bromine is rapid compared to the rate of appearance of [illegible], this apparent dependence on bromine concentration may be interpreted as originating from the bromide ion formed in the reaction sequence [illegible]. This was confirmed by experiments in which bromine was added to mixtures of [illegible] and potassium bromide in solution, where plots of [illegible] vs. ([illegible] + [Br^-]) yielded the same second-order rate constant ([illegible] M^{-1} sec^{-1}) as that obtained in the absence of potassium bromide ([illegible] M^{-1} sec^{-1}). Kinetic data for these processes are summarised in Table 11 (p. 76), those for other acidities being listed in Table 12 (p. [illegible]) and plotted against bromide ion concentration in Fig. 13 (p. [illegible]).

Second-order rate constants which include the bromide ion catalytic coefficient are linearly dependent on acidity. These values are summarised in Table 13 (p. [illegible]), and plotted against [illegible] in Fig. [illegible] (p. [illegible]).

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* Structures on p. [illegible]

Table 11.

Variation of the rate of appearance of 5-bromo-4,6-dihydroxy-pyrimidine with $[Br^-]$ in 1.00 M H_2SO_4

$[Br^-]$ x 10^4 M	[KBr] x 10^4 M	Total $[Br^-]$ x 10^4 M	k x 10^3 sec
2.00		2.00	5.43
2.01		2.01	5.41
3.02		3.02	10.2
4.04		4.04	14.0
5.05		5.05	14.5
6.06		6.06	17.0
7.07		7.07	18.4
8.08		8.08	19.7
9.09		9.09	19.9
10.1		10.1	22.1
10.0		10.0	27.1
11.2		11.2	28.0
12.3		12.3	28.4
16.4		16.4	36.0
10.0	4.0	10.0	24.2
10.0	10.3	10.0	35.2
10.0	13.6	10.0	41.0
10.0	19.7	24.3	44.0
10.0	20.9	30.9	59.3
4.53	27.3	31.8	69.0
4.43	28.3	32.7	67.0

* At this acidity, $[H_3O^+]$ = 0.811 M

Table 12

Variation of the rate of appearance of 5-bromo-4,6-dihydroxy-pyrimidine with $[Br^-]$ and $[H_3O^+]$

$[H_2SO_4]$ M					
$[H_2SO_4]$ M					

$[Br_2]$ x 10^4 M	k x 10^3 sec^{-1}	$[Br_2]$ x 10^4 M	k x 10^3 sec^{-1}	$[Br_2]$ x 10^4 M	k x 10^3 sec^{-1}	$[Br_2]$ x 10^4 M	k x 10^3 sec^{-1}
4.51	2.21	4.[illegible]	[illegible]	3.40	5.30	4.96	[illegible]
4.[illegible]	2.37	[illegible]	[illegible]	[illegible]	7.41	6.16	11.1
5.74	2.[illegible]	9.24	7.[illegible]	[illegible]	[illegible]	8.74	13.9
[illegible]	3.10	13.9	9.2[illegible]	6.40	8.35	9.47	15.0
9.19	3.34	13.[illegible]	10.4	10.[illegible]	13.4[illegible]	11.[illegible]	18.4
11.0	3.63	17.4	11.4	11.4	13.3	15.3	22.7

Variation of [illegible] with [Br^-]

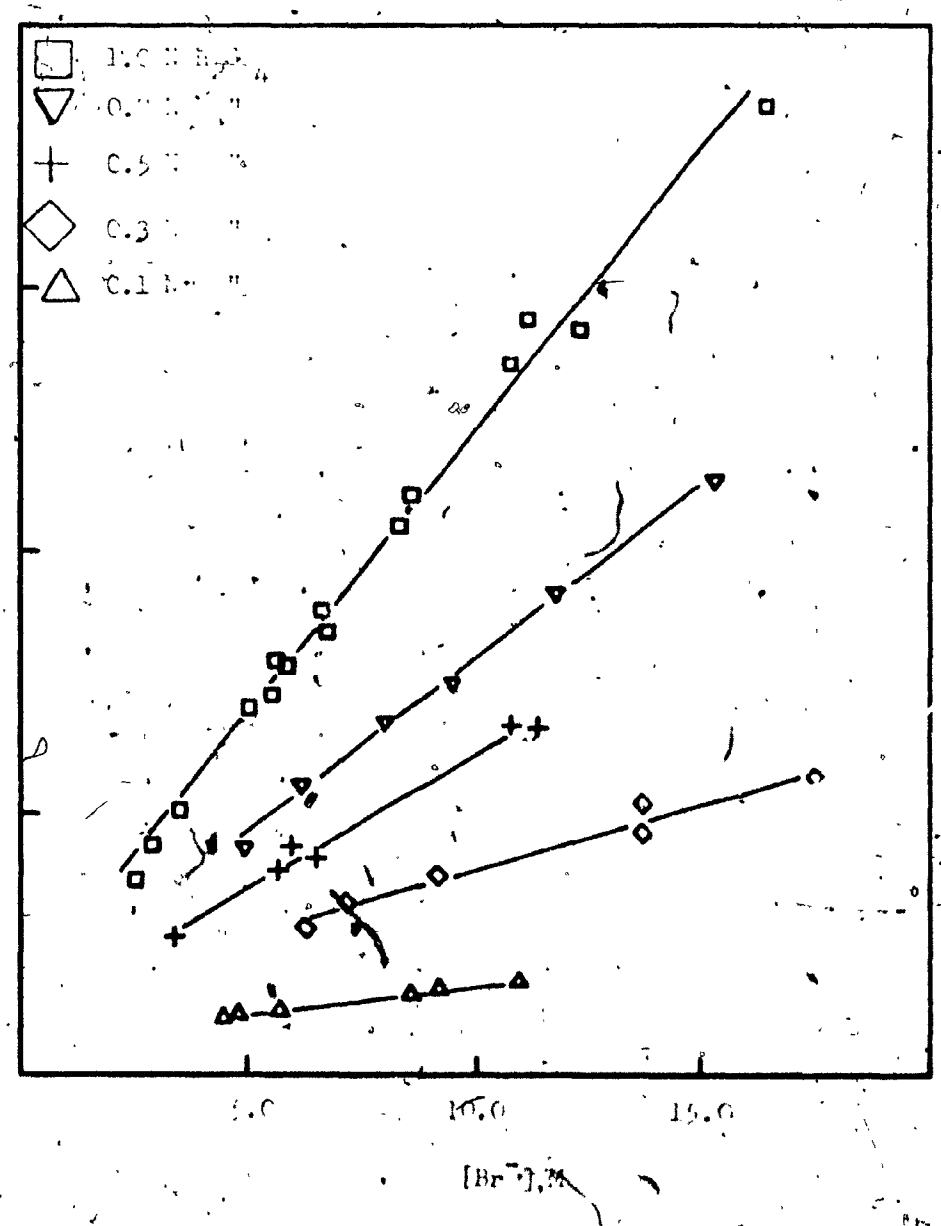


Table 13

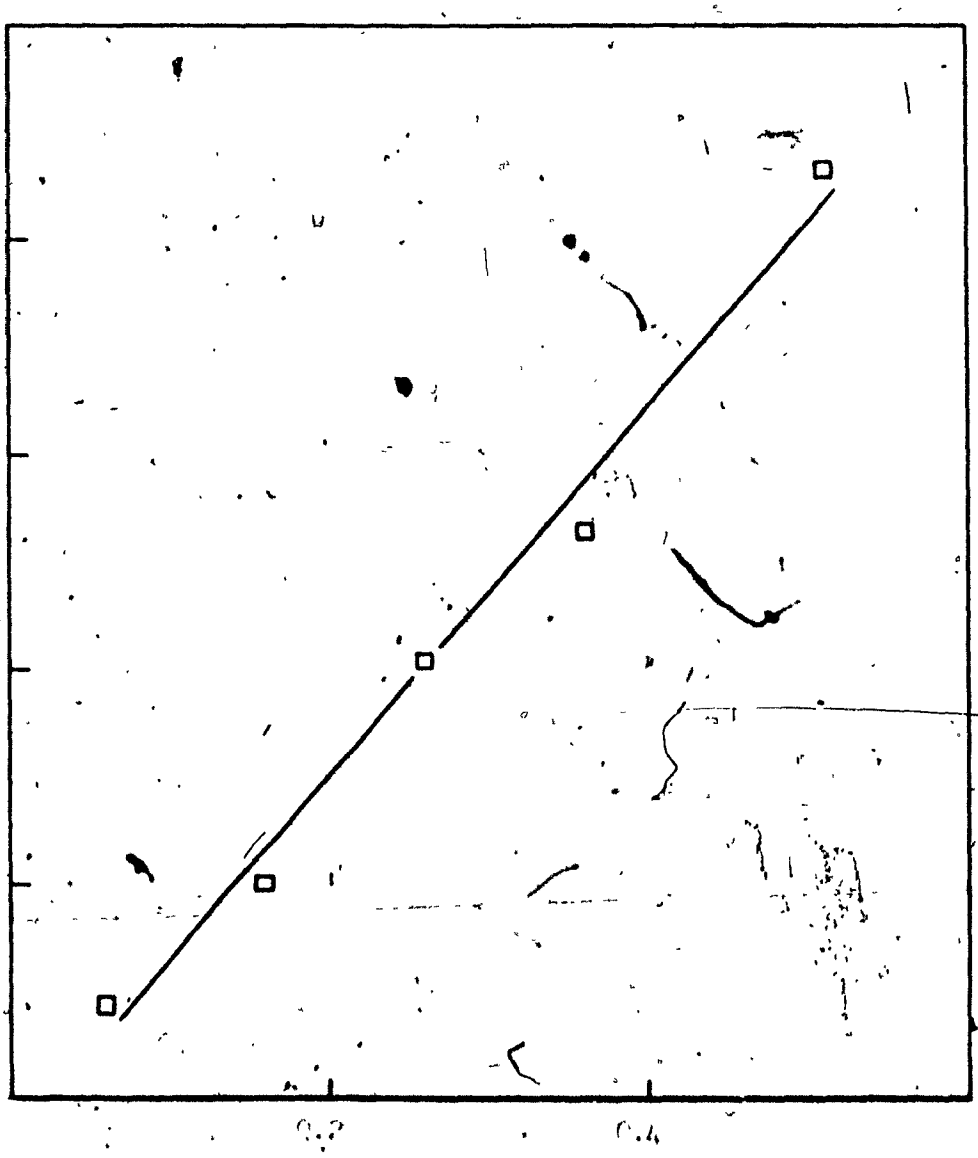
Variation of the second-order rate constant 'k' for the appearance of 5-bromo-4,6-dihydroxy-pyrimidine with $[H_3O^+]$

$[H_2SO_4]$ M	$[H_3O^+]$ M	k (moles^{-1} sec^{-1})
0.100	0.089	2.16
0.300	0.160	5.00
0.500	0.261	10.2
0.700	0.361	13.2
1.00	0.511	21.6
1.00	0.511	19.8*

* Rates were measured in the presence of KBr

Fig. 14

Variation of the second rate constant 'k' for the appearance of 5-bromo-4,6-dihydroxy-pyrimidine with $[H_3O^+]$



Thus, the conversion of 1C to the 5-bromo-derivative 2c seems to be subject to catalysis by bromide ion as well as by hydronium ion (Fig. 15, p. 82). The presence of potassium chloride, however, had no effect on the reaction rate. The small positive intercepts in Fig. 13 (p. 78) suggest that 1C is converted to 2c by an additional process not involving bromide ion. This is likely to be the water reaction on 2c or 1CC, i.e. the leaving bromine atom is lost as H_2OBr. Kinetics were also measured for the reaction of the 5-fluoro-derivative 1F (Table) with 2 in acidic solutions in the presence of bromide ion, and for the reaction of 1C (R=H) (generated by the addition of bromine to the 5-bromo-compound 2c) with 2. In all cases the rate constants obtained were identical within experimental error to those listed in Tables 11 and 12 (pp. 76, 77).

These findings may be rationalised by the sequence outlined in Fig. 16 (p. 82), and by using the following analysis :

$$1 + Br_2 \xrightarrow[\text{fast}]{k} 2 + H^+ + Br^- \quad \text{---(11)}$$

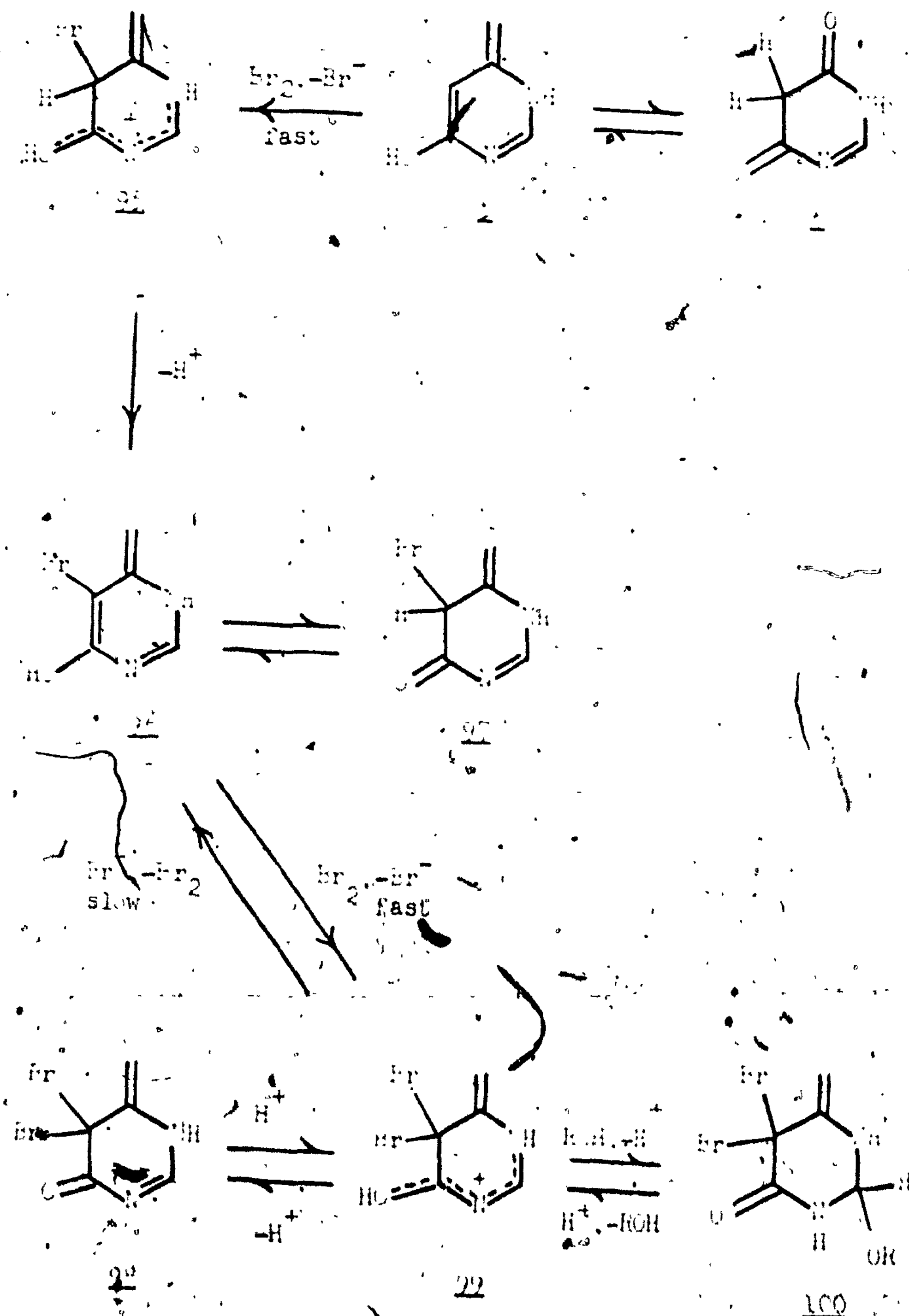
$$2 + Br_2 \xrightarrow[\text{fast}]{k_{-1}} 1CC + H^+ + Br^- \quad \text{---(12)}$$

$$1CC + H^+ + Br^- \xrightarrow[\text{slow}]{k_K} 2 + Br_2 \quad \text{---(13)}$$

An equivalent analysis pertains to the debromination reaction illustrated in Fig. 11 (p.66) for 5-methyl-uracil

Fig. 16

Mechanism of bromination of 4,6-dihydroxy-pyrimidine



Upon mixing of the substrate 2 and bromine there is rapid formation of both 96 and HOC (eqns. 11 and 12) and also of bromide ion up to a concentration essentially equal to that of the initial bromine. Only after essentially all of the bromine has been consumed by 2 and 96 does the slow back reaction HOC → 96 (eqn. 13) become apparent. Moreover, since 2 is in excess, and probably $k_1 > k_2$, any bromine produced by the k_3 step is scavenged by 2 and converted to 96. That is, during the slow latter stages of the reaction, bromine is present only in steady state amounts. The overall result of the reaction is thus that all of the bromine is converted to 96 (and HBr) since 2 is always in excess.

At any time the rate of formation of 96 is

$$\frac{d[96]}{dt} = (k_1[2] - k_2[96])[Br_2] + k_3[HOC][H^+][Br^-] \quad - - - (14)$$

and that of bromine is

$$\frac{d[Br_2]}{dt} = k_3[HOC][H^+][Br^-] - k_1[2][Br_2] + k_2[96][Br_2] \quad - - - (15)$$

During the latter stages of the reaction bromine is present in steady state amounts, since both of the processes which consume bromine (eqns. 11 and 12) are very much faster than that (eqn. 13) which produces it. Setting eqn. 15 = 0 gives

$$[Br_2] = \frac{k_3[HOC][H^+][Br^-]}{k_1[2] + k_2[96]}$$

Therefore $$\frac{d[\underline{Q_6}]}{dt} = \frac{2k_1k_3[\underline{5}][\underline{100}][H^+][Br^-]}{k_1[\underline{5}] + k_2[\underline{Q_6}]} \quad \text{---(16)}$$

Under the conditions used, $[\underline{5}] \gg [\underline{Q_6}]$, and since almost certainly $k_1 \gg k_2$, eqn. 16 simplifies to

$$\frac{d[\underline{Q_6}]}{dt} = 2k_3[\underline{100}][H^+][Br^-] \quad \text{---(17)}$$

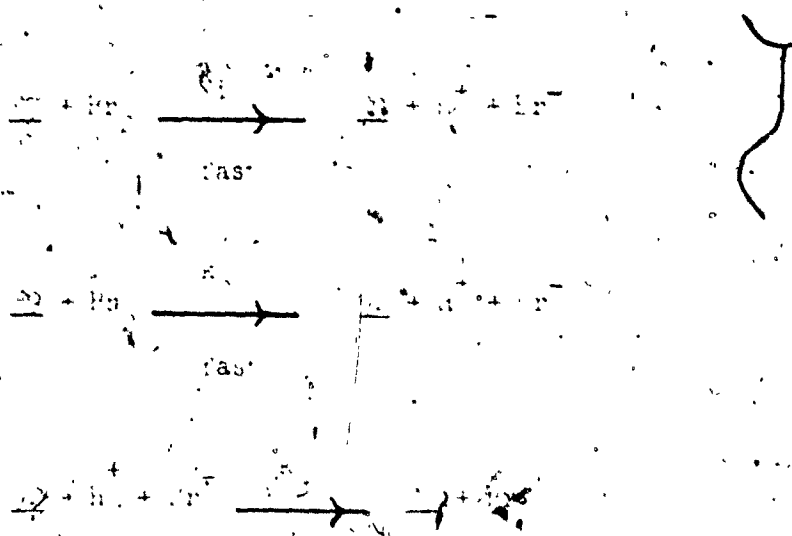
It is believed, therefore, that the slow appearance of $\underline{Q_6}$ which follows an initial rapid increase in absorbance due to $\underline{Q_5}$, arises from the bromide ion induced debromination of $\underline{Q_6}$ via $\underline{Q_5}$. This reaction (eqn. 13) is of course, the microscopic reverse of the bromination of $\underline{Q_5}$ (eqn. 12), and its rate should be dependent upon both acid and bromide ion concentration (eqn. 17) as observed.

If $\underline{5}$ were not in excess with respect to initial bromine, the concentration of $\underline{Q_6}$ might exceed that of $\underline{5}$ during the reaction and give rise to a breakdown of the inequality $k_1[\underline{5}] \gg k_2[\underline{Q_6}]$. Under these particular circumstances eqn. 16 would give rise to more complex kinetic behaviour as has been observed.

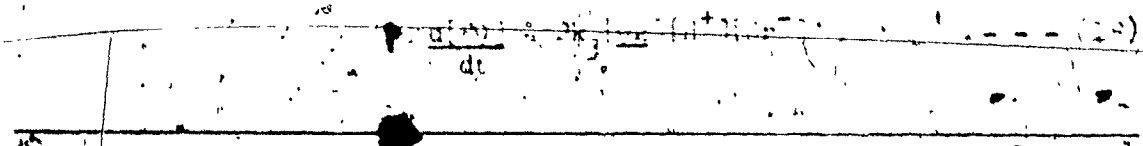
Similar kinetic behaviour was obtained for the reaction of 6-methyl-uracil with bromine, in that the observed first-order rate constants were linearly dependent on acid strength as well as on bromide ion concentration. However, pseudo-first-order behaviour resulted even under

conditions where substrate and bromine were of comparable concentrations. Kinetic data for this reaction compare well with those obtained from the reaction of 22 with 6-methyl-uracil in acidic solutions in the presence of potassium bromide, and imply that 22 is formed from a protonated species such as 24 derived from the dibromo-adduct 23, as illustrated in Fig. 11 (p. 34). Rate results are tabulated in Table 14 (p. 37), and the dependence of $f_{Br}(k_{obs}/[Br^-])$ with the acidity function H_0 is shown in Fig. 12 (p. 38).

Analysis of the sequence



along the lines outlined for the 4,6-dihydroxy-pyrimidine-bromine reaction yields



Structures overleaf

A water reaction on 22 would tend to deviate the plot towards non-linearity. However, the magnitude of this reaction is likely to be small.

Mechanism of Bromination of 6-methyl-uracil

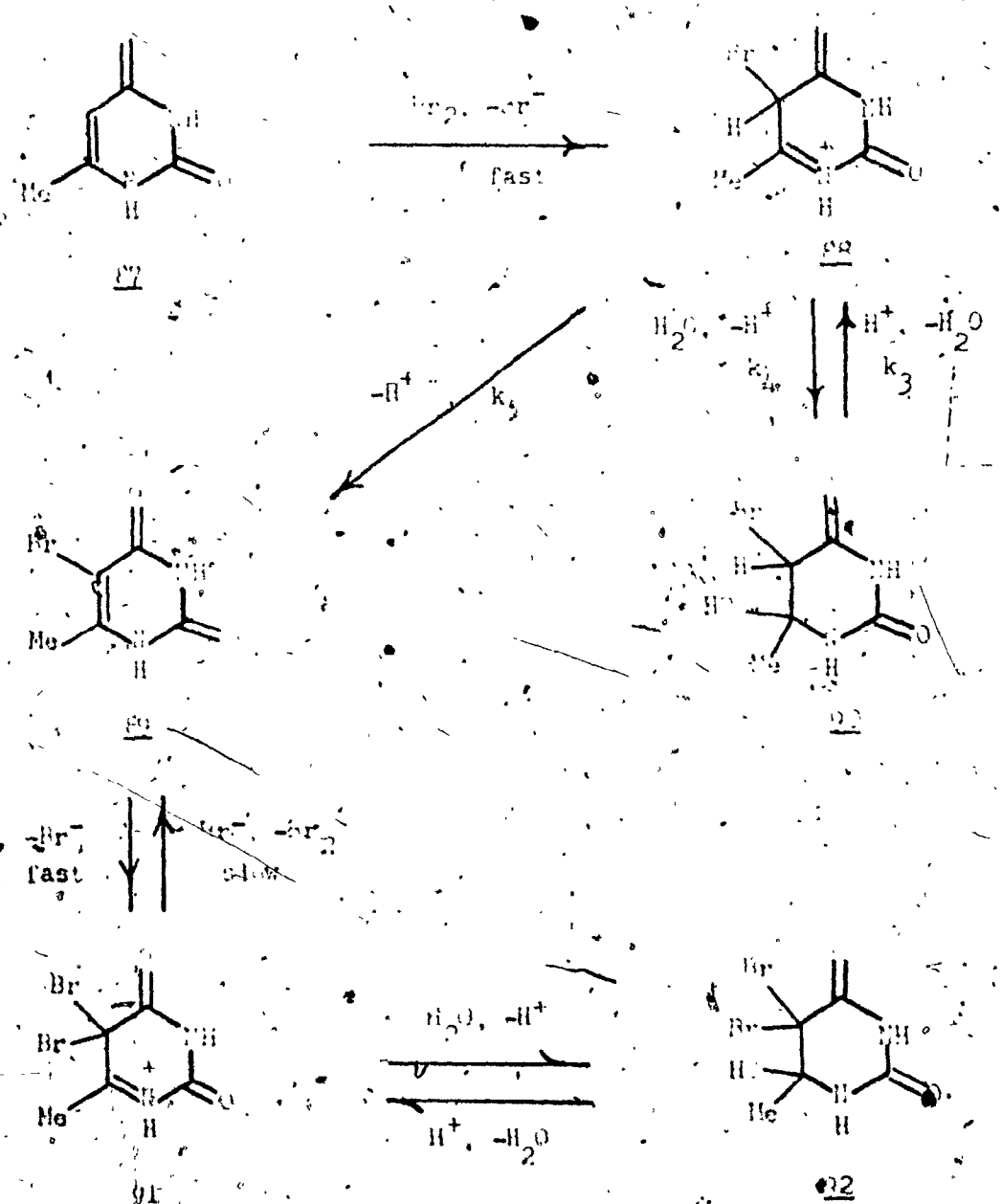


Table 14

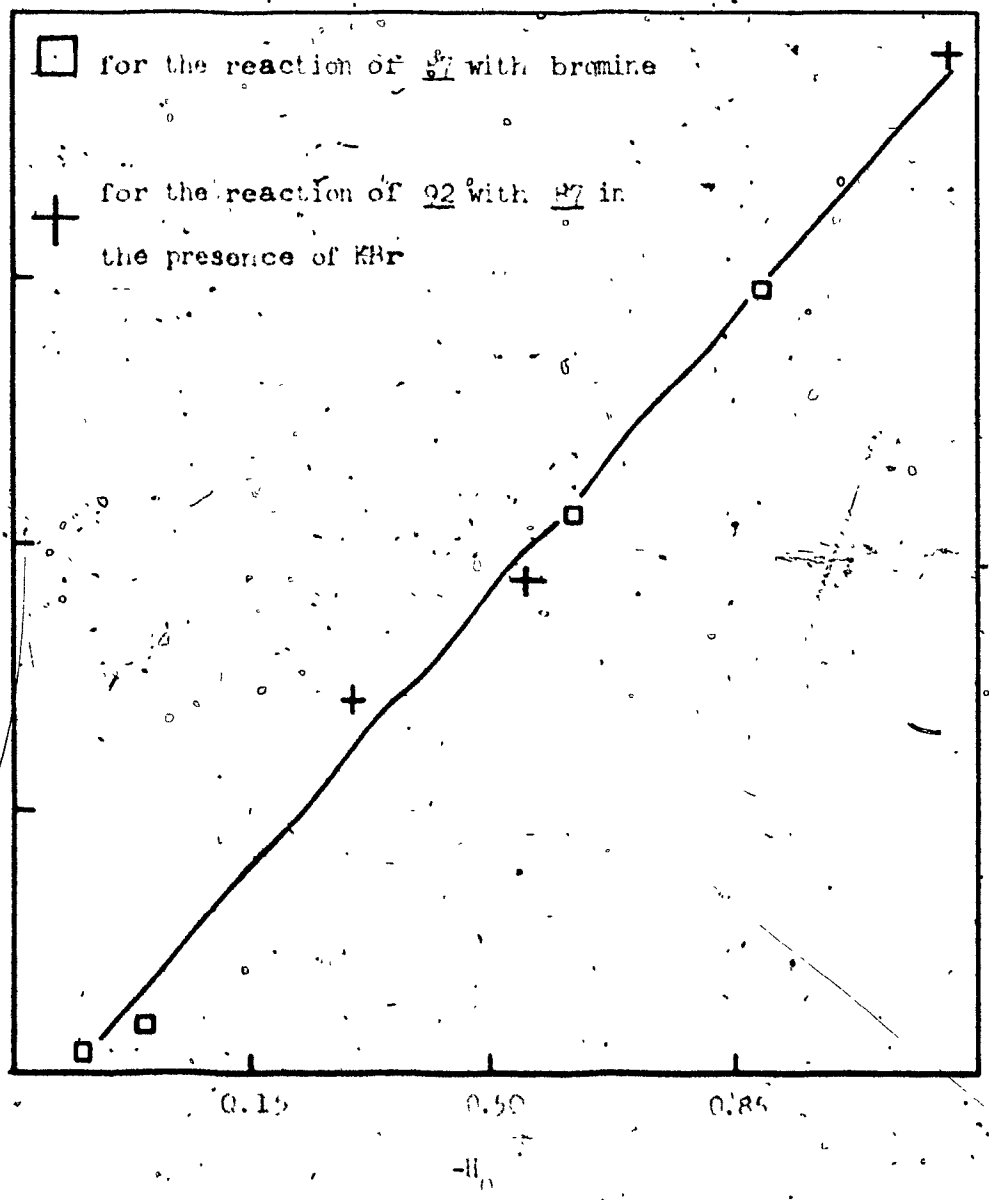
Variation of the rate of appearance of 5-bromo-6-methyl-uracil from 5,5-dibromo-6-hydroxy-6-methyl-dihydro-uracil with H_0

$[H_2SO_4]$ (N)	H_0	$k_{obs}/[Br^-]$[a] (M^{-1} min^{-1})	$\log (k_{obs}/[Br^-])$
1.00	0.10	0.270	-0.5686
1.20	0.01	0.287	-0.5272[b]
2.00[c]	-0.30	0.916	-0.0381
2.80[c]	-0.55	1.40	0.1461
3.00	-0.61	1.75	0.2430[b]
4.00	-0.89	3.80	0.5798
5.00[c]	-1.16	8.64	0.9365

[a] Average of two determinations; [b] single determination; [c] rate values refer to the reaction of authentic 5,5-dibromo-6-hydroxy-6-methyl-dihydro-uracil with 6-methyl-uracil

Fig. 16

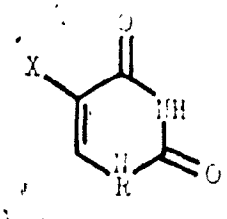
Variation of the rate of appearance of 5-bromo-6-methyl-uracil from 5,5-dibromo-6-hydroxy-6-methyl-dihydro-uracil with H_0



for the slow appearance of 89 during the latter stages of reaction of 87 with bromine. The derivation of eqn. 18 is dependent upon the validity of the inequality $k_1[87] \gg k_2[89]$. However, since it is not necessary to have a large excess of 6-methyl-uracil over bromine to obtain good pseudo-first-order kinetics, it would appear that $k_1 \gg k_2$, ie. the bromination of 6-methyl-uracil is very much faster than that of 5-bromo-6-methyl-uracil. The correspondence between this analysis of Fig. 11. (p. 88) and the observed kinetics suggests that the reaction followed was an acid-catalysed bromide ion induced debromination, namely 22 → 23.

These reactions appear to be of importance in biological processes. The importance of 5-fluoro-uracil 103 (R =H)[142] and 5-fluoro-2'-deoxy-uridine 103 (R = 2'-deoxy-ribosyl; X=F)[143] as cancerostatic drugs[144,145] has prompted a study on the release of these compounds, both in vivo and in vitro from the dihalo-adducts 104 (R_1=H, Me, Et, tBu etc., R_2 = H, 2'-deoxy-ribosyl, X=Br, Cl); it was shown that a qualitative correlation exists between the stability of 104 towards reduced glutathione, and its activity against mouse leukemia B82A.

Dehalogenation from 5-halo-uracils also occurs via loss of halonium ion. In acidic media, 5-iodo-uracil is converted to uracil by an addition-



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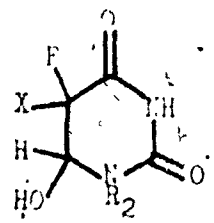

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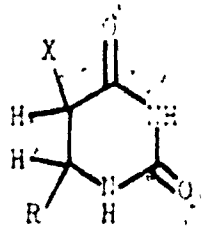

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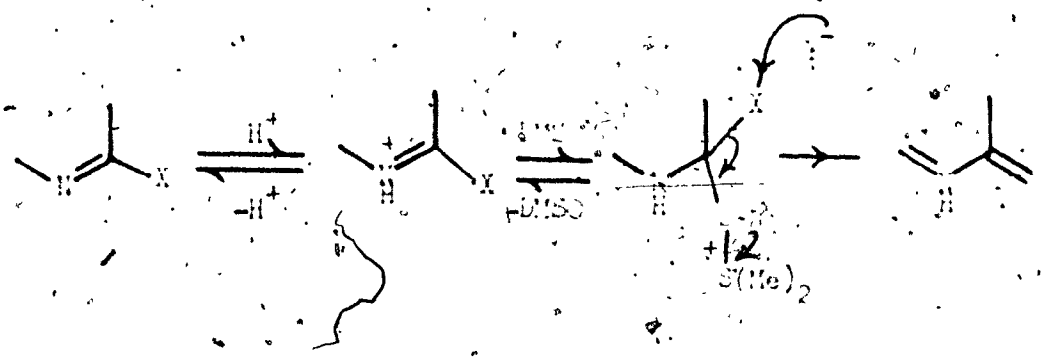
elimination mechanism, the deiodination step occurring from the intermediate 104 (R=OH; X=I)[43]. More recently, 103 (R=H; X=Cl, Br, I) has been shown to dehalogenate in the presence of sodium bisulfite by way of a similar intermediate 104 (R=SO_3H; X=Cl, Br, I)[44].

The conversion of halo-pyridines and quinolines to their corresponding oxo-derivatives in acidic DMSO-solutions have been proposed to involve dehalogenation by an addition-elimination process as illustrated below:[44,149]



A related observation by the author suggests that an analogous mechanism might be operative in the formation of 2-pyrimidone from 2-bromo-pyrimidine under similar reaction conditions.

Consideration of Figs. 11 (p. 88) and 15 (p. 92) shows that the bromination-debromination processes 80 ⇄ 82 and 96 ⇄ 100 proceed in each case through identical transition states, and therefore, differ only in sense rather than in mechanism. An analogy may be drawn to the bromination of olefins in polar solvents, where the addition reaction occurs via rate-determining attack of water on the electrophile[150], and consequently, elimination from the resulting vicinal dibromo-adduct is subject to catalysis by halide ion[151]. Thus, if in the bromination of

the mono-bromo-derivatives 89 and 96, the formation of the cations 91 and 99 is rate-controlling, the slow step in the reverse reaction may be inferred to be the loss of bromonium ion.

SUMMARY

The data reported in the present study enable a quantitative evaluation of the mechanism of bromination of mono- and dioxo-pyrimidines to be made. In aqueous acidic media both 2- and 4-pyrimidones undergo halogenation by way of neutral covalent hydrate or pseud-base species present in very low equilibrium concentrations. The charged intermediate obtained immediately after the attack of electrophile may deprotonate directly (as in the case of 1-methyl-4-pyrimidone and 4-methyl-uracil) to the 5-bromo-derivative, or may be acted upon by water to yield an identifiable adduct. No conclusions may be drawn for the 4,6-dihydroxy-pyrimidine system, where the formation of the 5-bromo-product occurs too rapidly to allow measurement by conventional techniques.

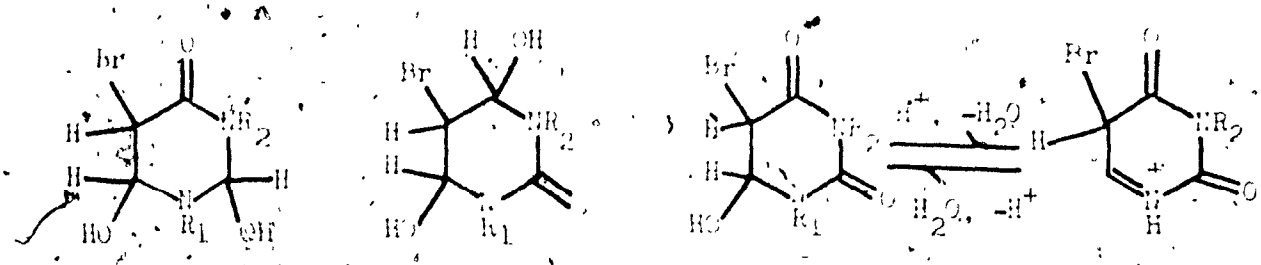
A measure of the influence of the 4-oxo-substituent in directing the reactivities of these intermediates may be obtained by comparison of the rates of formation of the 5-bromo-products. Table 1 (p. 93) lists representative rate data for the substrates studied under comparable conditions of solvent acidity. Although a quantitative correlation cannot be achieved owing to the differences in the dependence of the observed rates on acidity, these values illustrate the stability of the intermediates relative to one another within an order of magnitude. Thus, it is easily seen that the presence of a carbonyl group alpha to NH in [illegible] (derived from 4-pyrimidone) increases its rate of aromatisation by a factor of approximately 1×10^{3} over a similar elimination from [illegible]

Structures on p. 94

Table 15

Rates of formation of 5-bromo-pyrimidines from their corresponding mono-bromo-pyrimidine adducts

5-bromo-	H_2SO_4 (N)	$k \times 10^3$ (min^{-1})
2-pyrimidone	1.00	~0.412
1-methyl-2-pyrimidone	"	1.20
1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium hydrogen sulfate	"	6.33
4-pyrimidone	2.80	636
1-methyl-4-pyrimidone	"	942
3-methyl-4-pyrimidone	"	1330
1,4 (3,4)-dihydro-1,3-dimethyl-4-oxo-pyrimidinium perchlorate	"	1200
uracil	1.00	1.14
1-methyl-uracil	"	1.11
3-methyl-uracil	"	2.64
6-methyl-uracil	"	1760
1,3-dimethyl-uracil	"	2.11



68 — 33 — 74 — K — 75

R_1=H or Me; R_2=H or Me

(from 2-pyrimidones).

The similarity in the rates of formation of the 5-bromo-derivatives of 2-pyrimidone and uracil shows that the presence of an additional carbonyl group in 74 does not significantly aid the dehydration step. This in part may arise from the increased reactivity of 33 over 74, by virtue of its possessing two potential sites of protonation. However, such effects are likely to be small, and it seems more probable that the rate enhancing effect of the carbonyl group in 74 is more than offset by its rate retarding contribution in raising the equilibrium constant K.

The above trends are well illustrated by the change in isotope effect (k_H/k_D for 5H) with alteration in structure. These values are summarised in Table 16 (p. 95). The polarisation afforded to the C_5–H bond by the carbonyl group in 68 tends to favour an early transition state for the deprotonation step, and thus the isotope effect obtained for 68 is significantly less than the corresponding value for 33.

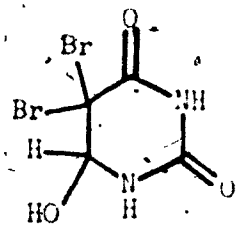
Table 16

Isotope effects (at the 5-position) for the formation of 5-bromo-pyrimidines from their corresponding mono-bromo-pyrimidine adducts.

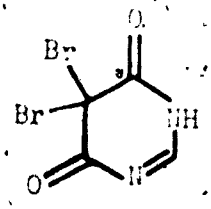
5-bromo-	k_H/k_D	adduct
1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium hydrogen sulfate	5.91	33 (R_1=R_2=Me)*
3-methyl-4-pyrimidone	1.58	68 (R_1=H, R_2=Me)*
1,4(3,4)-dihydro-1,3-dimethyl-4-oxo-pyrimidinium perchlorate	1.87	68 (R_1=R_2=Me)*
uracil	4.32	74 (R_1=R_2=H)*
6-methyl-uracil	2.33	88Δ
1,3-dimethyl-uracil	3.46	74 (R_1=R_2=Me)*

* Δ

Structures on p. 94, p. 86



92



98

Finally, the reversal of the dibromo-adducts 92 and 98 obtained from 6-methyl-uracil and 4,6-dihydroxy-pyrimidine respectively are similar in nature to the dehydration mechanisms discussed above, and proceed via closely related mechanisms. Comparison of the bimolecular rate constants obtained in 1.00 N H_2SO_4 for the debromination of 92 ($0.27\ M^{-1}\ min^{-1}$) and 98 ($1190\ M^{-1}\ min^{-1}$) shows that the greater reactivity of the latter is in keeping with the β-diketo structure of 92.

APPENDIX

KINETICS OF THE RAPID BROMINATION OF HYDROXO-PYRIMIDINES

Earlier, it was suggested that the salts of 2-pyrimidone 12 (p. 9) react rapidly with bromine through the covalent adducts 13. A similar mechanism was proposed to be operative in the bromination of the 4-pyrimidones 14 (p. 41). A kinetic study of these fast reactions was initiated, in order to directly confirm these postulates, and the results obtained are discussed in the present section.

2-Pyrimidone

The 2-oxo-pyrimidinium salts 12 and 32 convert rapidly to the adducts 33 and 34 respectively on addition of bromine, the reactions being accompanied by loss of the u.v. absorption bands of the substrates. In the former case, however, 33 undergoes acid-catalysed elimination to 35, and kinetic studies are complicated by the reaction of the final product 35 with bromine. Rate measurements were therefore restricted to the conversion of 32 to 34, where the intermediate 34 has previously been assumed to be of kinetic importance.

In media of acidity greater than 1.6 N H_2SO_4, a quantitative reaction between 32 and bromine is not obtained. Consequently at these acidities

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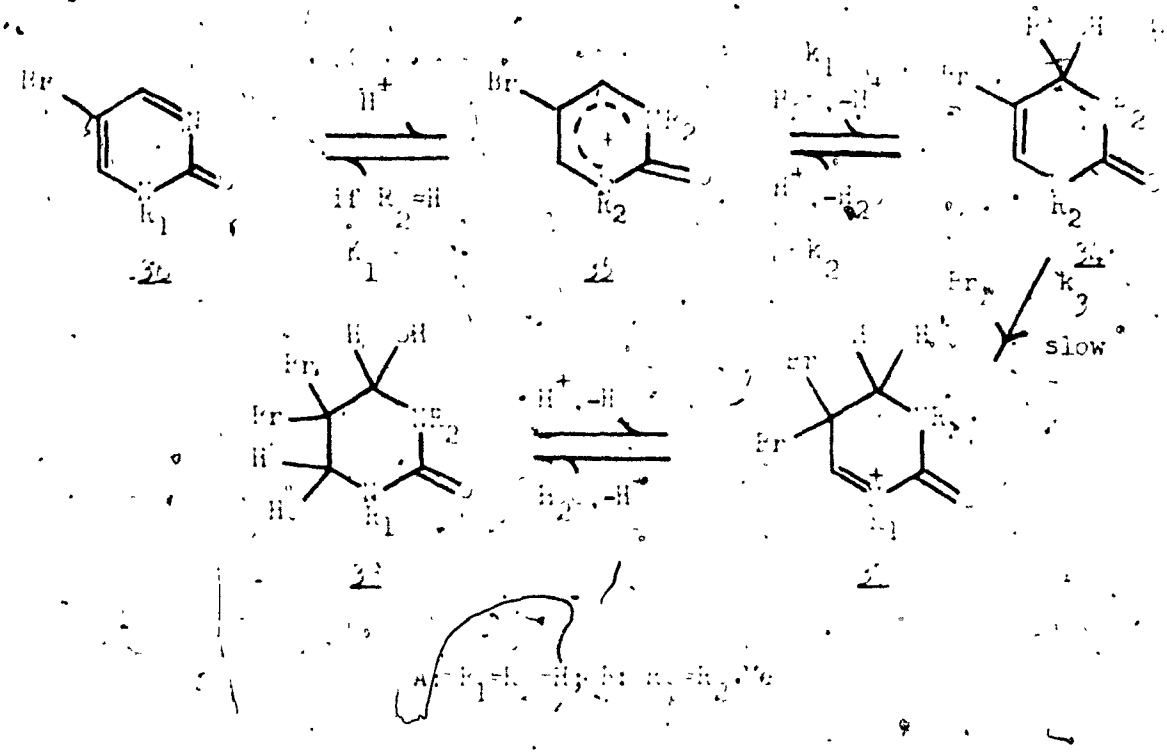
* Structures overleaf



bromine can be detected even in the presence of a tenfold excess of substrate. In the acidity region (4.60 – 11.3 in H_{R^+}), the reaction proceeds to completion, and the decrease of absorbance follows a first-order rate law with respect to bromine if substrate is maintained in excess.

The concentration of 22 was maintained in 7–10 fold excess of that of bromine, and the initial substrate concentration was taken to be $([22]_0 - [Br_2]_0)$ in order to more closely realize first-order conditions. Second-order rate constants (k) were obtained from plots of k_{obs} vs. $([22]_0 - [Br_2]_0)$, and these are presented in Table 17 (p. 99). The acidity dependence of these rates is likely to arise from the effect of acidity on the hydration equilibrium 21 ⇌ 22, and the data in Table 18 are consequently plotted against the acidity function H_{R^+} (H_{R^+} is the acidity function derived from carbinol – carbonium ion equilibria [83,141]) in Fig. 17 (p. 100).

Table 17

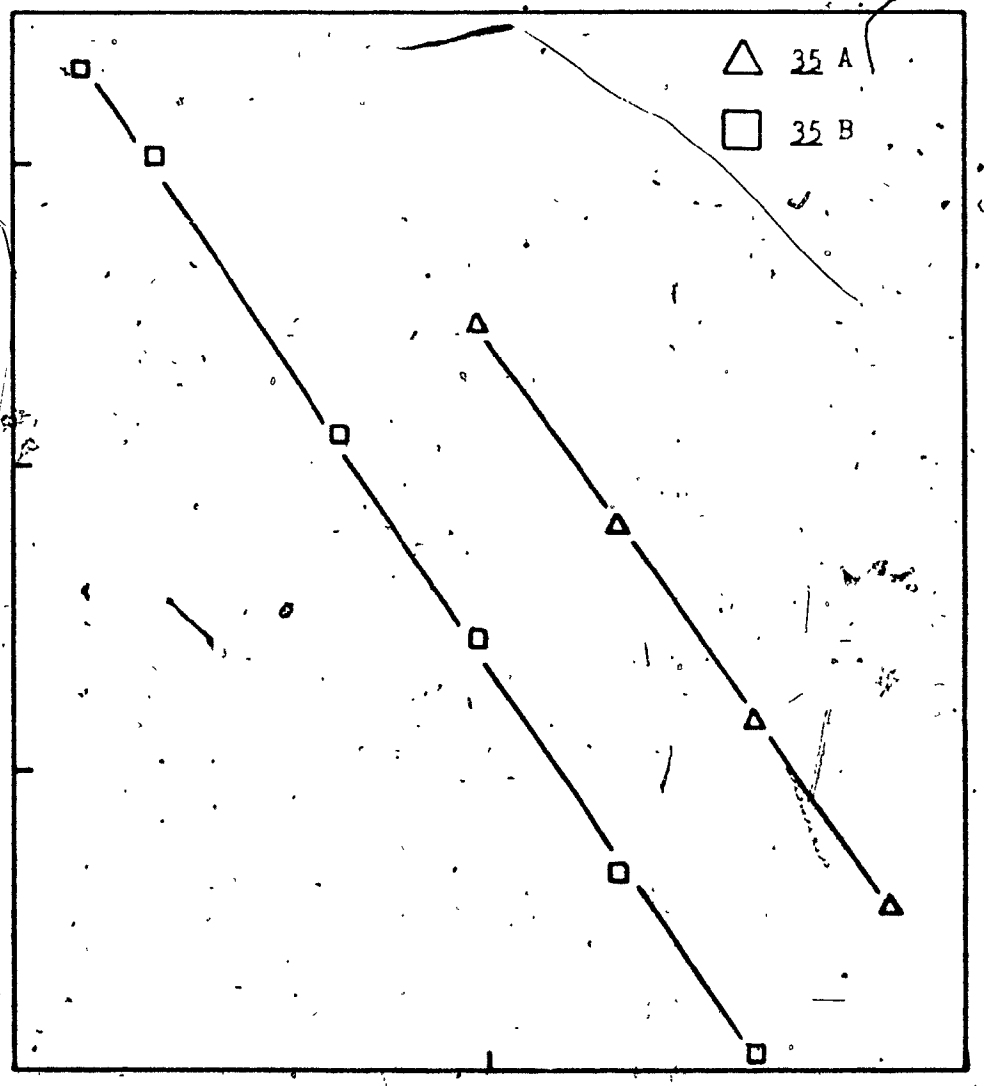
Variation of the rate of bromination of the 5-bromo-2-pyrimidones with acidity

H_2SO_4 (N)	H_R	k_A[a,b]	log k_A	k_B[a,b]	log k_B
4.00	-0.97			942	2.974
5.00	-1.53			424	2.627
7.60	-2.91			33.3	1.522
9.50[c]	-3.92	90.3	1.956	5.16	0.712
11.4	-4.93	14.4	1.159	0.610	-0.215
13.3	-5.94	2.44	0.388	0.116	-0.934
15.2	-6.95	0.445	-0.351		

[a] k_A And k_B refer to second-order rate constants in M^{-1} sec^{-1} for the bromination of 35A and 35B respectively; [b] average of 2 - 12 determinations; [c] addition of up to 1 x 10^{-2} M KBr had no effect on the reaction rate. At higher KBr concentrations, the rate decreased. Since the concentration of Br^- did not exceed 1 x 10^{-3} M in these experiments, the effect of Br^- on the rates was ignored.

Fig. 17

Variation of the rate of bromination of 5-bromo-2-pyrimidone with H_R



If the reaction proceeds via 34, then the steady state approximation may be applied to 34 (since the equilibrium 35A ⇌ 34A has pK=3.08[3]). Hence,

$$\frac{d[34]}{dt} = k_1[35] - (k_2[H^+] + k_3[Br_2])[34] = 0$$

ie.
$$[34] = \frac{k_1[35]}{k_2[H^+] + k_3[Br_2]}$$

If $k_2[H^+] \gg k_3[Br_2]$,

$$[34] = \frac{k_1[35]}{k_2[H^+]} = \frac{K_2[35]}{[H^+]},$$

where $K_2 = k_1/k_2$.

Now, since $-\frac{d[Br_2]}{dt} = k_3[34][Br_2]$,

$$k_{obs} = \frac{k_3K_2[35]}{[H^+]}$$

and the observed second-order rate constant $k = k_3K_2/[H^+]$

The experimental results are consistent with these equations, and support the mechanism proposed on p. 98. Extrapolation of the data to H_R=0 for the dimethyl derivative 34B yields $k_3 = 7.9 \times 10^6$ M^{-1} sec^{-1}. Rate constants of this magnitude have been obtained by Bell and Ramsden[152] for the bromination of aromatic amines.

It may be noted from Table 17 (p. 99) that the parent substrate 35A is more reactive than 35B by a factor of ca 20. The values of k_3 (p. 98) for these derivatives are likely to be similar, and therefore, this rate difference probably arises from a difference in pK for the equilibrium 35 ⇌ 34. Since, the pK for the dimethyl-derivative 35B is 3.08[3], the corresponding value for 35A is inferred to be < 2. A similar effect has been previously noted in the hydrogen-deuterium exchange of 2-pyrimidones[30].

4-Pyrimidone

It has been shown (p. 41), that the 5-bromo-derivatives 72 and 63 react rapidly and quantitatively with one equivalent of bromine to give non-chromophoric products. These are likely to be the dibromo-derivatives 64, and p.m.r. spectra obtained after the addition of bromine to solutions of 63 are consistent with the proposed structure 64.

The kinetics of bromination of 63 were determined by measurement of the change in the bromine/bromide ion potential with a platinum redox electrode[152]. Good first-order behaviour was observed in the presence of an excess of substrate (10 - 100 fold), and second-order rate constants (k) obtained from plots of k_{obs} vs. initial substrate concentration are listed in Table 18 (p. 104).

Rate profiles constructed from these data deviate considerably from

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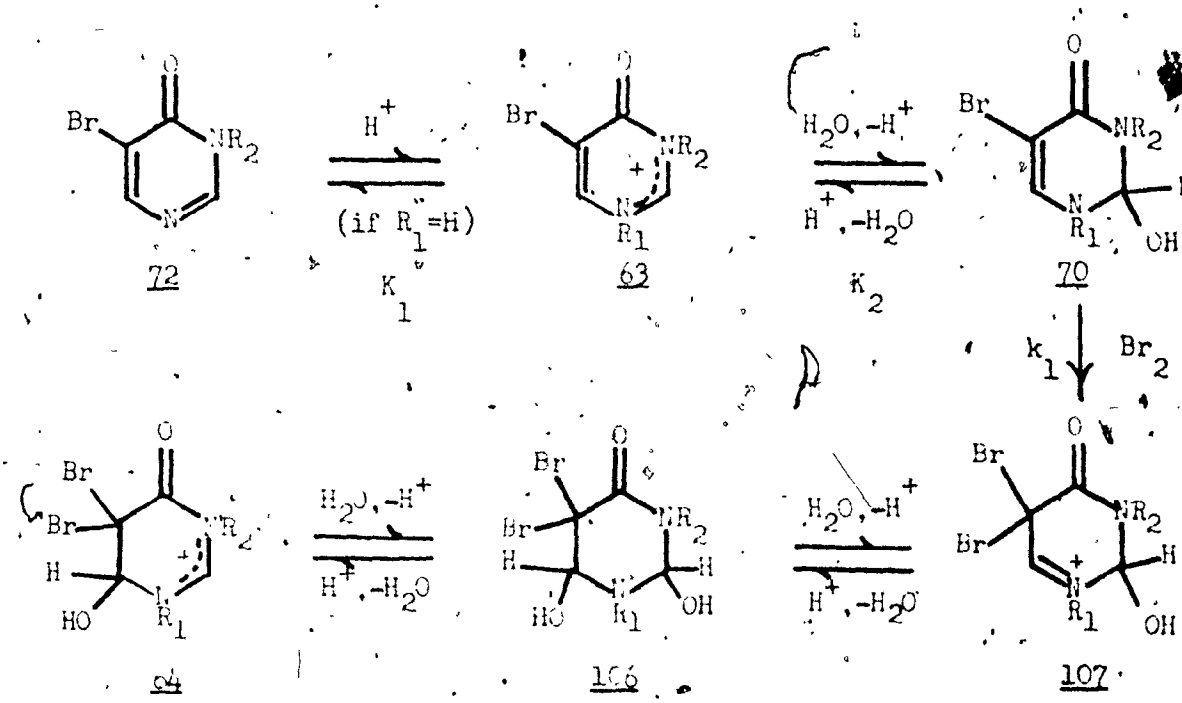
Structures overleaf



A: $R_1=R_2=H$; B: $R_1=R_2=Me$

ideal behaviour (Fig. 18, p. 105). The variation of log (k) with pH, although linear for the dimethyl-derivative 63B, has a slope of 1.48 instead of unity. Furthermore, the log (k) - pH plot for 63A is curved approximately about the protonation pK of 72 (measured to be 0.43), but does not show the expected invariance of rate with acidity at pH > 0.43. These effects do not arise from ionic strength effects since rates obtained for 72A in 0.1 M H_2SO_4 are unchanged by the addition of 0.3 M $NaNO_3$. However, the overall shape of the rate profiles suggests reaction via free base species, and is therefore qualitatively consistent with the mechanism outlined above. Thus, if bromination occurs on the adduct 70, it may be shown that

$$k_A = k_3 K_2''/([H^+] + K_1)$$

and

$$k_B = k_3 K_2/[H^+]$$

Table 18

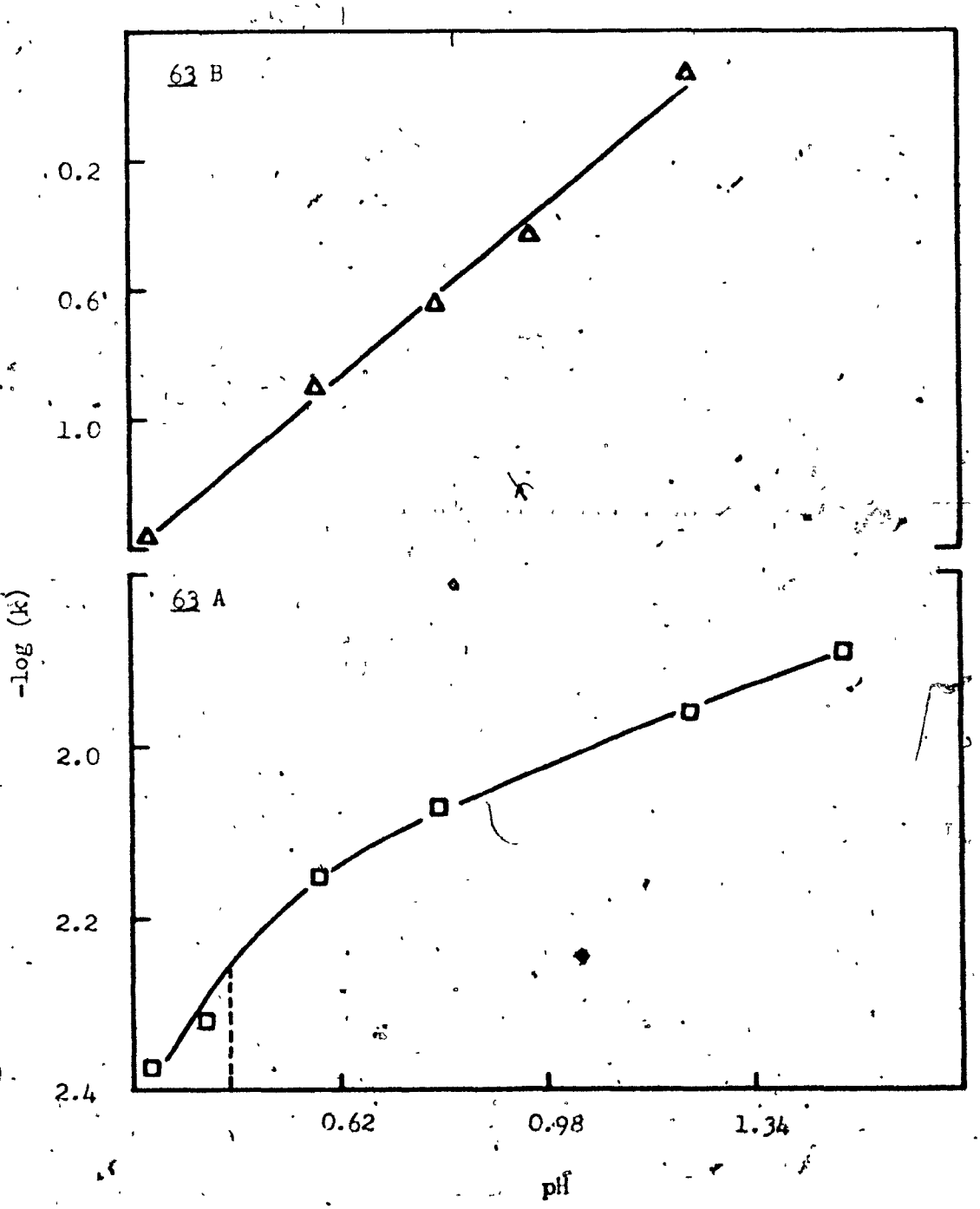
Variation of the rate of bromination of 5-bromo-4-pyrimidone with acidity

H_2SO_4 (N)	pH[a]	$k_A \times 10^{-2}$ [b-d]	$k_B \times 10^{-2}$ [b-d]
0.020	1.84	1.73	
0.050	1.50	1.28	
0.100	1.23	1.09	115
0.200	0.96		36.4
0.300	0.80	0.847	22.5
0.500	0.58	0.704	12.4
0.800	0.39	0.479	
1.00	0.29	0.422	4.30

[a] Calculated from the normality; [b] k_A and k_B refer to second-order rate constants in M^{-1} sec^{-1}; [c] average of 4 - 6 determinations; [d] k_A and k_B include corrections for the formation of tribromide ion, ie. k_A or B $= k^{\circ}_{obs}/[\text{Substrate}](1 + 16 \times 9.396 \times 10^{-3})$ where the concentration of Br^- was maintained at 9.396×10^{-3} M, and the ionisation constant for the formation of Br_3^- was taken to be 16[153].

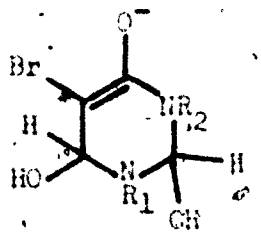
Fig. 18

Variation of the rate of bromination of 5-bromo-4-pyrimidone with acidity



where k_A and k_B are second-order rate constants for the compounds 72A and 72B respectively.

The deviations of the rate profiles in Fig. 19 from the behaviour predicted by the above equations appear to originate from a small additional inverse dependence of rate on acidity. Thus, if the adduct 70 exists in equilibrium with anionic species such as 108, then the reaction of 108 with bromine could account for the observed inconsistencies. It is difficult however, to quantify these arguments in view of the limited data available, and justification for the involvement of 108 in the reaction is consequently not presented here.



108

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